NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
October 2023

Leukocyte interleukin with cyclophosphamide, indomethacin, and zinc for neoadjuvant therapy of squamous cell carcinoma of the head and neck

Company/Developer	CEL-SCI Corp

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 5578	NICE TSID: 10203	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Leukocyte interleukin (LI) in combination with cyclophosphamide, indomethacin, and zinc is in clinical development for previously untreated, locally advanced squamous cell carcinoma of the head and neck (SCCHN) of the oral cavity and soft palate. SCCHN is a cancer that begins in the squamous cells (thin, flat cells that line various organs and skin) in areas of head and neck, including nasal cavity, sinuses, lips, mouth, salivary glands, throat and voice box. Locally advanced means that cancer has grown outside the area it started in but has not yet spread to other parts of the body. With current standard of care, most patients with SCCHN still experience disease recurrence or develop distant metastases (spread to distant organs or lymph nodes), therefore novel treatment options are needed.

LI is a combined immunotherapy, administrated as local injection. It is made by a mixture of small proteins called cytokines. These cytokines play a crucial role in our immune response. The cytokine mixture in LI contains 36 different types of these proteins, such as interleukins, interferons, chemokines, and colony-stimulating factors. LI can activate the anti-tumour response of the immune system prior to any other therapy and help it become more effective at fighting the cancer cells in patients with SCCHN. If licensed, LI can offer a new first-line treatment option in adults with locally advanced SCCHN.

Proposed Indication

Neoadjuvant therapy of adult patients with locally advanced primary squamous cell carcinoma of the head and neck (SCCHN).[1]

Technology

Description

Leukocyte interleukin (LI) (Multikine) is an immunotherapeutic agent that belongs to a new class of experimental immunotherapy called combination immunotherapy. It is a defined mixture of 36 pro-inflammatory cytokines, tumouricidal, tumouristatic, chemotactic, and lymphoproliferative cytokines and other small molecules obtained from qualified human donor blood.[a] The cytokine mixture includes interleukins, interferons, chemokines, and colony stimulating factors; all of which are molecules which stimulate the body's healthy immune response and activate the anti-tumour immune response.[2,3]LI is non-autologous, meaning that it is not made from the patient's own blood. [a]

LI in combination with cyclophosphamide, indomethacin, and zinc supplement has been in clinical development for the neoadjuvant treatment of patients with locally advanced SCCHN. In phase III clinical trial (NCT01265849), 400 international unit (IU) (2.0 mL total daily; 1.0 mL peritumoural, 1.0 mL perilymphatic) of LI has been administered via local/regional injection 5 times per week for 3 consecutive weeks, alongside cyclophosphamide 300mg/m^2, indomethacin 25mg and one capsule of zinc.[4]

Key Innovation

The current standard of care for locally advanced SCCHN is an aggressive combined modality therapy. With current treatment the risk of recurrence, distant metastases, and death (5-year survival rate) for patients remains high.[5]

LI is a mixture of natural human cytokines and cellular products that is administrated by local injection.[a] The LI injection utilizes naturally occurring, immune-regulating cytokines, and could be the first investigational immunotherapeutic to be used in locally advanced SCCHN.[6] Results from phase III clinical trial (NCT01265849) indicated a statistically significant 5-year survival benefit with LI immunotherapy produced in patients receiving surgery plus radiotherapy, representing approximately 40% of the study population.[7] If licensed, LI will offer the first-line neoadjuvant treatment in previously untreated patients with SCCHN prior to standard of care.

Regulatory & Development Status

LI does not currently have Marketing Authorisation in the UK for any indication.

LI is currently not in any clinical trial for other indications.

LI was granted orphan drug designation by the US FDA as neoadjuvant therapy in patients with SCCHN in 2007.[8]

[a] The information provided by CEL-SCI Corp

Patient Group

Disease Area and Clinical Need

SCCHN develops from the mucosal epithelium in the oral cavity, pharynx and larynx and are the most common malignancies that arise in the head and neck. The burden of SCCHN varies across countries/regions and has generally been correlated with exposure to tobacco-derived carcinogens, excessive alcohol consumption, or both.[9] About 60% of newly diagnosed SCCHN are detected as locally advanced disease.[10] Locally advanced means that cancer has grown outside the body part it started in, but has not yet spread to other organs.[11] The classic presenting symptoms of SCCHN depend on both the anatomical site of the primary tumour and the aetiology of the tumour, but can include painful chewing, dysarthria , dysphagia , odynophagia , otalgia, dyspnoea and epistaxis.[9]

There are more than 12,400 new head and neck cancer cases in the UK every year (2016- 2018). Head and neck cancer is the 8th most common cancer in the UK, accounting for 3% of all new cancer cases (2016-2018). There are around 4,100 head and neck cancer deaths in the UK every year, that is 11 every day (2017-2019).[12] Head and neck cancer incidence rates are projected to rise by 3% in the UK between 2023-2025 and 2038-2040, to 21 cases per 100,000 people on average each year by 2038-2040.[12] This includes a similar increase for males and females. About 90% of head and neck cancers are squamous cell carcinomas.[13] In England (2022- 23), there were around 13,585 finished consultant episodes (FCEs) and 12,269 admissions, 6,967 day cases and 40,165 bed days for a primary diagnosis of malignant neoplasms of tongue, mouth, palate and other un-specified parts of mouth (ICD-10 code C01 to C06).[14]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommended cetuximab in combination with radiotherapy for the treatment of locally advanced SCCHN. NICE has not provided any specific recommendation for neoadjuvant treatment of SCCHN.[15]

Clinical Trial Information

Trial	**IT-MATTERS**, NCT01265849, 2010-019952-35; Phase III Study of LI [Multikine] Plus SOC (Surgery + Radiotherapy or Surgery + Concurrent Radiochemotherapy) in Subjects With Advanced Primary Squamous Cell Carcinoma of the Oral Cavity/Soft Palate vs. SOC Only **Phase III** - Completed **Locations:** 8 EU countries, UK, Canada, USA, and other countries **Primary completion date:** May 2020
Trial Design	Randomized, Parallel Assignment, Open Label
Population	N=928 (actual); patients with previously untreated locally advanced primary squamous cell carcinoma of the oral cavity or soft palate; aged 18 years and older
Intervention(s)	LI 400 IU IV, cyclophosphamide 300mg/m^2 IV, indomethacin 25mg oral capsule, zinc oral capsule
Comparator(s)	Standard of care (surgery followed by either radiotherapy or combined radio-chemotherapy

Outcome(s)	Primary outcome measures: • Overall Survival (OS) [Time frame: From the date of treatment assignment to death or the last follow-up date. Maximum follow-up was approximately 113 months.] • OS in Low-Risk Subjects [Time frame: From the date of treatment assignment to death or the last follow-up date. Maximum follow-up was approximately 113 months.] See trial record for full list of other outcomes.
Results (efficacy)	Pre-surgery responders (PSR; CR/PR) in ITT LI treated (+/- CIZ) groups were 8.5% (45/529; overall LI) and 16% (34/212; LR LI) vs no SOC PSRs. Early response lowered death rate to 22.2% (ITT LI treated) vs 54.1% for non-PSRs (two-sided Fisher Exact (2FE) p < 0.0001), for ITT LR LI PSRs with 17.6% vs 42.7% (2FE p = 0.0067), and for ITT LR LI responders (LI+CIZ+SOC) 12.5% vs 41% (2FE p = 0.0101). Proportional hazard (PH) ITT LR LI treated HR = 0.348 (95% CI: [0.152, 0.801]), ITT LR LI+CIZ+SOC HR = 0.246 (95% CI: [0.077, 0.787]). For all ITT LR (n = 380), LI+CIZ+SOC demonstrated significant OS advantage vs SOC (log rank p = 0.0478; Cox HR = 0.68 (95% CI: [0.48-0.95]), Wald p = 0.0236 [controlling for tumour stage, tumour location and geographic region]. The absolute OS advantage in ITT LR LI+CIZ+SOC vs SOC was 4.9%/9.5%/14.1%, at 36/48/60 months (M), representing 72.4% vs 67.5% (36 M); 67.3% vs 57.8% (48 M), and 62.7% vs 48.6% (60 M) with a 46.5 M median OS advantage (101.7 M [LI+CIZ+SOC] vs 55.2 M [SOC]). [4]
Results (safety)	Percent treatment emergent adverse events (TEAEs) were comparable among all treated groups. No excess safety was reported for LI treatment over SOC alone.[4]

Estimated Cost

The cost of LI is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Xevinapant with platinum-based chemotherapy and radiotherapy for untreated locally advanced squamous cell head and neck cancer (TA11166). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Atezolizumab for adjuvant treatment of high-risk locally advanced squamous cell head and neck cancer (TA10933). Expected date of issue to be confirmed.
- NICE technology appraisal. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (TA145). June 2008.
- NICE guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). June 2018.
- NICE quality standard. Head and neck cancer (QS146). March 2017.

NHS England (Policy/Commissioning) 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: 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

- The Spanish Society of Medical Oncology. SEOM clinical guidelines for the treatment of head and neck cancer (2020). May 2021.[16]
- National Comprehensive Cancer Network (NCCN). Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. July 2020.[17]
- The Journal of Laryngology and Otology. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. March 2016.[18]
- 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. May 2010.[19]

Additional Information

CEL-SCI Corp did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 CEL SCI. *Clinical Trial Status*. 2023. Available from: https://cel-sci.com/multikine-2/ [Accessed 29/08/2023].

2 CEL SCI. *What is the investigational therapy Multikine® (Leukocyte Interleukin, Injection)?* 2023. Available from: https://cel-sci.com/what-is-multikine/ [Accessed 29/08/2023].

3 PharmacyTimes. *Leukocyte Interleukin Injection Immunotherapy Produces Significant Survival Benefit in Landmark Head, Neck Cancer Study*. 2021. Available from: https://www.pharmacytimes.com/view/leukocyte-interleukin-injection-immunotherapy-produces-significant-survival-benefit-in-landmark-head-neck-cancer-study [Accessed 29/08/2023].

4 Clinical Trials.gov. *Efficacy and Safety Study of Leukocyte Interleukin,Injection (LI) to Treat Cancer of the Oral Cavity (IT-MATTERS). Trial ID: NCT01265849*. 2010. Status: completed. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01265849 [Accessed 29/08/2023].

5 Zhang Z, Wu B, Peng G, Xiao G, Huang J, Ding Q, et al. Neoadjuvant chemoimmunotherapy for the treatment of locally advanced head and neck squamous cell carcinoma: a single-arm

phase 2 clinical trial. *Clinical Cancer Research*. 2022;28(15):3268-76. https://aacrjournals.org/clincancerres/article/28/15/3268/707102/Neoadjuvant-Chemoimmunotherapy-for-the-Treatment.

6 Hayley Virgil. 10-Year Follow-Up Findings of Leukocyte Interleukin Injection Demonstrate Promise in Locally Advanced Primary SCCHN. 2022. https://www.cancernetwork.com/view/10-year-follow-up-findings-of-leukocyte-interleukin-injection-demonstrate-promise-in-locally-advanced-primary-scchn.

7 CEL SCI. *Phase III Trial Design*. 2023. Available from: https://cel-sci.com/multikine-2/ [Accessed 29/08/2023].

8 FDANEWS, A WCG Company. *Cel-Sci Receives Orphan Drug Designation for Its Cancer Drug Multikine*. 2007. Available from: https://www.fdanews.com/articles/94614-cel-sci-receives-orphan-drug-designation-for-its-cancer-drug-multikine#:~:text=Cel-Sci%20announced%20that%20its%20cancer%20drug%20Multikine%20has,of%20the%20head%20and%20neck%20by%20the%20FDA. [Accessed 05/09/2023].

9 Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nature Reviews Disease Primers*. 2020;6(1). Available from: https://doi.org/10.1038/s41572-020-00224-3.

10 Perri F, Ionna F, Muto P, Marzo MD, Caponigro F, Longo F, et al. Genetics and management of locally advanced carcinomas of the head and neck: role of altered fractionation radiotherapy. *Future Science OA*. 2019;5(1):FSO347. Available from: https://doi.org/10.4155/fsoa-2018-0058.

11 American Cancer Society. *Understanding Advanced and Metastatic Cancer*. 2020. Available from: https://www.cancer.org/cancer/managing-cancer/advanced-cancer/what-is.html#:~:text=Advanced%20cancers%20can%20be%20locally,other%20parts%20of%20the%20body. [Accessed 05/09/2023].

12 Cancer Research UK. *Head and neck cancers statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers [Accessed 05/09/2023].

13 Mcmillan Cancer Support. *The Rich Picture-People with head and neck cancer*. 2017. Available from: https://www.macmillan.org.uk/_images/head-neck-cancer_tcm9-282784.pdf [Accessed 05/09/2023].

14 NHS Digital. *Hospital Admitted Patient Care Activity 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 28/09/2023].

15 National Institute for Health and Care Excellence(NICE). *Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck*. Last Update Date: 2014. Available from: https://www.nice.org.uk/guidance/ta145 [Accessed 05/09/2023].

16 Mesia R, Iglesias L, Lambea J, Martínez-Trufero J, Soria A, Taberna M, et al. SEOM clinical guidelines for the treatment of head and neck cancer (2020). *Clinical and Translational Oncology*. 2021;23(5):913-21. Available from: https://doi.org/10.1007/s12094-020-02533-1.

17 Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2020;18(7):873-98. Available from: https://doi.org/10.6004/jnccn.2020.0031.

18 Vinidh Paleri NR. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal ofLaryngology& Otology*. 2016;130. https://bahno.org.uk/_userfiles/pages/files/ukheadandcancerguidelines2016.pdf.

19 Grégoire V, Lefebvre JL, Licitra L, Felip E. 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(Supplement 5):v184-v6. Available from: https://doi.org/10.1093/annonc/mdq185.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.