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Newcastle University

Health Technology Briefing
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Xevinapant with platinum-based chemoradiotherapy for previously untreated locally advanced squamous cell carcinoma of the head and neck

Company/Developer	Merck Serono Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13221	NICE ID: Not available	UKPS ID: 666337

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

Xevinapant in combination with chemoradiotherapy (CRT) is currently in clinical development for previously untreated locally advanced squamous cell carcinoma of the head and neck (SCCHN). SCCHN is 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. For patients with unresected locally advanced SCCHN who cannot undergo surgery, the current standard of care is high-dose cisplatin-based CRT, however most patients will still experience disease recurrence or develop distant metastases (spread to distant organs or lymph nodes), therefore novel treatment options are needed.

Xevinapant is a new type of cancer treatment that restores the sensitivity of cancer cells to apoptosis (programmed cell death), and enhances the effects of anticancer treatments, such as chemotherapy and radiotherapy. Xevinapant will be administered as an oral solution. If licensed, xevinapant in combination with CRT will offer an additional treatment option for patients with locally advanced SCCHN.

Proposed Indication

The proposed indication was confidential at the time of writing this briefing.

Technology

Description

Xevinapant (Debio 1143) is a first-in-class, potent, small-molecule antagonist of inhibitors of apoptosis proteins (IAPs) that restores the sensitivity of cancer cells to apoptosis.[1,2] IAPs are a class of proteins that regulate apoptosis induced by intrinsic or extrinsic factors. In healthy cells, different IAPs [such as X-linked IAP (XIAP) and cellular IAPs 1 and 2 (cIAP1/2)] block apoptotic signalling through different mechanisms. IAPs are frequently overexpressed in cancer cells, including SCCHN, increasing the resistance of cancer cells to apoptosis. Xevinapant can restore cancer cell apoptosis by inhibiting XIAP and cIAP1/2 and thereby releasing the blockade on downstream caspase activity crucial for the intrinsic and extrinsic apoptotic pathways.[1]

Xevinapant in combination with chemo-radiation therapy (CRT) is in clinical development for the treatment of patients with previously untreated LA SCCHN, suitable for definitive CRT. In the phase III clinical trial (TrilynX, NCT04459715), 200mg xevinapant will be administered as an oral solution from day 1 to 14, every 21-day cycle, in combination with three cycles of high-dose cisplatin (100 mg/m^2 on day 2) and intensity-modulated radiotherapy (IMRT; 70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days for 7 weeks) followed by three cycles of xevinapant monotherapy (200 mg/day, days 1–14, 3 weeks per cycle).[1,3]

Key Innovation

Approximately 40% of patients are diagnosed with early-stage (stage I–II) SCCHN, for which standard treatment options of surgery or radiotherapy provide cure rates of up to 90%. However, the majority (approximately 60%) of patients are diagnosed with LA (stages III, IVa and IVb) disease, which cannot be removed by surgical resection in 50% of the cases, or less commonly (approximately 10%), with metastatic (stage IVc) disease. With currently available treatment options, half of the patients with unresectable LA SCCHN will ultimately have local disease recurrence or develop metastatic disease within 2 years of completing treatment. For patients with LA SCCHN who cannot undergo surgical resection, the current standard of care is high-dose cisplatin-based CRT. However, because most patients with LA SCCHN will experience disease recurrence or develop distant metastases, novel treatment options are needed.[1]

Both chemotherapy and radiotherapy induce DNA damage, resulting in downstream caspase activation and proapoptotic signalling. However, because apoptosis is suppressed in cancer cells, resistance to chemotherapy and radiotherapy is common. By restoring cancer cell sensitivity to apoptosis, xevinapant is hypothesized to enhance the effects of anticancer treatments, such as chemotherapy and radiotherapy. Supporting this hypothesis, in preclinical models of SCCHN, xevinapant enhanced cancer cell death induced by chemotherapy or radiotherapy, leading to sustained tumour regression. Xevinapant was shown to induce the production of inflammatory cytokines and activated immune cells in preclinical models, and may also increase anticancer effects mediated by immune cells.[1] If licensed, xevinapant in combination with CRT will offer an additional treatment option for patients with previously untreated LA SCCHN.

Regulatory & Development Status

Xevinapant does not currently have Marketing Authorisation in the EU/UK for any indication.

Xevinapant in combination with intensity modulation radiation therapy (IMRT) is currently in phase III clinical trial for the treatment of resected, high risk LA SCCHN.[4]

Xevinapant was granted Breakthrough Therapy designation by the US FDA for the treatment of previously untreated LA-SCCHN in combination with platinum-based chemotherapy and standard fractionation IMRT, in February 2020.[2]

Patient Group

Disease Area and Clinical Need

Squamous cell carcinoma of the head and neck (SCCHN) is cancer of the head and neck that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes, various internal organs, and the lining of hollow organs and ducts of some glands). SCCHN includes cancers of the nasal cavity, sinuses, lips, mouth, salivary glands, throat (pharynx), and larynx (voice box). Most head and neck cancers are squamous cell carcinomas.[5] Oral cavity and larynx cancers are generally associated with tobacco consumption, alcohol abuse or both, whereas pharynx cancers are increasingly attributed to infection with human papillomavirus (HPV), primarily HPV-16. The classic presenting symptoms of SCCHN depend on both the anatomical site of the primary tumour and the aetiology of the tumour, and include painful chewing, dysarthria (difficulty speaking), dysphagia (difficulty eating), odynophagia (pain when swallowing), otalgia (ear pain), dyspnoea (difficulty breathing) and epistaxis (nosebleed).[6] Locally advanced means that cancer has grown outside the body part it started in but has not yet spread to other parts of the body.[7]

There are around 12,400 new head and neck cancer cases in the UK every year, that's 34 every day (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's 11 every day (2017-2019). Between 28% and 67% of people diagnosed with head and neck cancers in England survive their disease for five years or more (2009-13).[8] About 90% of head and neck cancers are squamous cell carcinomas.[9] Applying this to the estimate of 12,400 new cases of head and neck cancer annually in the UK, it can be estimated that 11,160 of those cases would be SCCHN.[8,9] In England (2020-21), there were 352 finished consultant episodes (FCEs) and 312 admissions for a primary diagnosis of malignant neoplasm of other and ill-defined site: head, face and neck (ICD-10 code C76.0), which resulted in 209 day cases and 533 FCE bed days.[10]

Recommended Treatment Options

NICE recommends cetuximab in combination with radiotherapy for patients with LA SCCHN whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy treatment are contraindicated.[11]

Clinical Trial Information

Trial	**TrilynX; NCT04459715, EudraCT-2020-000377-25**; A Randomized, Double-Blind Placebo-Controlled, Phase 3 Study of Xevinapant (Debio 1143) in Combination With Platinum-Based Chemotherapy and Standard Fractionation Intensity-Modulated Radiotherapy in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy **Phase III** – Recruiting

	Location(s) – 11 countries in EU, UK, USA, Canada and other countries **Primary completion date –** December 2024
Trial Design	Randomised, parallel assignment, quadruple-masked, placebo-controlled
Population	N = 700 (estimated); Subjects with histologically confirmed diagnosis of previously untreated LA SCCHN; 18 years and older
Intervention(s)	Three cycles (3 weeks per cycle) of xevinapant oral solution (200 mg/day, days 1–14) plus three cycles of high-dose cisplatin intravenous (IV) infusion (100 mg/m2 on day 2) and (IMRT; 70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days for 7 weeks) followed by three cycles of xevinapant monotherapy (200 mg/day, days 1–14, 3 weeks per cycle).[1,1]
Comparator(s)	Matched placebo with concomitant CRT
Outcome(s)	Event-Free Survival (EFS) [Time Frame: Up to 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT02022098; A Phase I/II Randomized Study to Determine the Maximum Tolerated Dose, Safety, Pharmacokinetics and Antitumor Activity of Debio 1143 Combined With Concurrent Chemo-Radiation Therapy in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck **Phase I/II –** Completed **Location(s) –** France, Switzerland **Study completion date –** April 2022
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 144 (actual); Subjects with LA SCCHN; 18 Years to 75 years
Intervention(s)	Xevinapant (oral) or via feeding tube with concomitant CRT daily for 14 days every three weeks (on days 1-14, 22-35 and 43-56).
Comparator(s)	Matched placebo with concomitant CRT
Outcome(s)	Phase II: Percentage of participants achieving Locoregional Control (LRC) at 18 months from the end of chemo-radiation therapy (CRT) [Time Frame: within 4 years] See trial record for full list of other outcomes.
Results (efficacy)	Locoregional control 18 months after chemoradiotherapy was achieved in 26 (54%; 95% CI 39-69) of 48 patients in the xevinapant group versus 16 (33%; 95% CI 20-48) of 48 patients in the placebo group (odds ratio 2·69 [95% CI 1·13-6·42], p=0·026).[12]
Results (safety)	Grade 3 or worse adverse events were reported in 41 (85%) of 48 patients in the xevinapant group and in 41 (87%) of 47 patients in the placebo group. The

	most common grade 3-4 adverse events were dysphagia (in 24 [50%] patients in the xevinapant group vs ten [21%] in the placebo group), mucositis (in 15 [31%] vs ten [21%]), and anaemia (in 17 [35%] vs 11 [23%]). Serious treatment-emergent adverse events were recorded in 30 (63%) of 48 patients in the xevinapant group and 28 (60%) of 47 in the placebo group. In the placebo group, two (4%) deaths were due to adverse events (one multiple organ failure and one asphyxia; neither was considered to be related to treatment). No deaths due to adverse events occurred in the xevinapant group.[12]

Estimated Cost

The cost of xevinapant is not yet known.

Relevant Guidance

NICE Guidance

- 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.[13]
- National Comprehensive Cancer Network (NCCN). Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. July 2020.[14]
- The Journal of Laryngology and Otology. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. March 2016.[15]
- 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.[16]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of head and neck cancer – SIGN 90. October 2006.[17]

Additional Information

Merck Serono entered into a worldwide in-licensing agreement with Debiopharm for the development and commercialization of xevinapant on March 2021.[2]

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