

**NIHR Innovation Observatory
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NBTXR3 (PEP-503) for head and neck squamous cell carcinoma in elderly patients

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LAY SUMMARY

Squamous cell carcinoma is a cancer that arises from particular cells called squamous cells, a type of skin cell. They 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. Head and neck squamous cell cancer develops in the mucous tissues of the mouth, nose and throat. Head and neck squamous cell cancer accounted for three percent of all cancers in the United Kingdom in 2014.

NBTXR3 is under development for the treatment of head and neck squamous cell cancer and is currently in phase I/II clinical trials. If effective NBTXR3 will enhance current treatment options. As a first in class treatment designed to penetrate cancer cells and remain within the tumour, increasing the radiation dose in the tumour but not in the surrounding healthy tissue. NBTXR3 is administered as an intra-tumoural or intra-arterial injection.

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

Head and neck squamous cell carcinoma (HNSCC) in elderly patients - for intra-operative application for post-operative radiotherapy.

TECHNOLOGY DESCRIPTION

NBTXR3 (PEP-503) is a nano-sized radio-enhancer device intended for use in the treatment of head and neck cancer. It is designed to provide effective tumour destruction and disease control using hafnium oxide-containing nanoparticle (NBTXR3) in combination with radiotherapy, based on the NanoXray technology. It has the ability to enhance the effect of radiotherapy without increasing damage to the surrounding tissue and it accumulates in the cancer cells when it is injected. The NBTXR3 particles emit huge amounts of electrons upon radiation due to the physical properties of hafnium oxide allowing the formation of radicals within the tumour cell, which in turn damage the cancer cells and cause their targeted destruction.¹

In a phase I study, NanoXray NBTXR3 is administered as a single intra-tumoural injection followed by intensity modulated radiation therapy to participants in one treatment arm and as a single intra-arterial injection followed by intensity modulated radiation therapy in a second treatment arm.²

In a phase Ib study, PEP-503 is administered through intra-tumoural injection, activated by concurrent chemoradiotherapy using a dose escalation method to identify the recommended intra-tumoural injection volume. In the phase II study, the recommended intra-tumoural injection volume of PEP-503 identified from the phase Ib study is applied both to the primary tumour and to ≥ 3 cm lymph node lesions.³

NanoXray NBTXR3 is also in the phase I/II development stage for liver cancers (hepatocellular carcinoma and liver metastases), prostate cancer and rectal cancer.⁴

INNOVATION and/or ADVANTAGES

Radiotherapy is widely used in the treatment of most oncology indications. However, there are still significant limitations to radiotherapy in its efficacy and toxicity due to the damage it can cause to surrounding healthy tissues. As a result, many cancer patients receive a dose of radiotherapy that is insufficient for tumour destruction. If licensed, NBTXR3 may increase the effectiveness of radiotherapy.⁴

DEVELOPER

Nanobiotix and PharmaEngine Inc.

PATIENT GROUP

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.⁵ 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.⁵ However, in developed countries, more than half of new HNSCC cases are diagnosed in people aged 65 years or older.⁶ 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.⁵

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 in swallowing and a change or hoarseness in the voice. Symptoms that may affect specific areas of the head and neck include the following:⁷

Oral cavity. A white or red patch on the gums, the tongue, or the lining of the mouth; a swelling of the jaw that causes dentures to fit poorly or become uncomfortable; and unusual bleeding or pain in the mouth.

Pharynx. Trouble breathing or speaking; pain when swallowing; pain in the neck or the throat that does not go away; frequent headaches, pain, or ringing in the ears; or trouble hearing.

Larynx. Pain when swallowing or ear pain.

Paranasal sinuses and nasal cavity. Sinuses that are blocked and do not clear; chronic sinus infections that do not respond to treatment with antibiotics; bleeding through the nose; frequent headaches, swelling or other trouble with the eyes; pain in the upper teeth; or problems with dentures.

Salivary glands. Swelling under the chin or around the jawbone, numbness or paralysis of the muscles in the face, or pain in the face, the chin, or the neck that does not go away.

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.⁸

CLINICAL NEED and BURDEN OF DISEASE

The age-standardized incidence rate of HNSCC in England was 18.5 per 100,000 population 2014, accounting for 3% of total cancer cases during the same year.⁹ In 2015-16, there were 522 hospital admissions, 554 finished consultant episodes and 797 bed days due to malignant neoplasm of other and ill-defined sites: head, face and neck (C76.0) in England.¹⁰

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck. In development.
- NICE technology appraisal. Head and neck cancer (squamous cell carcinoma) - cetuximab - CDF rapid reconsideration process. In development.
- NICE technology appraisal. Head and neck cancer - intensity modulated radiotherapy. In development.
- NICE technology appraisal. Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck. (TA172). June 2009.
- NICE guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). February 2016.
- NICE cancer service guideline. Improving outcomes in head and neck cancers (CSG6). November 2004.
- NICE quality standard. Head and neck cancer (QS146). March 2017.

NHS ENGLAND and POLICY GUIDANCE

- 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: Skin (Adult). A12/S/b.

OTHER GUIDANCE

Perri F, Parcelli R, Della Vittoria Scarpati G, Cella L, Giuliano M, Caponigro F, Pepe S. Radioresistance in head and neck squamous cell carcinoma: Biological bases and therapeutic implications. *Head Neck*. 2015 May;37(5):763-70.

CURRENT TREATMENT OPTIONS

Individuals with head and neck cancers are usually treated in specialist centers by a team of healthcare professionals.¹¹ For most people, the aim of treatment is to remove or destroy all of the cancer and to reduce the chances of it coming back. The treatment offered is dependent upon where the cancer is located in head or neck, the stage of the cancer, its size and the patient's general health.¹¹

Recommendations for the management and treatment of early stage HNSCC in relation to specific cancer types and stages (T refers to size and extent of the primary tumour; N refers to the number of nearby lymph nodes that have cancer),^{12,a} are as follows:^{13,b}

Squamous cell carcinoma of the larynx

- Offer transoral laser microsurgery to people with newly-diagnosed T1a squamous cell carcinoma of the glottic larynx.
- Offer a choice of transoral laser microsurgery or radiotherapy to people with newly-diagnosed T1b–T2 squamous cell carcinoma of the glottic larynx.
- Offer a choice of transoral surgery or radiotherapy to people with newly-diagnosed T1–T2 squamous cell carcinoma of the supraglottic larynx.

Management of the N0 neck in T1–2 squamous cell carcinoma of the oral cavity

- Offer surgical management of the neck to all people with early oral cavity cancer (T1–T2, N0).
- Offer sentinel lymph node biopsy instead of elective neck dissection to people with early oral cavity cancer (T1–T2, N0), unless they need cervical access at the same time (for example, free-flap reconstruction).

Squamous cell carcinoma of the oropharynx (T1–2, N0)

- Offer people the choice of transoral surgical resection or primary radiotherapy for T1–2 N0 tumours of the oropharynx.
- Consider postoperative radiotherapy, with or without concomitant chemotherapy, for T1–2 N0 tumours of the oropharynx if pathologically adverse risk factors have been identified.

Recommendations for the management and treatment of early stage HNSCC in relation to specific cancer types and stages (T refers to size and extent of the primary tumour; N refers to the number of nearby lymph nodes that have cancer),^{12,a} are as follows:^{13, b}

Squamous cell carcinoma of the larynx

Offer people with T3 squamous cell carcinoma of the larynx a choice of:

- radiotherapy with concomitant chemotherapy, or
- surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.

Discuss the following with people with T3 squamous cell carcinoma of the larynx and their carers, to inform their choice of treatment:

- the potential advantages of laryngeal preservation
- the risk of needing salvage laryngectomy (and its associated complications)

^a Stages of head and neck cancer: T0: this means there is no primary tumour, but there may be abnormal cells that are precancerous. T1 to T4: this refers to the increasing size and/or extent of the primary tumour, with 1 being smallest and 4 largest. N0: no lymph nodes contain cancer cells. N1 and upwards: increasing involvement of lymph nodes by cancer cells.

^b Note: this is not an exhaustive list of treatment options for the various types of head and neck cancer.

- the benefits of primary surgery in people with existing compromised swallowing and airway function
- likely voice and swallowing function after treatment (including the need for a long-term feeding tube).

For people with T4a squamous cell carcinoma of the larynx consider surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.

Squamous cell carcinoma of the hypopharynx

Offer larynx-preserving treatment to people with locally-advanced squamous cell carcinoma of the hypopharynx if radiation and neo-adjuvant and/or concomitant chemotherapy would be suitable for them and they do not have:

- tumour-related dysphagia needing a feeding tube
- a compromised airway
- recurrent aspiration pneumonias.

Offer radiotherapy with neo-adjuvant and/or concomitant chemotherapy if larynx-preserving treatment is suitable for the person.

Offer primary surgery followed by adjuvant radiotherapy to people if chemotherapy is not a suitable treatment for them.

Offer adjuvant radiotherapy to people having surgery as their primary treatment. Add concomitant chemotherapy if appropriate.

Efficacy and SAFETY	
Trial	GDME2035063, NCT02901483, phase Ib/II
Sponsor	PharmaEngine Inc.
Status	Ongoing, recruiting
Source of Information	Trial registry ³
Location	Taiwan
Design	Non-randomised, uncontrolled, single group assignment study
Participants	n=42 (planned), aged 20 years and older; histologically or cytologically confirmed squamous cell carcinoma of the oral cavity; advanced or recurrent disease: T4b, n any, who are not candidates for surgical resection, or T3-4, n any, who decline surgery or medical inoperable; No evidence of distant metastatic disease, as determined by negative PET scan or CT scan. Note: this is not an exhaustive list of the inclusion criteria
Schedule	Subjects receive PEP-503 by intra-tumoural route as slow injection. The study consists of two phases: Escalation portion (phase Ib): there are four levels (5%, 10%, 15% and 22%). Only primary tumour receives PEP-503 implementation through intra-tumoural

	<p>injection. A 3 + 3 dose escalation study design is adopted in this phase to detect the recommended intra-tumoural injection volumes of PEP-503.</p> <p>Expansion portion (phase II): the recommended volume identified from phase Ib is applied in this phase for both primary tumour and more than or equal to 3 cm lymph node lesions. After confirmation of recommended volumes, 18 additional subjects are enrolled at the recommended volume level to assess for safety and efficacy.</p>
Follow-up	-
Primary Outcomes	<p>Phase I: determination of the recommended doses and the dose limiting toxicities (DLT) [time frame: 24 months] To determine the recommended volumes and the DLT of PEP-503 administered as intra-tumoural injection, activated by concurrent chemoradiotherapy (CCRT).</p> <p>Phase II: the rate of locoregional control at one year [time frame: 24 months] To evaluate the rate of locoregional control at one year after PEP-503 intra-tumoural injection.</p> <p>Phase I and II: evaluation of safety profile of PEP503 [time frame: 24 months] Safety of PEP-503, as intra-tumoural injection schedule, activated by CCRT will be assessed in terms of incidence and severity of clinical and laboratory adverse events by NCI-CTCAE version 4.0.</p>
Secondary Outcomes	<p>Phase I: the body kinetic profile of PEP-503 [Time Frame: 24 months] To characterize the body kinetics on date of injection (DINJ) of PEP-503 administered by intra-tumoural injection before CCRT.</p> <p>Phase II: evaluation of objective tumour response as per response evaluation criteria in solid tumours (RECIST) [Time Frame: 24 months] To evaluate the objective tumour rate by using RECIST v1.1 after intra-tumoural injection schedule, activated by CCRT.</p> <p>Phase II: pathological response (pR) [Time Frame: 24 months] If patients receive tumour and/or neck lymph node dissection after treatment, to assess according to the evidence of viable tumour cell.</p> <p>Phase II: evaluation of progression free survival rate at 1 year [Time Frame: 24 months] To evaluate the progression free survival rate at 1 year after the intra-tumoural injection of PEP-503.</p>
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date estimated November 2018

ESTIMATED COST and IMPACT

COST

The cost of NanoXray NBTXR3 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other: | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other: | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs: | <input type="checkbox"/> Other reduction in costs: |
| <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|--|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified: | <input checked="" type="checkbox"/> None identified |
|--|---|

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- ¹³ National Institute for Health and Care Excellence. *Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over*. Available from: <https://www.nice.org.uk/guidance/NG36/chapter/Recommendations#treatment-of-early-stage-disease> [Accessed 19 Jul 2017].