

**NIHR Innovation Observatory
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Cemiplimab for advanced cutaneous squamous cell carcinoma – first line

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LAY SUMMARY

Cutaneous Squamous Cell Carcinoma (cSCC) is a skin cancer involving specific cells in the outer layers of the skin. It occurs mostly around the head and neck region and is related to excessive exposure to sunlight. It is the second most common skin cancer in the UK. Certain factors are thought to increase the chances of developing all types of skin cancer which include being fair skinned, history of sunburn, exposure to artificial UV light, certain skin conditions, certain treatment options for benign skin conditions, old age, a weakened immune system and exposure to certain chemicals.

Cemiplimab is an intravenous drug under development for advanced cSCC. It acts on specific proteins on immune cells, allowing the defence system of the body to inhibit the growth of the cancer cells. For patients who develop advanced cSCC, there are limited treatment options available. If licensed, cemiplimab may offer a new licenced treatment option for patients with advanced cSCC.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Cutaneous squamous cell carcinoma (cSCC) (Locally advanced unresectable and metastatic) – first line therapy

TECHNOLOGY

DESCRIPTION

Cemiplimab (REGN2810, SAR439684) is a fully human monoclonal antibody which inhibits Programmed Death-1 (PD-1),¹ acting as an immunostimulant.² PD-1 is expressed on the surface of activated T-cells and binds to ligands on the surface of antigen-presenting cells (PD-L1 and PD-L2). PD-L1 controls T-cells through PD-1 pathway and causes T-cells to switch off, making them unable to enter the tumour micro environment leading to tumour growth. The drug candidate, by inhibiting PD-1, blocks the interaction between PD-1 receptor and PD-L1 which enhances the T-cells ability to lyse the tumour cells.³ Therapies with antibodies targeting PD-1 and its ligands are shown to be associated with remarkable response rates in various cancers and have revolutionized cancer treatment.⁴

In the phase II clinical trial (NCT02760498), cemiplimab is administered through the intravenous route to patients with metastatic (nodal or distant) or unresectable locally advanced cutaneous squamous cell carcinoma in a dose of 3 mg/kg every 14 days or alternatively patients with metastatic (nodal & distant) squamous cell carcinoma receive cemiplimab in a dose of 350 mg every 21 days.

Cemiplimab is also at phase II and/or phase III development for the following indications: ³

- basal cell carcinoma
- non-small cell lung cancer
- cervical cancer
- solid tumours (in combination with other investigational agents)

Cemiplimab in combination with isatuximab is in phase I/II for relapsed or refractory multiple myeloma.

Cemiplimab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

For patients who develop unresectable locally advanced or metastatic cSCC, treatment options are limited. Currently there are no licenced treatments available for this population. Although there have been single-arm studies of several systemic treatments, none of these studies clearly demonstrate a therapeutic advantage.^{5,6} Given there is a dearth of data to guide clinical decision making, there is a significant unmet medical need for treatments for patients who develop unresectable locally advanced or metastatic disease.

If licensed, cemiplimab will offer a new licenced treatment option for patients with advanced cutaneous squamous cell carcinoma.

DEVELOPER

Regeneron Pharmaceuticals Inc. and Sanofi

AVAILABILITY, LAUNCH or MARKETING

Cemiplimab was designated Breakthrough Therapy for advanced cutaneous squamous cell carcinoma by the US FDA in September 2017.⁷

PATIENT GROUP

BACKGROUND

Cutaneous cancers are skin cancers generally divided into two types, melanoma and non-melanoma. The term non-melanoma distinguishes the more common types of skin cancer from the less common skin cancer known as melanoma, which can be more serious. In the UK, more than 100,000 new cases of non-melanoma skin cancer (NMSC) are diagnosed each year. It affects more men than women and is more common in the elderly.⁸

There are two types of NMSC: basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

cSCC is the second most common skin malignancy (after BCC) and represents around 23% of NMSCs. It is a cancer of the cells producing keratin; a waxy substance that helps to form the protective outer layer of the epidermis.⁸ It occurs mostly around the head and neck region and is related to excessive exposure to sunlight.⁹

Clinically, cSCC presents as a shallow ulcer with elevated margins, often covered by a plaque and usually located in a sun-exposed area. Typical surface changes may include scaling, deep ulceration, crusting, and cutaneous horn. A less common presentation of cSCC includes a pink cutaneous nodule without overlying surface changes. Regional metastasis of head and neck cSCC may result in enlarged and palpable submandibular or cervical lymph nodes. If cSCC invades the adjacent peripheral nerve, it causes numbness, pain, and muscle weakness. These may be some of the clinical signs of invasion other than palpable lymph nodes.¹⁰

In most cases, NMSC does not run in families. However, research has shown that some families have a higher than average number of members who develop the condition.¹¹ Certain other factors are thought to increase the chances of developing all types of skin cancer which include being fair skinned, history of sunburn, exposure to artificial UV light, skin conditions such as solar keratosis, xeroderma pigmentosum, certain treatment options for psoriasis and eczema, old age, a weakened immune system and exposure to certain chemicals.¹²

Most cSCCs are diagnosed at an early stage and can be successfully treated with surgery. Unfortunately, a minority of cSCC cases may recur or metastasise. The rate of metastasis in cSCC has been estimated to be 2-5%. These patients have a poor prognosis with a median overall survival of less than 2 years.¹³

CLINICAL NEED and BURDEN OF DISEASE

The incidence of NMCS is underreported in the UK due to inconsistent data collection. The incidence is known to be rising and is estimated to do so until 2040.¹⁴ SCCs represents around 23% of NMSCs. The increase in incidence of SCCs from 2000-2002 to 2008-2010 is similar to BCCs: 34% in males and

39% in females. The incidence rate of NMCS is higher in males than females, and this gender difference is wider than for BCCs. Scotland, Northern Ireland and Ireland have noticeably higher rates of SCCs relative to the English cancer registries than for BCCs. This may reflect the higher proportion of fair-skinned people in Celtic countries, although it seems unusual this would not also affect the incidence of BCCs. The higher incidence in the Celtic countries may also be due to more complete recording of SCCs, and for Scotland their policy of recording all SCCs per person.¹⁵

The Hospital Episodes Statistics for England 2015/2016 recorded 127,838 finished consultant episodes (FCE), 127,180 hospital admissions and 22,964 FCE beds due to malignant neoplasms of the skin (ICD-10 code C44).¹⁶

In 2015, the National Institute for Health and Care Excellence (NICE) published guidelines to help GPs recognise the signs and symptoms of skin cancer and refer people for the right tests faster.¹⁷

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Skin Cancer (QS130). September 2016.
- NICE interventional procedures guidelines. Photodynamic therapy for non-melanoma skin tumours. (IPG155) February 2006
- NICE diagnostic guidance. VivaScope 1500 and 300 imaging systems for detecting skin cancer lesions (DG19). November 2015.
- NICE public health guidance. Skin cancer prevention (PH32). January 2011, Updated February 2016.
- NICE cancer service guidelines. Improving outcomes for people with skin tumours including melanoma. (CSG8). February 2006
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- NICE medical technologies guidance. Ambulight PDT for the treatment of non-melanoma skin cancer. (MTG6). July 2011

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/s/b
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
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- NHS Northern England. Strategic Clinical Networks: NECN Skin Cancer Clinical Guidelines. May 2016

OTHER GUIDANCE

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CURRENT TREATMENT OPTIONS

Surgery, radiotherapy and chemotherapy have been the main approaches for treating cancer in previous decades.¹⁹ Most patients with non-melanoma skin cancer (NMSC) are treated with:

- surgical removal²⁰
- radiotherapy²¹

Less common approaches are:

- curettage²²
- cryotherapy²²
- chemotherapy²²

The choice of treatment modality is determined by factors including age, tumour size and functional/cosmetic outcome. Surgery is preferred for younger patients and early stages of cSCC. Primary radiotherapy is often preferred for regions around the lower eyelids, nose and ear, where better functional/cosmetic results can be achieved.²¹ Other options such as photodynamic therapy is being considered. However, NICE has not found evidence as to how well this works.²³

For advanced cSCC there is no standard of care and no licenced treatment available. Available guidelines suggest chemotherapy and EGFR inhibitors may be used in this population.¹³

EFFICACY and SAFETY

Trial	NCT02760498; NCI-2016-00692; CDR781026; EudraCT-2016-000105-36. cemiplimab, phase II
Sponsor	Regeneron Pharmaceuticals Inc. and Sanofi
Status	Ongoing
Source of Information	Trial registry ¹ ; Global data ³
Location	EU (Not UK), USA, Australia
Design	Non-randomised, open label
Participants	n=129 (planned); aged 18 years and older; male and female; cutaneous squamous cell carcinoma; advanced
Schedule	Cemiplimab given intravenously at a dose of 3mg/kg for every 14 days in patients with metastatic (group 1) and unresectable locally advanced cSCC (group 2), and at a dose of 350mg for every 21 days in patients with metastatic (nodal and distant) (group 3)
Follow-up	Subjects enrolled in group 1 and 2 will be assessed for tumours at the end of each 8 week cycle in the 12 treatment cycles (96 weeks) (Group not mentioned)

Primary Outcomes	<ul style="list-style-type: none"> • Overall Response Rate - During the 12 treatment cycles (96 weeks) • Overall Response Rate as determined by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 for Group 1 and/or assessed per composite response criteria (Group 2)
Secondary Outcomes	<ul style="list-style-type: none"> • Duration of response - From date of treatment until date of first documented progression or date of death, assessed up to 30 months • PFS (progression-free survival) - From date of treatment until date of death, assessed up to 30 months • Overall Survival - From date of treatment until date of death, assessed up to 30 months • change in scores of subject reported outcomes on EORTC QLQ-C30 - From date of treatment until date of first documented progression or date of death, assessed up to 24 months • impact of cemiplimab on quality of life using EORTC QLQ-C30 • complete response (CR) rate by central review • safety and tolerability of cemiplimab • pharmacokinetics (PK) of cemiplimab (at select sites only) • immunogenicity of cemiplimab • Adverse events • cemiplimab concentrations in serum • Anti- cemiplimab antibodies
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as Q2 2019 ^a

ESTIMATED COST and IMPACT

COST

The cost of cemiplimab is not yet known.

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

Decreased use of existing services

^a Confidential Company Information

Re-organisation of existing services Need for new services

Other: None identified

IMPACT ON COSTS and OTHER RESOURCE USE

Increased drug treatment costs (potential increase depending on comparator) Reduced drug treatment costs

Other increase in costs: Other reduction in costs:

Other: None identified

OTHER ISSUES

Clinical uncertainty or other research question identified: The clinical evidence to support cemiplimab will come from a single arm Phase 2 registrational study. There will therefore be uncertainty regarding the comparative effectiveness of cemiplimab. Overall survival data is also likely to be immature at the point of HTA submission. None identified

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