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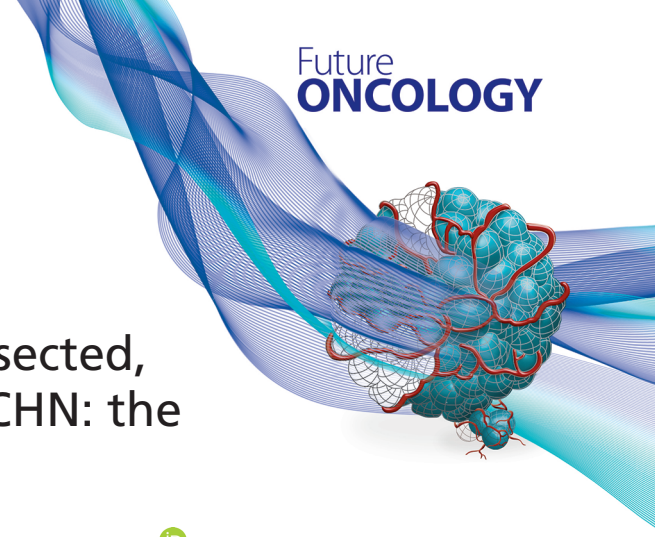

Xevinapant plus radiotherapy in resected, high-risk, cisplatin-ineligible LA SCCHN: the phase III XRay Vision study design

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There is a significant unmet need and lack of treatment options for patients with resected, high-risk, cisplatin-ineligible locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Xevinapant, a first-in-class, potent, oral, small-molecule IAP inhibitor, is thought to restore cancer cell sensitivity to chemotherapy and radiotherapy in clinical and preclinical studies. We describe the design of XRay Vision (NCT05386550), an international, randomized, double-blind, phase III study. Approximately 700 patients with resected, high-risk, cisplatin-ineligible LA SCCHN will be randomized 1:1 to receive 6 cycles of xevinapant or placebo, in combination with radiotherapy for the first 3 cycles. The primary end point is disease-free survival, and secondary end points include overall survival, health-related quality of life, and safety.

Plain language summary: Squamous cell carcinoma is the most common form of head and neck cancer (SCCHN) and includes cancers of the lips, mouth, throat, tongue and voice box. It is called 'locally advanced' when the cancer has spread to nearby areas but not to other parts of the body. Few treatment options are available for people with locally advanced SCCHN who have had surgery and are unable to receive a type of chemotherapy called cisplatin. Xevinapant is being developed as a possible new type of cancer treatment. It is a liquid that is taken by mouth or given through a feeding tube. Adding xevinapant to the standard treatment – called radiotherapy – aims to make radiotherapy more effective against the cancer. Researchers have started a large, international, phase III study called XRay Vision to see if adding xevinapant to radiotherapy can help stop the cancer from coming back after surgery and help people live longer.

Clinical Trial Registration: NCT05386550 (ClinicalTrials.gov)

Tweetable abstract: Xevinapant plus radiotherapy in resected, high-risk, cisplatin-ineligible LA SCCHN: the phase III XRay Vision study design.

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Keywords: hypopharynx • inhibitor of apoptosis protein • larynx • locally advanced squamous cell carcinoma of the head and neck • oral cavity • oropharynx • phase III • radiotherapy • resected • xevinapant

Head and neck cancer is the eighth most commonly diagnosed cancer globally, with 878,348 new cases and 444,347 deaths recorded in 2020 [1]. The majority of cases (≈90%) are squamous cell carcinomas [2], and approximately 60% of patients are diagnosed with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) [3].

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According to data from real-world studies, approximately 40% of patients who are diagnosed with LA SCCHN undergo surgical resection [4–6].

For patients who are at high risk of relapse postoperatively (meeting criteria defined in international guidelines, such as extracapsular nodal extension or positive resection margins [R1 or close margin of ≤1 mm]) [7–9], the current standard of care is adjuvant chemoradiotherapy (CRT; cisplatin [100 mg/m^2 every 3 weeks for 3 cycles] plus concomitant standard fractionation radiotherapy [RT]) [7,8]; the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend RT at a dose of 60–66 Gy in 30–33 fractions of 2 Gy/day over 6–6.5 weeks [7,8], whereas the European Society for Medical Oncology (ESMO) guidelines cite evidence supporting a similar range of 58–66 Gy, with higher doses recommended for patients with more risk factors [7,8]. Results from a recent phase II/III trial in Japan suggested that adjuvant CRT with weekly cisplatin 40 mg/m^2 was noninferior to CRT with cisplatin 100 mg/m^2 every 3 weeks for overall survival (OS; primary end point) in patients with resected LA SCCHN at high risk of relapse [10]. However, due to the relative toxicity of cisplatin, many patients are unable to receive cisplatin-based chemotherapy (CT) [11,12].

To inform treatment decisions, clinical guidelines and consensus documents have recommended criteria for absolute and relative contraindications [13–15]. Common absolute contraindications to cisplatin are poor performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] ≥3) [13–15], renal impairment (glomerular filtration rate of 50 ml/min/1.73 m^2 [13] or creatinine clearance <50 ml/min [14] or <40 ml/min [15]), hearing loss or tinnitus (grade ≥2 [13,15] or grade ≥3 [14]) and neurological disorders (grade ≥2) [13–15]. Relative contraindications are also common in clinical practice: age >70 years [15], poor performance status (ECOG PS ≥2) [14,15], hearing loss or tinnitus (grade 1) [14,15], and neuropathy (grade 1) [14,15]. The decision as to whether patients receive cisplatin relies on clinical judgment [12,14], particularly for patients with relative contraindications.

Due to the limited number of clinical studies, there is a lack of consensus in international guidelines regarding the adjuvant treatment of patients with resected LA SCCHN at high risk of relapse who are deemed ineligible to receive cisplatin. The ESMO guidelines do not recommend any specific treatments for this patient population other than adjuvant RT alone [8], whereas the National Comprehensive Cancer Network® (NCCN®) recommends docetaxel and cetuximab plus RT for patients with extracapsular nodal extension or positive resection margins (category 2B) as a potential treatment option, following the results of the phase II RTOG 0234 trial [7,16].

Recently, a phase III study of 356 patients with LA SCCHN in India who were deemed ineligible to receive cisplatin explored the combination of docetaxel plus RT versus RT alone in the adjuvant and definitive settings [17]. In the overall population, disease-free survival (DFS; 2-year DFS, 42 vs 30.3%; p = 0.002) and OS (2-year OS, 50.8 vs 41.7%; p = 0.035) were improved with docetaxel plus RT versus RT alone. However, for the subgroup of patients who received docetaxel plus RT in the adjuvant setting (n = 72 [39% of the study population]), DFS (p = 0.396) and OS (p = 0.478) were not improved. Additionally, this trial had several limitations. For example, it was carried out at a single centre in India and included a mixed population treated in the adjuvant and definitive settings; some patients received 2D or 3D conformal RT instead of intensity-modulated RT (IMRT), which is not standard of care in international guidelines, and data for high- and intermediate-risk patients were not presented.

Given the lack of conclusive benefit of any particular concurrent regimen compared with RT alone, RT alone remains the standard of care for patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin.

Disease-specific outcomes in this population are not well defined due to a lack of clinical data in these patients; however, based on the increased incidence of comorbidity in patients who are deemed ineligible to receive cisplatin, it is likely that the prognosis for this population is poor compared with patients who are deemed eligible to receive cisplatin. Therefore, patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin have a high unmet medical need, and novel treatment options are urgently required.

Xevinapant

Evasion of apoptosis is a key hallmark of cancer [18–20], and cancer cells can suppress apoptosis via several mechanisms, including alterations in the expression of intracellular proteins that regulate apoptosis. IAPs, such as cIAP1/2 and XIAP, are a class of proteins that block intrinsic and extrinsic apoptotic signalling pathways [21–25], promoting cell survival [21,23–25]. IAPs are overexpressed in various cancers, including SCCHN [26–29], and are thought to increase the resistance of cancer cells to apoptosis [30–33]. Furthermore, IAP overexpression is associated with poor prognosis in LA SCCHN [34–36] and has been shown to diminish the effects of CT and RT in preclinical models of SCCHN [37–39].

Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor that is thought to restore sensitivity of cancer cells to apoptosis (Figure 1) [40–43]. In preclinical studies, xevinapant was shown to inhibit XIAP and cIAP1/2 [40–42]. Thus, xevinapant is thought to release the blockade on downstream caspase activity and reactivate intrinsic and extrinsic apoptotic pathways, thereby enhancing the antitumour efficacy of CT and RT [41]. Inhibition of cIAP1/2 also activates noncanonical NF-κB signalling, resulting in the production of inflammatory cytokines that stimulate immune cells in response to TNF receptor signalling [41,44–46].

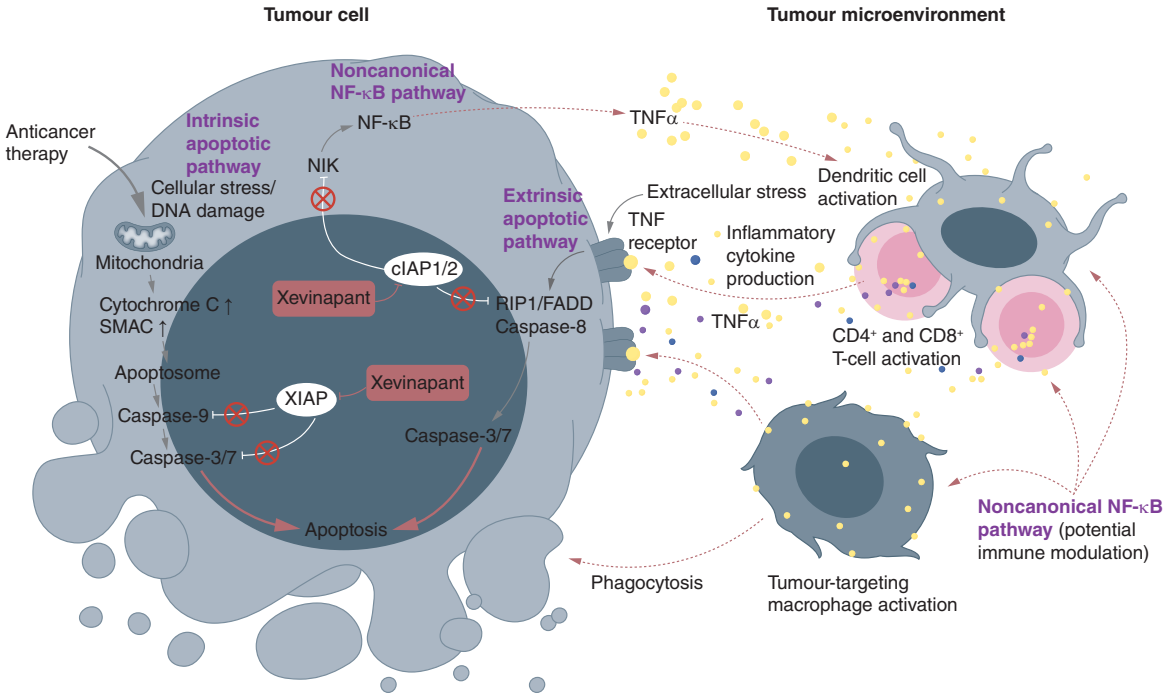

Figure 1. Xevinapant proposed mode of action. Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor. Xevinapant is thought to: 1) restore apoptosis in cancer cells by blocking XIAP and cIAP1/2, leading to activation of caspases downstream of the intrinsic mitochondrial and extrinsic TNF receptor signalling pathways, respectively, and 2) enhance the inflammatory antitumour response in immune cells of the tumour microenvironment by activating noncanonical NF-κB signalling through blocking of cIAP1/2 downstream of the TNF receptor. Adapted from [47]. Copyright © 2022 Future Medicine Ltd.

In a randomized phase II study of patients with unresected LA SCCHN, xevinapant plus CRT significantly improved locoregional control at 18 months after the end of CRT versus placebo plus CRT (54 vs 33%; odds ratio, 2.74; 95% CI: 1.15–6.53; p = 0.0232) [48,49]. Progression-free survival (hazard ratio [HR], 0.33; 95% CI: 0.17–0.67; p = 0.0019) and duration of response (HR, 0.21; 95% CI: 0.08–0.54; p = 0.0011) were also markedly improved after 3 years of follow-up, and the risk of death was halved after 5 years of follow-up (HR, 0.47; 95% CI: 0.27–0.84; p = 0.0101) [49]. Xevinapant has also shown synergistic activity with RT in preclinical models of SCCHN [41,50]. The promising clinical activity of xevinapant in combination with CRT, in addition to its preclinical antitumour activity in combination with RT alone, provides the rationale for evaluating xevinapant in combination with RT. Here, we present the design of the XRay Vision study.

The XRay Vision study design

XRay Vision is an international, randomized, double-blind, phase III study evaluating xevinapant plus IMRT versus placebo plus IMRT in patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin (Figure 2). Approximately 700 patients will be randomized in a 1:1 ratio using permuted block allocation and stratified according to primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx), tumour stage (III vs IV), and human papillomavirus (HPV) p16 status (oropharynx p16 positive vs oropharynx p16 negative or larynx/hypopharynx/oral cavity). Eligible patients will be randomized to receive 6 cycles of treatment with oral xevinapant 200 mg/day or matched placebo (days 1–14 of a 21-day cycle), in combination with standard fractionation IMRT for the first 3 cycles (Figure 2). No administration of any specific

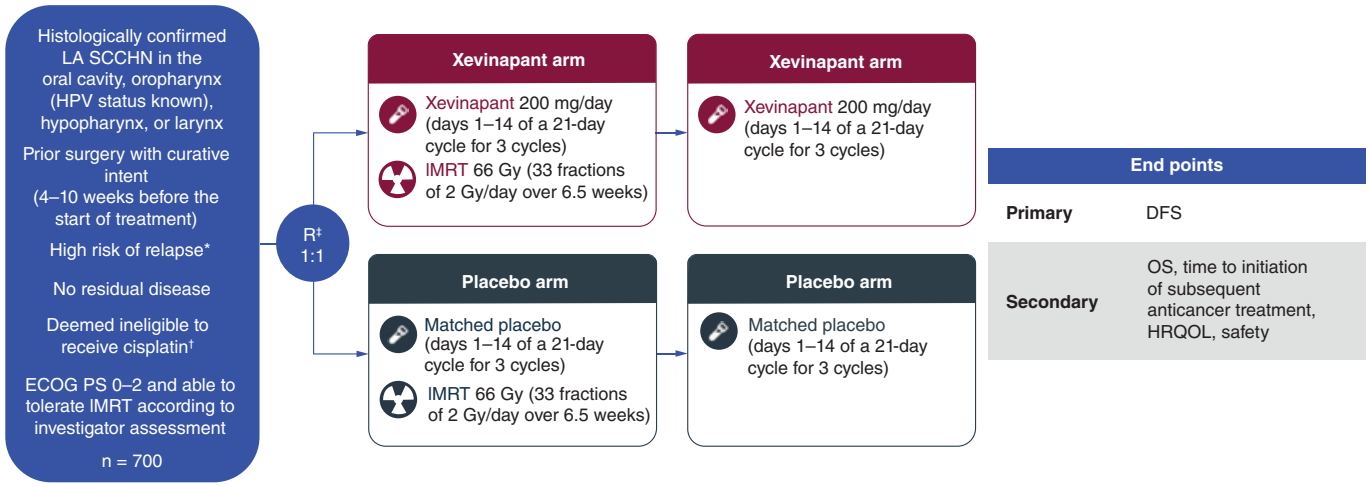

Figure 2. The phase III XRay Vision study design.
*Meeting 1 or 2 of the following criteria, confirmed by local histopathology: nodal extracapsular extension or positive resection margins (R1 or close margin of ≤1 mm).
†Meeting ≥1 of the following criteria: estimated glomerular filtration rate <60 ml/min/1.73 m^2; hearing loss (grade ≥2 audiometric hearing loss or grade ≥2 tinnitus); grade ≥2 peripheral neuropathy; and, if aged ≥70 years, unfit according to the G8 questionnaire (score ≤14).
‡Stratification factors: primary tumour site, oropharynx/oral cavity versus larynx versus hypopharynx; tumour stage, III versus IV; HPV p16 status for oropharynx primary tumour site, oropharynx p16 positive versus oropharynx p16 negative or larynx/hypopharynx/oral cavity.
DFS: Disease-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; HPV: Human papillomavirus; HRQOL: Health-related quality of life; IMRT: Intensity-modulated radiotherapy; LA SCCHN: Locally advanced squamous cell carcinoma of the head and neck; OS: Overall survival; R: Randomization.

Table 1. Summary of XRay Vision study end points.

Primary end point	**DFS:** Time from randomization to objective relapse or death from any cause
Secondary end points	**OS:** Time from randomization to death from any cause **Time to initiation of subsequent anticancer treatment**: Time from randomization to the start of the first subsequent cancer treatment **Health-related quality of life:** Assessed using the EORTC QLQ-H&N35 and QLQ-C30 questionnaires and the EuroQol EQ-5D-5L visual analogue scale **Safety:** Incidence and severity of AEs, serious AEs and AEs of special interest, and changes in laboratory values, vital signs and electrocardiogram results, all according to NCI-CTCAE v5.0

AE: Adverse event; DFS: Disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OS: Overall survival.

concomitant medication is required with xevinapant. The study started in October 2022, with an estimated primary completion date of October 2027.

IMRT was administered at a dose of 66 Gy (33 fractions of 2 Gy/day, 5 days per week over 6.5 weeks) for the first 3 cycles. The dose of 66 Gy was selected in line with international treatment guidelines [7,8]. In a preclinical study of xevinapant plus RT versus RT alone in an MC38 syngeneic mouse model, extended durations of xevinapant treatment following RT showed enhanced antitumour activity and prolonged survival compared with shorter durations of xevinapant treatment [51]. These data provide the rationale for 3 additional cycles of xevinapant after IMRT.

End points

In a meta-analysis of data from >22,000 patients with LA SCCHN enrolled in 104 trials comparing hyperfractionated or accelerated RT and concomitant, induction, or adjuvant CT, DFS was shown to be predictive of OS in studies of adjuvant CRT, at both the individual patient and study level [52]. Given the robustness of these data, the primary end point of the XRay Vision study is DFS. Secondary end points include OS, time to initiation of subsequent anticancer treatment, health-related quality of life, and safety. The primary and secondary end points are defined in Table 1.

Table 2. Key eligibility criteria.

Inclusion criteria	Exclusion criteria
• Age ≥18 years with histologically confirmed LA SCCHN in ≥1 of the following sites: oral cavity, oropharynx, hypopharynx, or larynx • Disease must be stage III, IVA, or IVB, except for patients with HPV-positive oropharynx tumours, who must be heavy smokers (>25 pack-years) with either T3 or T4 and N2 stage disease • Completed surgery with curative intent 4–10 weeks before the start of treatment • High risk of relapse (meeting 1 or 2 of the following criteria, confirmed by local histopathology: nodal extracapsular extension or positive resection margins [R1 or close margin of ≤1 mm]) • Deemed ineligible to receive cisplatin (meeting ≥1 of the following criteria: eGFR <60 ml/min/1.73 m^2; hearing loss [grade ≥2 audiometric hearing loss or grade ≥2 tinnitus†]; grade ≥2 peripheral neuropathy; and, if aged ≥70 years, unfit according to G8 questionnaire [score ≤14] or ineligible for cisplatin treatment due to age limit according to national guidelines) • ECOG PS 0–2 and able to tolerate IMRT according to investigator assessment • No residual disease by computed tomography or magnetic resonance imaging • Adequate renal, haematologic, and hepatic function (indicated by eGFR ≥30 ml/min/1.73^2, absolute neutrophil count ≥1,000 cells/μl, platelets ≥75,000 cells/μl, haemoglobin ≥9.0 g/dl, ALT and AST ≤2.5 × the upper limit of normal, and total bilirubin ≤1.5 × the upper limit of normal [bilirubin ≤2.0 × the upper limit of normal is permitted if the elevation is limited to indirect bilirubin, not direct bilirubin])	• Incomplete surgery • Primary tumour site unknown or in the nasopharyngeal sinuses, paranasal sinuses, nasal cavity, salivary gland, thyroid gland, parathyroid gland, or skin • Recurrent or metastatic disease • Prior definitive, neoadjuvant, concurrent, or adjuvant RT to the head and neck region that may jeopardise the primary tumour irradiation plan, or any other prior SCCHN systemic treatment

†In France, grade ≥3 audiometric hearing loss or grade ≥3 tinnitus.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: Estimated glomerular filtration rate; HPV: Human papillomavirus; IHC: Immunohistochemistry; IMRT: Intensity-modulated radiotherapy; LA SCCHN: Locally advanced squamous cell carcinoma of the head and neck; RT: Radiotherapy.

Key eligibility criteria

Key inclusion and exclusion criteria are summarised in Table 2. Eligible patients are aged ≥18 years with histologically confirmed LA SCCHN of the oral cavity, oropharynx, hypopharynx and/or larynx. All patients will have completed surgery with curative intent on these sites in the past 4 to 10 weeks before the start of treatment (if possible, it is recommended to start treatment within 8 weeks from surgery), have a high risk of relapse (meeting ≥1 of the following criteria: nodal extracapsular extension or positive resection margins [R1 or close margin of ≤1 mm]), and are deemed ineligible to receive cisplatin (meeting ≥1 of the following criteria: estimated glomerular filtration rate <60 ml/min/1.73 m^2; hearing loss [grade ≥2 audiometric hearing loss or grade ≥2 tinnitus]; grade ≥2 peripheral neuropathy; and, if aged ≥70 years, unfit according to the G8 questionnaire [score ≤14] or ineligible for cisplatin treatment due to age limit according to national guidelines). Patients are also required to have an ECOG PS score of 0–2 and be able to tolerate IMRT treatment per investigator; have no residual disease by computed tomography/magnetic resonance imaging; and have adequate renal, haematologic and hepatic function. Patients with oropharynx cancers must have a known HPV status as determined by p16 expression using immunohistochemistry. Patients with oral cavity, hypopharynx, larynx, or HPV-negative oropharynx cancers must have TNM stage III, IVA, or IVB disease. Patients with HPV-positive oropharynx tumours must be heavy smokers (>25 pack-years) with either T3 or T4 and N2 stage disease. Patients with dysphagia and/or ≥10% weight loss are recommended to have a feeding tube (nasogastric tube or percutaneous endoscopic gastrotomy); for patients with grade ≥3 dysphagia, a feeding tube is mandatory. Exclusion criteria include incomplete surgery; recurrent or metastatic disease; prior definitive, neoadjuvant, concurrent, or adjuvant RT to the head and neck region that may jeopardise the primary tumour irradiation plan; or any other prior systemic treatment for SCCHN. Patients with a primary tumour site in the nasopharyngeal sinuses, paranasal sinuses, nasal cavity, salivary gland, thyroid gland, parathyroid gland, or skin, or patients with an unknown primary tumour site are also excluded.

Evaluations

All patients will be followed up until the last patient has been assessed for 60 months post randomization or until premature discontinuation from the study, whichever occurs first. Clinical outcomes will be evaluated using a combination of clinical, radiological, and, if appropriate, fibreoptic endoscopy and pathological assessments. Imaging and clinical tumour assessments will be performed at the end of treatment (20 weeks), at 9 and 12 months in the first year, every 4 months in years 2 and 3, and every 6 months thereafter. Safety will be assessed at each visit and will be graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Treatment-related adverse events will be monitored until the end-of-therapy visit. Data on all adverse events

and serious adverse events will be collected until 28 months of follow-up. Thereafter, only predefined late-onset adverse events of special interest (myelodysplastic syndrome, acute myeloid leukaemia, or any second malignancy) and related serious adverse events will be collected. Patient-reported health-related quality of life will be assessed using the EuroQol EQ-5D-5L visual analogue scale and the European Organisation for Research and Treatment of Cancer QLQ-H&N35 and QLQ-C30 questionnaires. Other predictive biomarker assessments using blood and tumour tissue samples are planned.

Statistical analysis

The primary hypothesis is that xevinapant will prolong DFS (per investigator and independent review committee assessment) in patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin. The primary analysis population for efficacy and health-related quality of life will include all randomized patients. The safety analysis population will include all patients who received ≥1 dose of study treatment. The sample size of the study (≈700 patients) is driven by the primary end point of DFS and is powered at 81%, with a one-sided stratified log-rank test that preserves the type I error rate at 2.5%. The sequential testing procedure is DFS per investigator assessment, then DFS per independent review committee assessment, and then OS. DFS and OS between treatment arms will be compared using a one-sided stratified log-rank test that preserves the type I error rate at 2.5%. DFS, OS, and time to initiation of subsequent anticancer treatment will be summarised based on Kaplan–Meier estimates. The study will be considered positive if the primary hypothesis is statistically significant. The primary analysis will occur when 409 DFS events have been observed.

Conclusion

Patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin have limited treatment options, and novel treatments are urgently required. Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor that is thought to restore cancer cell sensitivity to apoptosis, thereby enhancing the antitumour effects of CT and RT. The phase II data in unresected LA SCCHN and promising preclinical antitumour activity in combination with RT provide strong rationale for the investigation of xevinapant in combination with RT in the XRay Vision study. As of August 2023, XRay Vision was the only ongoing phase III study with the specific objective of improving outcomes in patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin. At the time of writing, enrolment was ongoing in 21 countries worldwide, including the USA, Mexico and countries in Asia, Europe and South America.

Executive summary

- Head and neck cancer is the eighth most commonly diagnosed cancer globally and was responsible for >440,000 deaths in 2020.
- The majority of cases (>90%) are squamous cell carcinoma of the head and neck (SCCHN), and more than half of patients are diagnosed with locally advanced (LA) disease.
- For patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin, treatment options are limited and prognosis is poor.
- Radiotherapy (RT) alone remains the standard-of-care treatment for these patients.

Xevinapant

- Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor that is thought to restore cancer cell sensitivity to apoptosis and thereby enhance the efficacy of chemotherapy and RT.
- Xevinapant significantly improved efficacy with chemoradiotherapy versus placebo plus chemoradiotherapy in a phase II study of patients with unresected LA SCCHN and has shown promising synergistic activity with RT in preclinical models of SCCHN, providing the rationale for evaluating xevinapant in combination with RT.

The XRay Vision study design

- XRay Vision is an international, randomized, double-blind, placebo-controlled, phase III study.
- Approximately 700 patients with histologically confirmed resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin will be randomized 1:1 to receive 6 cycles of treatment with oral xevinapant 200 mg/day or matched placebo (days 1–14 of a 21-day cycle), in combination with intensity-modulated RT (66 Gy [33 fractions of 2 Gy/day], 5 days per week over 6.5 weeks) for the first 3 cycles.
- The primary study end point is disease-free survival.
- As of August 2023, XRay Vision was the only phase III study that has the specific objective of improving outcomes in patients with resected LA SCCHN who are at high risk of relapse and are deemed ineligible to receive cisplatin.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0774

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Competing interests disclosure

RL Ferris has stock and other ownership interests in Novasenta; has served in a consulting or advisory role for Achilles Therapeutics, Adagene Incorporated, Aduro Biotech, Bicara Therapeutics, Bristol Myers Squibb, Brooklyn ImmunoTherapeutics LLC, Cantenion, Coherus BioSciences, Everest Clinical Research, F. Hoffmann-La Roche, Genocea Biosciences, Hookipa Pharma, Instil Bio, Lifescience Dynamics, MacroGenics, MeiraGTx LLC, Merck, Mirati Therapeutics, Mirror Biologics, Nanobiotix, Novartis, Novasenta, Numab, Oncocyte, Pfizer, PPD, Rakuten Medical, Sanofi, Seagen, SIRPant Immunotherapeutics, Vir Biotechnology, and Zymeworks; and has received research funding from AstraZeneca/MedImmune, Bristol Myers Squibb, Merck, Novasenta, and Tesaro. H Mehanna reports employment with Warwickshire Head and Neck Clinic; has stock and other ownership interests in Warwickshire Head and Neck Clinic; has served in leadership roles for Warwickshire Head and Neck Clinic; reports an immediate family member having served in leadership roles for Warwickshire Head and Neck Clinic; has served in speaker roles for Merck, MSD, and Sanofi Pasteur; has received honoraria from AstraZeneca; and has received research funding from AstraZeneca, GSK, MSD, and Sanofi Pasteur. JD Schoenfeld reports employment with Dana-Farber Cancer Institute; has stock and other ownership interests in Doximity and Immunitas; has served in a consulting or advisory role for ACI Clinical, Astellas Pharma, Castle Biosciences, Debiopharm, Genentech, Immunitas, Merck, SIRPant Immunotherapeutics, and STIMIT; has provided expert testimony for Heidell, Pittoni, Murphy & Bach, and Kline & Specter PC; and has received research funding from Bristol Myers Squibb, Merck, MSD, and Regeneron. M Tahara has served in a consulting or advisory role for Astellas Pharma, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genmab, Lilly, Janssen, MSD, Nanobiotix, Nektar, Ono Pharmaceutical, Pfizer, and Rakuten Medical; has received honoraria from Bayer, Bristol Myers Squibb, Lilly, Merck, MSD, and Ono Pharmaceutical; and has received research funding from AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Lilly, Merck, MSD, Novartis, Ono Pharmaceutical, Pfizer, and Rakuten Medical. SS Yom has received research funding from BioMimetix, Bristol Myers Squibb, Genentech, Merck, and MSD; and reports patents, royalties, or other intellectual property in Springer and UpToDate. R Haddad reports employment with Dana-Farber Cancer Institute; has served in leadership roles for NCCN; has served in a consulting or advisory role for Achilles Therapeutics, AstraZeneca, Bayer, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Coherus BioSciences, Genentech, Genmab, Gilead Sciences, GSK, Immunomic Therapeutics, Loxo, Merck, Mirati Therapeutics, MSD, Pfizer, and Vaccinex; has received research funding from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Genentech, Kura Oncology, Merck, and Pfizer; reports patents, royalties, or other intellectual property in UpToDate; and reports other relationships with Boehringer Ingelheim, ISA Pharmaceuticals, and Nanobiotix. A König, P Witzler, and M Bajars report employment with Merck Healthcare KGaA, Darmstadt, Germany. C Le Tourneau has served in a consulting or advisory role for Amgen, AstraZeneca, Bristol Myers Squibb, GSK, Merck, MSD, Nanobiotix, and Roche; has received travel and accommodation expenses from AstraZeneca, Bristol Myers Squibb, and MSD; and has received honoraria from Bristol Myers Squibb, GSK, Merck, MSD, Nanobiotix, Novartis, and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

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Ethical conduct of research

The XRay Vision study is being conducted in compliance with the protocol (v5.0; 25 July 2023), and in accordance with the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, as well as the Good Clinical Practice rules. All patients will provide written informed consent before enrolment.

Availability of data & materials

For all new products or new indications approved in both the European Union and the USA after 1 January 2014, Merck (CrossRef Funder ID: 10.13039/100009945) will share patient-level and study-level data after deidentification, as well as redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researcher's request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data sharing portal. More information can be found at www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. Where Merck has a co-research, co-development, or co-marketing/co-promotion agreement or where the product has been out-licenced, it is recognised that the responsibility for disclosure may be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

Previous presentation

The study design reported in this manuscript was previously presented at the 2023 ASCO Annual Meeting, 2–6 June 2023 [53].

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