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Nivolumab in combination with Ipilimumab for recurrent or metastatic head and neck cancer – first line

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LAY SUMMARY

Head and neck cancer is the eighth most common cancer in the United Kingdom. It refers to many different cancers which affect the head and neck, such as mouth and throat cancer. These cancers usually develop in the squamous cells which line the moist tissues in the head and neck, and are often curable if diagnosed at an early stage. The biggest risk factors include smoking tobacco and drinking alcohol. Symptoms may include sore throat, difficulty swallowing, pain in the ear and others. Treatment options for cancer that has spread or reoccurs after initial treatment usually involve chemotherapy or radiotherapy and focus on relieving symptoms and prolonging life rather than curing the cancer.

Nivolumab is a drug that works by improving the activity of T-cells (a type of white blood cells) and thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab is another drug that works in a different way to also increase the activity of T-cells. Both drugs are given by injection into the veins. It is thought these drugs when used together may be more effective than each drug on its own. If licenced, nivolumab in combination with ipilimumab will offer additional treatment option to prolong the lives of people with head and neck cancers.

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TARGET GROUP

Head and neck cancer (recurrent or metastatic, platinum-eligible) – first line

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo, BMS-936558, ONO-4538, MDX-1106) is a human IgG4 monoclonal antibody which binds to the programmed death-1 (PD-1) receptor, blocking its interaction with PD Ligand-1 (PDL-1) and PDL-2. PDL-1 and PDL-2 are sometimes expressed by tumour cells resulting in the inhibition of T-cell proliferation and cytokine secretion. Therefore blocking PD-1 receptor potentiates the T-cell response, including anti-tumour responses, leading to decrease tumour growth.[1]

Ipilimumab (Yervoy, Winglore, BMS-734016, MDX-010, MDX-101, MDX-CTLA-4 and monoclonal antibody CTLA-4) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor which blocks T-cell inhibitory signals (produced by the CTLA-4 pathway) and increases the number of reactive T-effector cells which then directly attack tumour cells. Ipilimumab can also block T-regulatory cell function which may contribute to the anti-tumour immune response.[2]

In the ongoing phase III clinical trial (CheckMate 651 - NCT02741570) for nivolumab and ipilimumab combination in patients with metastatic or recurrent head and neck cancer, nivolumab was administered by intravenous infusion at a dose of 10mg/ml and ipilimumab was administered by IV infusion at a dose of 5 mg/ml on specified days until disease progression or unacceptable toxicity.[3]

Nivolumab + Ipilimumab in combination is licenced in the EU for the treatment of advanced (unresectable or metastatic) melanoma in adults.[4]

Very common (≥ 1/10) adverse effects reported for nivolumab and ipilimumab combination include; hypothyroidism, decreased appetite, headache, dyspnoea, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue, pyrexia, increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemiac, hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia.[1]

Nivolumab + Ipilimumab combination is currently in phase III trials in the EU for the treatment of:[5]

- Non-small cell lung cancer
- Gastric cancer
- Small-cell lung cancer (second line)
- Malignant pleural mesothelioma (first line)
- Esophageal cancer
- Metastatic transitional (urothelial) tract cancer
- Metastatic renal cell carcinoma

INNOVATION and/or ADVANTAGES

If licensed, nivolumab in combination with ipilimumab will offer an additional treatment option for patients with metastatic or recurrent head and neck cancer who are eligible for platinum-based

chemotherapy (cisplatin or carboplatin). This combination of drugs has been previously found to improve anti-tumour responses in metastatic melanoma patients.[1]

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

PATIENT GROUP

BACKGROUND

Head and neck cancer is a collective term for many types of cancer which usually originate from the squamous cells which line the mucosal surfaces (although cancer can also occur in different cell types within the salivary glands). Head and neck cancer is further subcategorized according to the area in which it starts and includes: oral cancer (including lips, two thirds of the tongue, gums, cheek lining, mouth floor, hard palate and behind the wisdom teeth), pharynx (including nasopharyngeal, occurring within the upper pharynx behind the nose, oropharyngeal, occurring in the middle of the pharynx including the soft plate at the back of the mouth, and hypopharyngeal, occurring in the lower pharynx), larynx, paranasal sinuses and nasal cavity, salivary glands.[6]

It is estimated that 75% of head and neck cancers are caused by alcohol and tobacco use and people who use both tobacco and alcohol have a higher risk of developing head and neck cancers than those who use either alone. Infection with human papillomavirus (HPV), particularly type 16, is a risk factor for developing head and neck cancers, especially oropharyngeal cancers. Other potential risk factors for different head and neck cancers include use of paan (a type of chewing tobacco), consumption of preserved/salted food, poor oral hygiene, occupational exposure to certain chemicals/pollutants, radiation exposure, Epstein Barr virus infection and Asian ethnicity. [6] Symptoms of head and neck cancer depend on the cancer type and include:[7]

- Mouth cancer: persistent mouth ulcers, lumps in the mouth
- Laryngeal cancer: change in voice, pain when swallowing, noisy breathing, shortness of breath, persistent cough and lump/swelling in the neck
- Oropharyngeal /hypopharyngeal cancer: persistent sore throat and difficulty swallowing
- Salivary gland cancer: lump/swelling on/near the jaw, mouth or neck, facial numbness and drooping on one side of the face
- Paranasal and sinus cancer: persistent blocked nose (usually one side), nosebleeds, decreased sense of smell and mucus running from nose or down the throat
- Nasopharyngeal cancer: lumps in the neck, blocked nose, nosebleeds and hearing loss (usually one ear)

If diagnosed early, cancers of the head and neck are often preventable or curable. However, patients often present with advanced disease that is incurable or requires aggressive treatment.[6] In most patients, platinum based chemotherapy is used and has demonstrated survival advantages. However, treatment options are limited once platinum based therapy has failed.[8]

CLINICAL NEED and BURDEN OF DISEASE

Head and neck cancer is the eighth most common cancer in the UK accounting for 3% of total new cancer cases. In the UK in 2014 there were 11,449 new cases of head and neck cancer; 7,918 (69%) in

males and 3,531 (31%) in females. The age standardised incidence rates for head and neck cancer in England in 2014 was 18.5 per 100,000.[9]

The incidence and prevalence of head and neck cancers depend on the specific subtype of cancer, as follows:

- Mouth cancer: Squamous cell carcinoma accounts for 90% of mouth cancer cases. Approximately 6,800 people are diagnosed with mouth cancer per year in the UK (accounting for about 2% of all cancers diagnosed).[10] Mouth cancer affects approximately 1 in 75 men and 1 in 150 women in their lifetime and mainly affects older people with 40% mouth cancers diagnosed in those over 65 years old.[11]
- Laryngeal cancer: Approximately 2,400 new cases of laryngeal cancer are diagnosed in the UK per year.[12] 1 in 175 men and 1 in 800 women will be diagnosed with laryngeal cancer in their lifetime.[13]
- Salivary gland cancer: Salivary gland cancer is very rare, affecting 720 people in the UK per year. [14]
- Paranasal and sinus cancer: In the UK approximately 400 cases of paranasal and sinus cancer are diagnosed per year.[15]
- Nasopharyngeal cancer: This is a rare cancer with approximately 240 people per year diagnosed in the UK. Men are about 3 times more likely to be affected by nasopharyngeal cancer than women.[16]

Survival rates for head and neck cancer vary according to the cancer subtype with survival highest in salivary glands cancer and lowest in hypopharyngeal cancer. The age standardised survival rates for adults with head and neck cancer subtypes in the UK during 2009-2013 are as follows:[17]

- Hypopharyngeal cancer: 1 year survival rate – 60.5%, 5 year survival rate – 27.8%, 10 year survival rate – 19.1%.
- Laryngeal cancer (men only – data for women is unavailable due to the low number of cases): 1 year survival rate – 85.3%, 5 year survival rate – 65.4%, 10 year survival rate – 54.7%.
- Oral cavity cancer: 1 year survival rate – 78.4%, 5 year survival rate – 56.1%, 10 year survival rate – 45.2%.
- Oropharyngeal cancer: 1 year survival rate – 83.7%, 5 year survival rate – 65.6%, 10 year survival rate – 57.7%.
- Salivary glands cancer: 1 year survival rate – 85.8%, 5 year survival rate – 67.0%, 10 year survival rate – 59.3%.
- Sinus Cancer: 1 year survival rate – 74.8%, 5 year survival rate – 51.4%, 10 year survival rate – 42.6%.
- Tongue Cancer: 1 year survival rate – 80.6%, 5 year survival rate – 60.3%, 10 year survival rate – 5.2%.

In 2016-2017 in England there were:[18]

- 11,014 admissions and 12,480 finished consultant episodes for malignant neoplasm of the lip, base of tongue, other/unspecified parts of the tongue, gum, floor of moth, palate and other unspecified parts of the mouth (ICD 10 C00-06).
- 1,360 admissions and 1,498 finished consultant episodes for malignant neoplasm of the parotid gland and other and unspecified major salivary glands (ICD 10 C07-08).
- 4,180 admissions and 4,680 finished consultant episodes for malignant neoplasm of the oropharynx, nasopharynx and hypopharynx (ICD 10 C10, C11 and C13).

- 910 admissions and 1,030 finished consultant episodes for malignant neoplasm of the oropharynx, nasopharynx and hypopharynx (ICD 10 C12).
- 865 admissions and 899 finished consultant episodes for malignant neoplasm of the other and ill-defined sites in the lip, oral cavity and pharynx (ICD 10 C14).
- 452 admissions and 483 finished consultant episodes for malignant neoplasm of other and ill-defined sites: head, face and neck (ICD 10 C76.0).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Head and neck cancer – contusugene ladenovec (ID76). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy (ID1066). Expected October 2018.
- NICE technology appraisal guidance. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA490). November 2017.
- NICE technology appraisal guidance. Cetuximab for treating recurrent of metastatic squamous cell cancer of the head and neck (TA473). June 2008.
- NICE quality standard. Head and neck cancer (QS146). March 2017.
- NICE Cancer service guideline. Improving outcomes in head and neck cancers (CSG6). November 2004.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Cancer Drugs Fund List. V1.31. 15 June 2017.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

Paleri V, Roland N. Head and Neck Cancer – United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Ontology, Vol 130 (S2), 2016

CURRENT TREATMENT OPTIONS

Both surgery and radiotherapy are used for the treatment of head and neck cancer; in general, function is better after radiotherapy than surgery, but treatment time for surgery is shorter. Inoperable disease may be treated with combinations of chemotherapy and radiotherapy. In advanced stages outcomes are usually poor, and focus is put on treating the symptoms of a patient rather than curing the disease.[19] Drugs approved by the US FDA for the treatment of head and neck cancer are:[20]

- Bleomycin

- Cetuximab (also approved by EMA for this indication)[21]
- Docetaxel (also approved by EMA for this indication)[22]
- Hydroxyurea
- Pembrolizumab
- Methotrexate

It is suggested that fit patients who are symptomatic from their recurrent or metastatic disease should be considered for platinum-based, multi-agent regimes that combine cytotoxic chemotherapy with cetuximab. Single agent chemotherapy regimens are appropriate for many asymptomatic patients with a low burden of disease. Platinum-resistant patients should be treated with cetuximab-based regimen, either alone or in combination with paclitaxel. Targeted therapy may include epidermal growth factor receptor (EGFR) inhibitor therapies. EGFR is commonly expressed in squamous cell head and neck cancer and overexpression is associated with poorer prognosis. Cetuximab is a monoclonal antibody to the EGFR to be routinely used in targeted therapy. Palliative radiation therapy is used to relief symptoms of patients with recurrent disease. Supportive care, such as pain specialists, is recommended.[23]

EFFICACY and SAFETY

Trial	**CheckMate 651, NCT02741570, CA209-651, 2016-000725-39, EudraCT-2016-000725-39, NCI-2016-01450, CDR783978, JapicCTI-163389; Nivolumab + Ipilimumab vs. standard chemotherapy regime (cetuximab, cisplatin, carboplatin + fluorouracil); phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing - recruiting
Source of Information	Publication[24], trial registry[3],
Location	10 EU countries (incl UK), USA, Australia, Brazil, Israel, Japan, Republic of Korea, Mexico and Taiwan
Design	Randomised, active-controlled, parallel assignment
Participants	n=700 (planned); aged 18 years and older; squamous cell carcinoma of the head and neck; metastatic or recurrent; no prior systemic cancer therapy for recurrent or metastatic disease
Schedule	Randomised to one of two treatment arms: 1. Experimental arm: participants receive 3mg/kg nivolumab every 2 weeks and 1mg/kg ipilimumab every 6 weeks on specified days. 2. Active control: EXTREME regime – participants receive Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100 mg/m2) or carboplatin (AUC of 5 mg per millilitre per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information). Treatment continues until disease progression, withdrawal of informed consent or unacceptable toxicity.
Follow-up	Follow-up from start of randomisation to final analysis of OS is expected to be approximately 39 months, assuming 20 months accrual duration.
Primary Outcomes	Overall survival (OS), Progression Free Survival (PFS)

Secondary Outcomes	Objective Response Rate (ORR), Duration of Response (DOR), PD-L1 expression as a predictive biomarker for ORR, PFS and OS.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date is reported as 17 Jan 2019 and study completion date is reported as 05 March 2020.

Trial	**CheckMate 714, NCT02823574, 2016-001645-64, EudraCT-2016-001645-64, CA209-714, NCI-2016-01106, CDR782510; Nivolumab + Ipilimumab vs. Nivolumab + placebo; phase II**
Sponsor	Bristol-Myers Squibb
Status	Ongoing - recruiting
Source of Information	publication[25], trial registry[26]
Location	11 EU countries (incl UK), USA, Canada, Argentina, Brazil, Mexico, Russian Federation, South Africa and Turkey
Design	Randomised, placebo-controlled, double blind, parallel assignment
Participants	n=400 (planned) (n=216 platinum refractory and approximately n=180 platinum eligible); aged 18 years and older; squamous cell head and neck cancer; metastatic or recurrent disease; platinum refractory (defined as histologically confirmed SCCHN that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting) or platinum eligible (defined as subjects with histologically confirmed SCCHN who are platinum naive, or have recurred 6 months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting).
Schedule	Participants are randomised to one of two treatment arms 1. Experimental arm: participants receive 3mg/kg nivolumab every 2 weeks and 1mg/kg ipilimumab every 6 weeks on specified days. 2. Placebo arm: participants receive 3mg/kg nivolumab and an ipilimumab placebo on specified days. Active treatment continues until disease progression, withdrawal of informed consent or unacceptable toxicity.
Follow-up	The analysis of ORR for each of the platinum eligible and platinum refractory subgroups will be conducted after the sufficient number of randomized subjects in the subgroup have been followed for at least 6 months.
Primary Outcomes	Overall response rate (ORR) in platinum refractory subgroup (defined as recurrence of head and neck cancer <6 months after completion of previous platinum based chemotherapy and no prior therapy for recurrent/metastatic disease), Duration of response (DOR) in platinum refractory group.
Secondary Outcomes	ORR in platinum eligible group (defined as recurrence of head and neck cancer >6 months after completion of previous platinum based chemotherapy and no prior therapy for recurrent/metastatic disease), DOR in the platinum eligible

	group, PFS and OS in platinum eligible and platinum refractory subgroups (separately and overall), PD-L1 expression as a predictive biomarker for ORR, DOR, PFS and OS in platinum eligible and platinum refractory subgroups (separately and overall), HPV p-16 expression as a predictive biomarker for ORR, DOR, PFS and OS in platinum eligible and platinum refractory subgroups (separately and overall).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study primary completion date is reported as 30 May 2018 and estimated study completion date is reported as 17 October 2020.

ESTIMATED COST and IMPACT

COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg vial (10mg/mL) costs £1097 (hospital only) and a 40mg vial (10mg/ml) costs £439 (hospital only).[27]

Ipilimumab (Yervoy) is already marketed in the UK; a 200mg vial (5mg/mL) costs £15,000 (hospital only) and a 50mg vial (5mg/ml) costs £3750 (hospital only).[28]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services: additional drug required for IV administration in hospital setting

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs	☐ Reduced drug treatment costs
☒ Other increase in costs: additional costs for IV administration in clinic	☐ Other reduction in costs
☐ Other	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

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