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HEALTH TECHNOLOGY BRIEFING
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Durvalumab for recurrent or metastatic squamous cell carcinoma of the head and neck – first line

NIHRIO ID	27684	**NICE ID**	10286
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	653732

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Durvalumab is a medicinal product currently in development for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). SCCHN is a cancer that arises from cells called squamous cells. Squamous cells are found in the outer layer of skin and in the mucous membranes, the moist tissues that line body cavities such as the airways and intestines. SCCHN develops in the mouth, nose and throat. Recurrent or metastatic SCCHN typically exhibits poor patient outcomes, for which more effective therapies are required.

Durvalumab is given by infusion into the vein. Durvalumab works by blocking an immune protein called programmed cell death ligand-1 (PD-L1). Normally, the immune system recognises and kills cancer cells. However, cancer cells can develop PD-L1 on their surface, allowing the cancer cells to avoid recognition by the immune system. By blocking PD-L1, durvalumab allows the immune system to recognise and target the cancer cells in SCCHN. Using durvalumab may improve outcomes in patients with recurrent or metastatic SCCHN who currently have few effective therapies available.

PROPOSED INDICATION

First-line treatment of adults with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).[1]

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi; MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with programmed cell death protein 1 (PD-1) and CD80 (B7.1).[1,2] Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.[2]

Durvalumab is currently in clinical development for the treatment of recurrent or metastatic SCCHN. In the phase III clinical trial (NCT02551159; KESTREL), patients in the monotherapy arm will receive durvalumab (1500mg) administered as an intravenous infusion every 4 weeks until disease progression.[1,3]

INNOVATION AND/OR ADVANTAGES

Patients with recurrent or metastatic SCCHN are currently considered incurable.[4] Even with the established standard EXTREME regimen for cancers that started in the oral cavity, consisting of cetuximab, a platinum, and 5-fluorouracil, the expected survival is only 10 months with progression expected within 6 months.[5] Hence, there is still a need for more efficacious therapies. Furthermore, delivery of the EXTREME regimen can be challenging in a population of patients who are older and have multiple comorbidities. Therefore, a regimen that is more efficacious and better tolerated would be of value.[a]

SCCHN tumours are thought to inhibit immune activity by different mechanisms, including T-cell suppression and downregulation of molecules that promote antigen processing and T-cell recognition. PD-1 receptor is a key immune checkpoint receptor on activated T cells.[6] PD-1 and its ligand PD-L1 are frequently upregulated in SCCHN.[7] Durvalumab monotherapy has demonstrated a manageable tolerability profile and encouraging antitumor activity across multiple tumour types, including NSCLC and SCCHN.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab is currently licenced in the EU/UK as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[2]

[a] Information provided by AstraZeneca UK Ltd

Very common (≥10%) adverse events associated with durvalumab include: upper respiratory tract infections, pneumonia, hypothyroidism, cough/productive cough, pneumonitis, diarrhoea, abdominal pain, rash, pruritus and pyrexia.[2]

Durvalumab is in phase II and phase III clinical development as a monotherapy or combination treatment for several oncology indications such as rectal cancer, pancreatic cancer, oesophageal cancer, etc.[9]

PATIENT GROUP

DISEASE BACKGROUND

Squamous cell carcinoma of the head and neck SCCHN 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. SCCHN typically develops in the mucous membranes of the mouth, nose and throat.[10] Head and neck cancer is a general term that covers many different types of cancer, including the oral cavity, pharynx (throat – includes nasopharynx, oropharynx and hypopharynx), larynx (voice box).[11]

SCCHN 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 SCCHN. HPV infection accounts for the increasing incidence of SCCHN in younger people.[10] However, in developed countries, more than half of new SCCHN cases are diagnosed in people aged 65 years or older.[12]

Researchers have identified mutations in many genes in people with SCCHN, 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 SCCHN, 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 SCCHN.[10]

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.[13]

In addition to the life threatening nature of SCCHN, 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.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017, there were a total of 7,587 registrations of malignant neoplasm of the lip, oral cavity and pharynx (ICD-10 codes C00-C14). This equates to a directly age-standardised rate of 20.1 cases per 100,000 males and 9.3 cases per 100,000 females. Overall, malignant

neoplasm of the lip, oral cavity or pharynx accounted for roughly 2.5% of cancer registrations for that year.[15]

Statistics from Cancer Research UK report that in 2016, head and neck cancer was the 8th most common cancer in the UK. Head and neck cancer disproportionately affects men, where it is the 4th most common cancer, whilst in females, it is the 13th most common. The majority of head and neck cancers occurs in the larynx. Incidence rates in the UK for head and neck cancer are highest in people aged 70-74 (2014-2016) and in England, it more commonly affects people living in deprived areas. Over the last decade, incidence rates in the UK have increased by more than a fifth (22%).[16]

In England in 2018-19, there were 28,486 finished consultant episodes, and 25,557 admissions with a primary diagnosis of malignant neoplasm of the lip, oral cavity or pharynx (ICD-10 codes C00-C14), resulting in 14,515 day cases and 77,853 bed days.[17]

In the UK, there are around 4,000 deaths from head and neck cancer every year (2015-2017). Mortality rates for head and neck cancer in the UK are highest in people aged 90 or over (2015-2017).[16] Head and neck cancer European age-standardised mortality rates for females and males combined decreased by 9% in the UK between 1971-1973 and 2015-2017.[18]

Over 80% (83.9%) of people diagnosed with cancer of the larynx in England survive their disease for 1 year or more (2013-2017) and over half (63.9%) survive their disease for 5 years or more (2013-2017).[19] Survival varies by head and neck cancer subtype in England and is highest in salivary glands cancer and lowest in hypopharyngeal cancer (one-, five- and ten-year survival, 2009-2013). Head and neck cancers survival in England is generally higher for people diagnosed aged 15-49 compared with other age groups, though the association with age varies by subtype.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatment is to maximise locoregional control and survival with minimal resulting functional damage. Cancers of the head and neck are managed by specialists as part of a multidisciplinary team. The team should include:[21]

- A radiologist
- A pathologist
- Specialist head and neck cancer surgeons (i.e. ear nose and throat; maxillofacial)
- A clinical oncologist
- A restorative dentist
- A clinical nurse specialist
- A speech and language therapist
- A dietician

Treatment options for SCCHN vary according to the specific sites involved. In some people with recurrent disease, the tumour is treated with surgery or radiotherapy with curative intent. In people with metastatic disease or who have previously received radiotherapy, palliative chemotherapy is normally given to control the disease and improve quality of life. Platinum-based chemotherapy is commonly used for recurrent or metastatic head and neck cancer.[22]

CURRENT TREATMENT OPTIONS

Cetuximab in combination with platinum-based chemotherapy is recommended as an option for treating recurrent or metastatic SCCHN in adults only:[23]

- If the cancer started in the oral cavity.
- When the company provides the drug in line with the commercial access agreement with NHS England.

PLACE OF TECHNOLOGY

If licensed, durvalumab will offer an additional first-line treatment option for patients with recurrent or metastatic SCCHN, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**KESTREL, NCT02551159, D419LC00001; aged between 18 to 130 years; durvalumab vs SOC; Phase III.**
Sponsor	AstraZeneca.
Status	Ongoing.
Source of Information	Abstract[3], trial registry[1].
Location	EU (incl. UK), USA, Canada and other countries.
Design	Randomised, open-label.
Participants	N = 823; aged 18 to 130 yrs; Documented evidence of recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, or larynx); No prior systemic chemotherapy for recurrent or metastatic disease; A fresh tumour biopsy for the purpose of screening or an available archival tumour sample; World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrolment; No prior exposure to immune-mediated therapy.
Schedule	Participants randomised (2:1:1) to either flat doses of tremelimumab 75 mg every 4 wks (max 4 doses) + durvalumab 1500 mg every 4 wks; durvalumab 1500 mg every 4 wks; or standard of care (SoC) EXTREME regimen (carboplatin or cisplatin + 5FU + cetuximab), all until disease progression.
Follow-up	12 months.
Primary Outcomes	Overall Survival (OS) [Time Frame: 2 yrs]

Secondary Outcomes	• Duration of Response (DoR)* • Time to First Subsequent Therapy (TFST)* • Time to Second Subsequent Therapy (TSST)* • Best Objective Response (BoR)* • Proportion of patients Alive and Progression Free at 6 and 12 Months (APF6, APF12)* • Progression Free Survival (PFS) and Second Progression (PFS2)* • Overall Survival (OS) and Overall Survival at 12, 18 and 24 months (OS12, OS18, OS24)* • Objective Response Rate (ORR)* • Pharmacokinetics (PK) analysis of durvalumab and tremelimumab using Area Under the Curve (AUC)** • Immunogenicity of durvalumab and tremelimumab* • Health-related quality of life (HRQoL)* • PK analysis of durvalumab and tremelimumab using Maximum Plasma Concentration (Cmax)** *[Time Frame: 2 years] **[Time Frame: up to 6 months]
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Primary completion date was September 2019.

ESTIMATED COST

Durvalumab is already marketed in the UK for the treatment of non-small-cell lung cancer; a 120mg/2.4ml concentrate for solution for infusion vial costs £592 and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.[24]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal in development. Nivolumab with ipilimumab for untreated recurrent or metastatic squamous cell cancer of the head and neck cancer (ID1429). TBC.
- NICE Technology Appraisal in development. Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck (ID1140). 12 February 2020.
- NICE Technology Appraisal. Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473). 31 August 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/13 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a

OTHER GUIDANCE

- Spanish Society of Medical Oncology (SEOM). SEOM clinical guidelines for the treatment of head and neck cancer (2017). 2018.[25]
- The Journal of Laryngology and Otology. Head and Neck Cancer: United Kingdom Multidisciplinary Guidelines. 2016.[26]
- European Society for Medical Oncology (ESMO). Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2010.[27]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 90. Diagnosis and Management of Head and Neck Cancer. 2006.[21]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Phase III Open Label Study of MEDI 4736 With/Without Tremelimumab Versus Standard of Care (SOC) in Recurrent/Metastatic Head and Neck Cancer (KESTREL). Trial ID: NCT02551159*. 2015. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02551159 [Accessed 23 October 2019].

2 electronic Medicines Compendium (eMC). *Imfinzi 50 mg/mL concentrate for solution for infusion.* 2019. Available from: https://www.medicines.org.uk/emc/product/9495#PHARMACOLOGICAL_PROPS [Accessed 23 October 2019].

3 Seiwert TY, Weiss J, Baxi SS, Ahn M, Fayette J, Gillison ML, et al. A phase 3, randomized, open-label study of first-line durvalumab (MEDI4736) ± tremelimumab versus standard of care (SoC; EXTREME regimen) in recurrent/metastatic (R/M) SCCHN: KESTREL. *Journal of Clinical Oncology*. 2017;34:no. 15_suppl. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS6101.

4 Bauml JM, Aggarwal C, Cohen RB. Immunotherapy for head and neck cancer: where are we now and where are we going? *Annals of Translational Medicine*. 2019;7(Suppl 3):S75. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685871/.

5 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. *The New England Journal of Medicine,*. 2008;359:1116-27. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa0802656.

6 Segal NH, Ou SI, Balmanoukian A, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a phase I/II expansion cohort. *European Journal of Cancer*. 2019;109:154-61. Available from: https://www.sciencedirect.com/science/article/pii/S0959804919300073?via%3Dihub.

7 Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: Results from a single-arm, phase II study in patients with ⩾25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. *European Journal of Cancer*. 2019;107:142-52. Available from: https://doi.org/10.1016/j.ejca.2018.11.015.

8 Rebelatto MC, Midha A, Mistry A, Sabalos C, Schechter N, Li X, et al. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. *Diagnostic Pathology*. 2016;11(95):1-14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5055695/.

9 ClinicalTrials.gov. *Durvalumab | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3*. 2019. Available from: https://clinicaltrials.gov/ct2/results?term=Durvalumab&flds=abcy&recrs=b&recrs=a&recrs=f&r

ecrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 30 October 2019].
10 Genetics Home Reference. *Head and neck squamous cell carcinoma*. 2019. Available from: https://ghr.nlm.nih.gov/condition/head-and-neck-squamous-cell-carcinoma [Accessed 30 October 2019].
11 Macmillan Cancer Support. *Types of head and neck cancer*. 2018. Available from: https://www.macmillan.org.uk/information-and-support/head-and-neck-cancers/understanding-cancer/types-head-neck-cancer.html#2936 [Accessed 30 October 2019].
12 Szturz P, Vermorken JB. Treatment of Elderly Patients with Squamous Cell Carcinoma of the Head and Neck. *Frontiers in Oncology*. 2016;6:199. Available from: https://doi.org/10.3389/fonc.2016.00199.
13 National Cancer Institute. *Head and Neck Cancers*. 2017. Available from: https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet [Accessed 30 October 2019].
14 Melo Filho M, Rocha B, Oliveira Pires M, Fonseca E, Freitas E, Martelli H, et al. Quality of life of patients with head and neck cancer. *Brazilian Journal of Otorhinolaryngology*. 2013;79(1):82-8. Available from: https://doi.org/10.5935/1808-8694.20130014.
15 Office for National Statistics. *Cancer Registration Statistics, England, 2017*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 25 October 2019].
16 Cancer Research UK. *Head and Neck Cancers Mortality* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-One [Accessed 31 October 2019].
17 NHS. *Hospital Admitted Patient Care Activity: Diagnosis, 2018-19*. 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 25 October 2019].
18 Cancer Research UK. *Head and neck cancers mortality statistics*. 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/mortality#heading-Two [Accessed 31 October 2019].
19 Office for National Statistics. *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 25 October 2019].
20 Cancer Research UK. *Head and Neck Cancers Survival* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-Two [Accessed
21 Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of Head and Neck Cancer (90)*. Last Update Date: Available from: https://www.uhb.nhs.uk/Downloads/pdf/CancerPbDiagnosisHeadAndNeckCancer.pdf [Accessed 31 October 2019].
22 National Institute for Health and Care Excellence (NICE). *Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck (Final Scope) (ID1140)*. Last Update Date: Available from: hhttps://www.nice.org.uk/guidance/gid-ta10181/documents/final-scope [Accessed 31 October 2019].
23 National Institute for Health and Care Excellence (NICE). *Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473)*. Last Update Date: 31 August 2017. Available from: https://www.nice.org.uk/guidance/ta473/chapter/1-Recommendations [Accessed 31 October 2019].
24 National Institute for Health and Care Excellence (NICE). *DURVALUMAB: Medicinal Forms*. 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 29 November 2019].
25 Spanish Society of Medical Oncology (SEOM). SEOM clinical guidelines for the treatment of head and neck cancer (2017). *Clinical and Translational Oncology*. 2018;20(1):75–83. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785598/.
26 Paleri V, Roland N. Head and Neck Cancer: United Kingdom National Multidisciplinary Guideline. *The Journal of Laryngology and Otology*. 2016;130(Suppl. S2):S3-S4. Available from:

https://www.cambridge.org/core/services/aop-file-manager/file/57fbbd73983d5b2b18ef2ac9/JLO-Head-and-Neck-Single-File.pdf.

27 European Society for Medical Oncology (ESMO). Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*,. 2010;21(suppl_5):v184–v6. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS6101.

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