European Journal of Cancer 183 (2023) 24–37

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Extended follow-up of a phase 2 trial of xevinapant plus chemoradiotherapy in high-risk locally advanced squamous cell carcinoma of the head and neck: a randomised clinical trial

Yungan TAO [a,1], Xu-Shan Sun [b,1], Yoann Pointreau [c], Christophe Le Tourneau [d], Christian Sire [e], Marie-Christine Kaminsky [f], Alexandre Coutte [g], Marc Alfonsi [h], Benôit Calderon [h], Pierre Boisselier [i], Laurent Martin [j], Jessica Miroir [k], Jean-Francois Ramee [l], Jean-Pierre Delord [m], Florian Clatot [n], Frederic Rolland [o], Julie Villa [p], Nicolas Magne [q], Olgun Elicin [r], Elisabeta Gherga [b], France Nguyen [a], Cédrik Lafond [c], Guillaume Bera [e], Valentin Calugaru [s], Lionnel Geoffrois [f], Bruno Chauffert [g], Lars Damstrup [t], Philippa Crompton [t], Abdallah Ennaji [t], Kathrin Gollmer [t], Heidi Nauwelaerts [t], Jean Bourhis [u,*]

[a] *Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France*
[b] *Department of Radiation Oncology, Nord Franche-Comté de Montbéliard and CHRU de Besançon, Besançon, France*
[c] *Oncologie-Radiothérapie, Institut Inter-Régional de Cancérologie, Centre Jean Bernard, Le Mans, France*
[d] *Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France*
[e] *South Brittany Hospital Center, Hôpital du Scorff Radiothérapie, Lorient, France*
[f] *Institut Cancérologie de Lorraine - Alexis Vautrin, Oncologie Médicale, Vandoeuvre-lès-Nancy, France*
[g] *CHU Amiens Picardie, Oncologie-Radiothérapie, Amiens, France*
[h] *Institut Sainte Catherine, Radiothérapie, Avignon, France*
[i] *Institut du Cancer de Montpellier, Val d'Aurelle, Oncologie-Radiothérapie, Montpellier, France*
[j] *Centre de Radiothérapie Guillaume le Conquérant, Le Havre, France*
[k] *Jean Perrin Center, Radiothérapie, Clermont-Ferrand, France*
[l] *CHD Vendée, Radiothérapie, La Roche-sur-Yon, France*
[m] *Medical Oncology Dept, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France*
[n] *Henri Becquerel Centre, Service Oncologie Médicale rue d'Amiens, Rouen, France*
[o] *Institut de Cancérologie de l'Ouest, Centre René Gaudducheau, Saint-Herblain, France*
[p] *CHU Grenoble, Radiothérapie, Pôle de Cancérologie, Grenoble, France*
[q] *Institut de Cancérologie Lucien Neuwirth, Radiothérapie, Saint-Priest-en-Jarez, France*
[r] *Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*
[s] *Radiotherapy Oncology Department, Institut Curie, Paris-Saclay University, Paris, France*

* *Corresponding author*: Service de Radio-oncologie Bâtiment Hospitalier, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tel: +41 21 314 46 66.
E-mail address: jean.bourhis@chuv.ch (J. Bourhis).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejca.2022.12.015

[t] Debiopharm International, Lausanne, Switzerland
[u] CHUV, Radiation Oncology Department, Bâtiment Hospitalier, Lausanne, Switzerland

Received 10 October 2022; received in revised form 14 December 2022; accepted 17 December 2022
Available online 9 January 2023

KEYWORDS
Xevinapant;
Chemoradiotherapy;
Locally advanced squamous cell carcinoma of the head and neck;
Survival;
Efficacy

Abstract ***Introduction:*** We report long-term efficacy and overall survival (OS) results from a randomised, double-blind, phase 2 study (NCT02022098) investigating xevinapant plus standard-of-care chemoradiotherapy (CRT) vs. placebo plus CRT in 96 patients with unresected locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).
Methods: Patients were randomised 1:1 to xevinapant 200 mg/day (days 1–14 of a 21-day cycle for 3 cycles), or matched placebo, plus CRT (cisplatin 100 mg/m^2 every 3 weeks for 3 cycles plus conventional fractionated high-dose intensity-modulated radiotherapy [70 Gy/35 F, 2 Gy/F, 5 days/week for 7 weeks]). Locoregional control, progression-free survival, and duration of response after 3 years, long-term safety, and 5-year OS were assessed.
Results: The risk of locoregional failure was reduced by 54% for xevinapant plus CRT vs. placebo plus CRT but did not reach statistical significance (adjusted hazard ratio [HR] 0.46; 95% CI, 0.19–1.13; $P = .0893$). The risk of death or disease progression was reduced by 67% for xevinapant plus CRT (adjusted HR 0.33; 95% CI, 0.17–0.67; $P = .0019$). The risk of death was approximately halved in the xevinapant arm compared with placebo (adjusted HR 0.47; 95% CI, 0.27–0.84; $P = .0101$). OS was prolonged with xevinapant plus CRT vs. placebo plus CRT; median OS not reached (95% CI, 40.3-not evaluable) vs. 36.1 months (95% CI, 21.8–46.7). Incidence of late-onset grade ≥3 toxicities was similar across arms.
Conclusions: In this randomised phase 2 study of 96 patients, xevinapant plus CRT demonstrated superior efficacy benefits, including markedly improved 5-year survival in patients with unresected LA SCCHN.

1. Introduction

Head and neck cancer is the eighth most common cancer worldwide with 878,348 new cases and 444,347 deaths reported in 2020 [1]. Squamous cell carcinoma of the head and neck (SCCHN) accounts for >90% of all head and neck cancers [2], and most patients (≈60%) are diagnosed with locally advanced (LA) disease [3]. The current standard of care (SoC) for patients with LA SCCHN is surgery followed by chemoradiotherapy (CRT; concurrent high-dose cisplatin and radiotherapy) or definitive CRT for the approximately 50% of patients who will not undergo surgery [2,4,5]. Within 2 years of completing treatment, approximately half of patients with LA SCCHN have local disease recurrence or develop metastatic disease [6–13], and the prognosis for these patients is poor (median overall survival [OS] of ≈12 months) [7,9,14,15]. Despite the poor long-term outcomes for patients with disease recurrence, the SoC for unresected LA SCCHN has remained relatively unchanged for more than 2 decades. Novel treatment options are therefore urgently needed to improve outcomes for patients with unresected LA SCCHN.

Treatment resistance is one of the key factors in local or distant failure [16] and has in part been attributed to the evasion of apoptosis, enabling cancer cells to resist cell death induced by anticancer treatments [17–19]. Inhibitors of apoptosis proteins (IAPs), including X-linked IAP (XIAP) and cellular IAP 1 and 2 (cIAP1/2), are a class of proteins that regulate apoptosis via the inhibition of caspase activity or through inhibiting the formation of proapoptotic complexes at tumour necrosis factor (TNF) receptors [20–24]. IAPs are frequently overexpressed in cancer [21,25], including SCCHN [26], increasing the resistance of cancer cells to apoptosis and preventing cell death induced by anticancer treatments [19,27–29]. Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor that blocks XIAP and cIAP1/2 and has been shown to restore cancer cell sensitivity to apoptosis, thereby enhancing the effects of anticancer treatments such as chemotherapy and radiotherapy [30–32].

In the double-blind, randomised phase 2 portion of the phase 1/2 study (NCT02022098), xevinapant plus CRT significantly improved locoregional control (LRC) vs. placebo plus CRT at 18 months after the completion

of CRT (54% vs. 33%; odds ratio based on database relock in 2021 [see Methods], 2.74; 95% CI, 1.15–6.53, $P = .0232$; primary end-point) in patients with unresected LA SCCHN. The addition of xevinapant to CRT was well tolerated, with a predictable and manageable safety profile [33]. Here, we present results from the extended efficacy follow-up period (3 years after the last patient was randomised) and long-term survival follow-up (5 years after the last patient was randomised).

2. Methods

2.1. Study design

The design of the double-blind, multicentre, randomised phase 2 portion of the phase 1/2 study (NCT02022098) in 96 patients has been reported previously [33] and is detailed in the supplement.

Efficacy analyses were conducted in the intention-to-treat (ITT) population, which included all randomised patients. Safety was analysed in all patients who received at least ≥1 dose of study treatment. Disease status was evaluated according to Response Evaluation Criteria in Solid Tumours 1.1, based on the investigator's blinded clinical assessment. Progression was histologically confirmed. After a 2-year standard follow-up period, patients could enter extended follow-up, which covered the period after the primary results of the study were reported. During extended follow-up, disease status and late-onset toxicity were assessed every 3–6 months until the end of study, which was defined as 3 years after the last patient had been randomised. Following the end of study assessment, patients could enter the long-term survival follow-up, which continued until approximately 5 years after the last patient had been randomised.

2.2. End-points and statistical analysis

The primary end-point for this study was the proportion of patients achieving LRC (defined as the documented absence of locoregional failure), evaluated 18 months after the end of CRT. Patients with missing data were assumed to be in locoregional failure for this binary end-point.

After the 3-year analysis database lock, upon unblinding, it was discovered that for 6 patients, the randomisation had been performed under the wrong

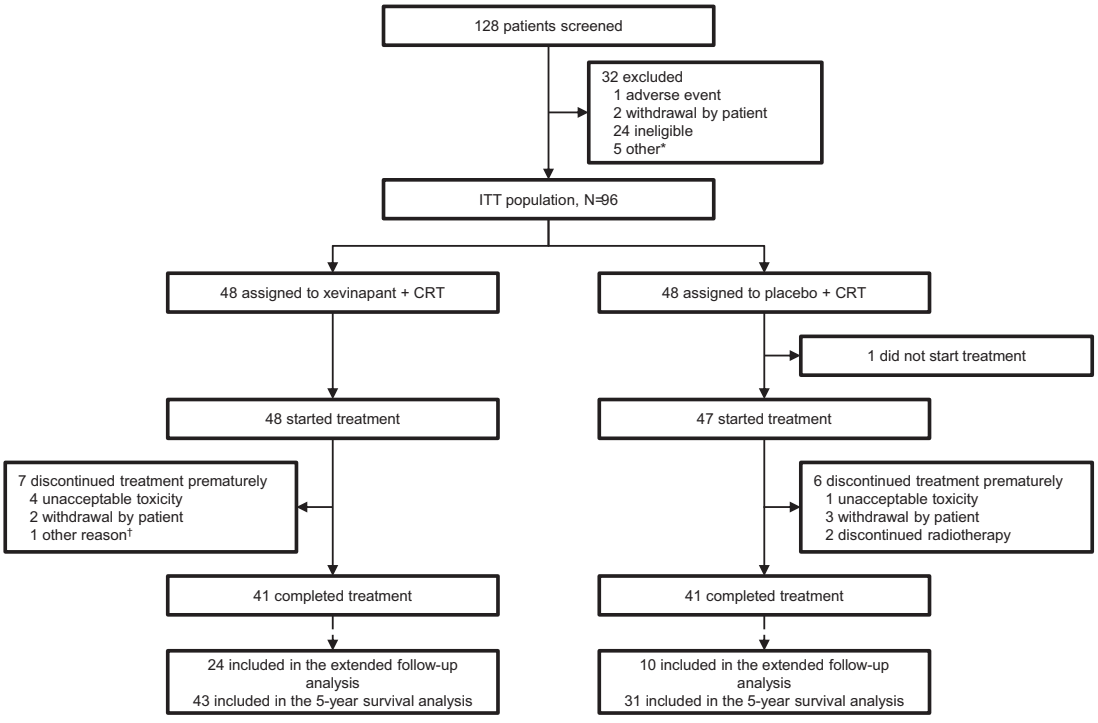

Fig. 1. CONSORT diagram. CRT, chemoradiotherapy; ITT, intention-to-treat. *Other reasons were investigator decision (left ventricular ejection fraction was <50%), death of patient, respiratory insufficiency due to tumour, investigator decision (due to comorbidities), and a logistical reason. †Patient found the taste of the study drug too bitter.

value of at least one of the stratification factors (nodal involvement or primary tumour). These values had later been corrected in the CRF, and the previous, blinded, analysis had been performed using these true values of the strata, instead of the strata assigned at randomisation. To retain the integrity of the ITT principle of a randomised study, the primary end-point was reanalysed using the strata assigned at randomisation, leading to an updated odds ratio for the LRC of 2.74 (95% CI, 1.15–6.53, $P = .0232$). For other end-points, the updated 3-year and 5-year analyses using as-randomised strata are presented here.

Secondary end-points included duration of LRC, progression-free survival (PFS), duration of response (DoR), and OS (details of end-points are given in the supplement). Time-to-event end-points were analysed for all randomised patients using Cox regression, adjusted for the randomisation stratification factors. Medians for time-to-event end-points and probabilities of being event free at specified timepoints were derived using Kaplan–Meier methodology. Efficacy was also evaluated on an exploratory basis in the subgroup of patients with human papillomavirus (HPV)-negative oropharyngeal cancer and in patients with non-oropharyngeal cancer. The small number of patients with HPV-positive oropharyngeal cancer (3 [6%] in the xevinapant group and 5 [10%] in the placebo group) precluded a meaningful analysis of efficacy in that subgroup. Long-term safety was evaluated for all patients who received ≥1 dose of study drug and consisted of summaries of the incidence of late-onset toxicities (defined as adverse events starting or worsening ≥30 days after the end of treatment date) for each treatment group by preferred term, according to the Medical Dictionary for Regulatory Activities version 19.0, and grade, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The updated findings reported here represent the final analysis of LRC, PFS, DoR, and safety at the end of the extended efficacy follow-up (3 years after

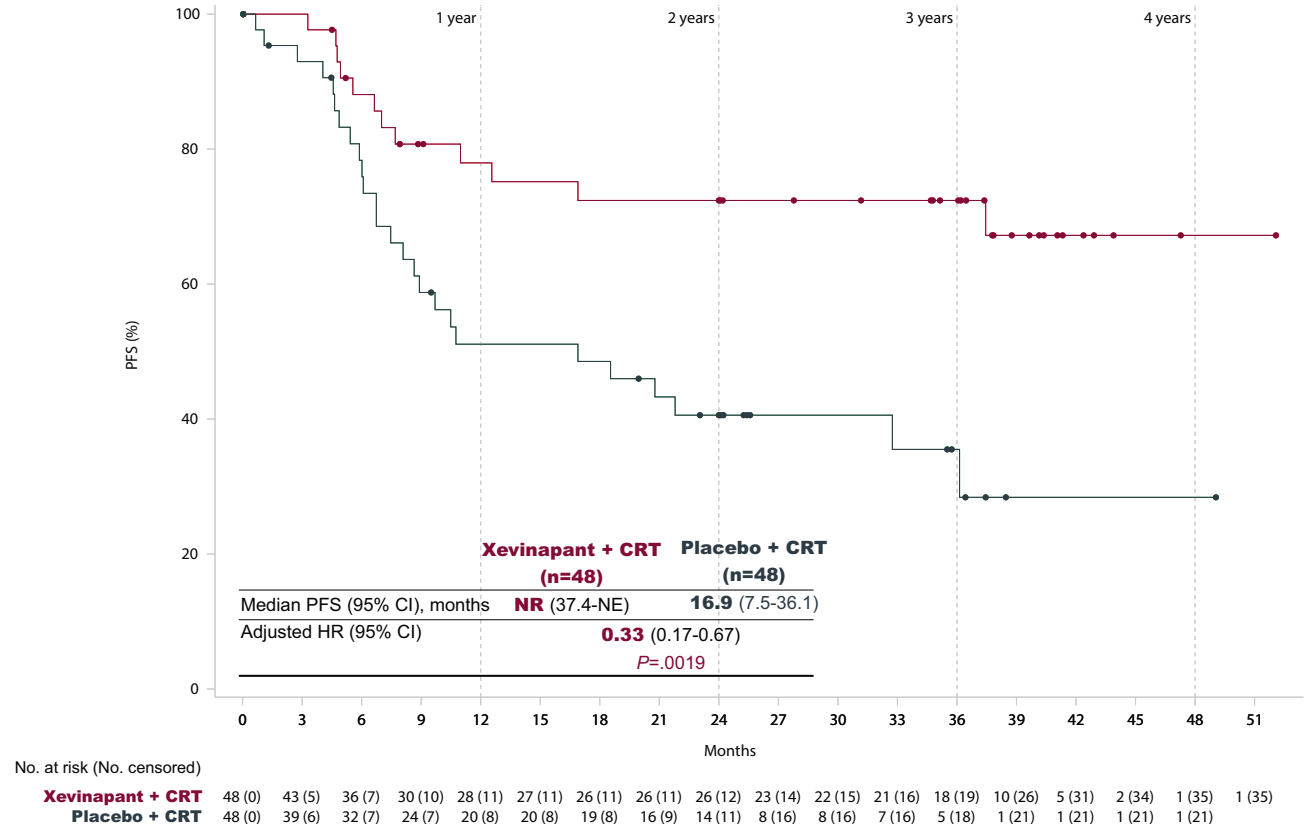

Fig. 2. Kaplan–Meier analysis of (A) PFS, (B) LRC, and (C) DoR in the ITT population after 3 years of follow-up. CRT, chemoradiotherapy; DoR, duration of response; HR, hazard ratio; ITT, intention-to-treat; LRC, locoregional control; NE, not estimable; NR, not reached; PFS, progression-free survival.

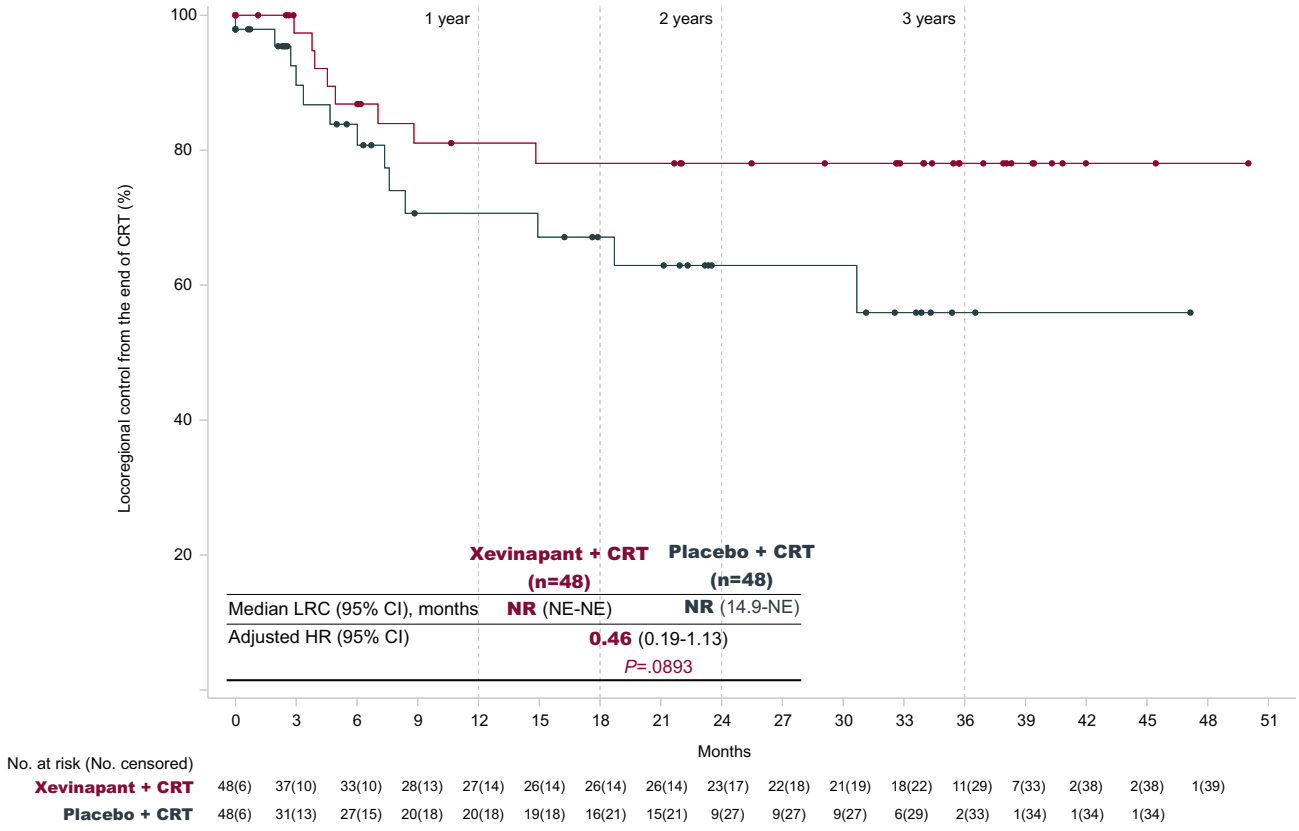

Fig. 2. (Continued).

the last patient was randomised) and are hereafter referred to as 3-year follow-up. OS was evaluated following long-term survival follow-up (5 years after the last patient was randomised) and are hereafter referred to as 5-year follow-up. All data analyses reported here were conducted using SAS® (version 9.4).

The study protocol was approved by the institutional review boards or ethics committees of all 19 participating centres. The study was conducted in accordance with the protocol, the principles of the Declaration of Helsinki, and applicable regulatory requirements. All patients provided written informed consent in advance of study-specific procedures.

3. Results

3.1. Patient disposition

Between January 25, 2016, and April 24, 2017, 96 patients were randomised to receive either xevinapant (n = 48) or placebo (n = 48) plus CRT (ITT population); one patient from the placebo arm did not receive study treatment (Fig. 1). The baseline characteristics were comparable between the treatment groups, as reported previously, with no relevant differences between treatment arms [33]. Of the 48 patients in the xevinapant plus CRT arm, 43 entered the extended survival follow-up period, as did 31 of the 48 patients in the placebo plus CRT arm (Supplementary Fig. 1). For the 3-year follow-up analysis (data cut-off, July 21, 2020), median follow-up was 35.9 months (range, 0.6–52.0 months) in the xevinapant plus CRT arm and 25.8 months (range, 0.1–49.2 months) in the placebo plus CRT arm; for the 5-year follow-up analysis, median follow-up was 60.1 months (range, 7.1–70.5 months) and 39.2 months (range, 4.8–71.2 months), respectively.

3.2. 3-Year follow-up efficacy analysis

In the 3-year follow-up analysis, efficacy benefits were improved for xevinapant plus CRT vs. placebo plus

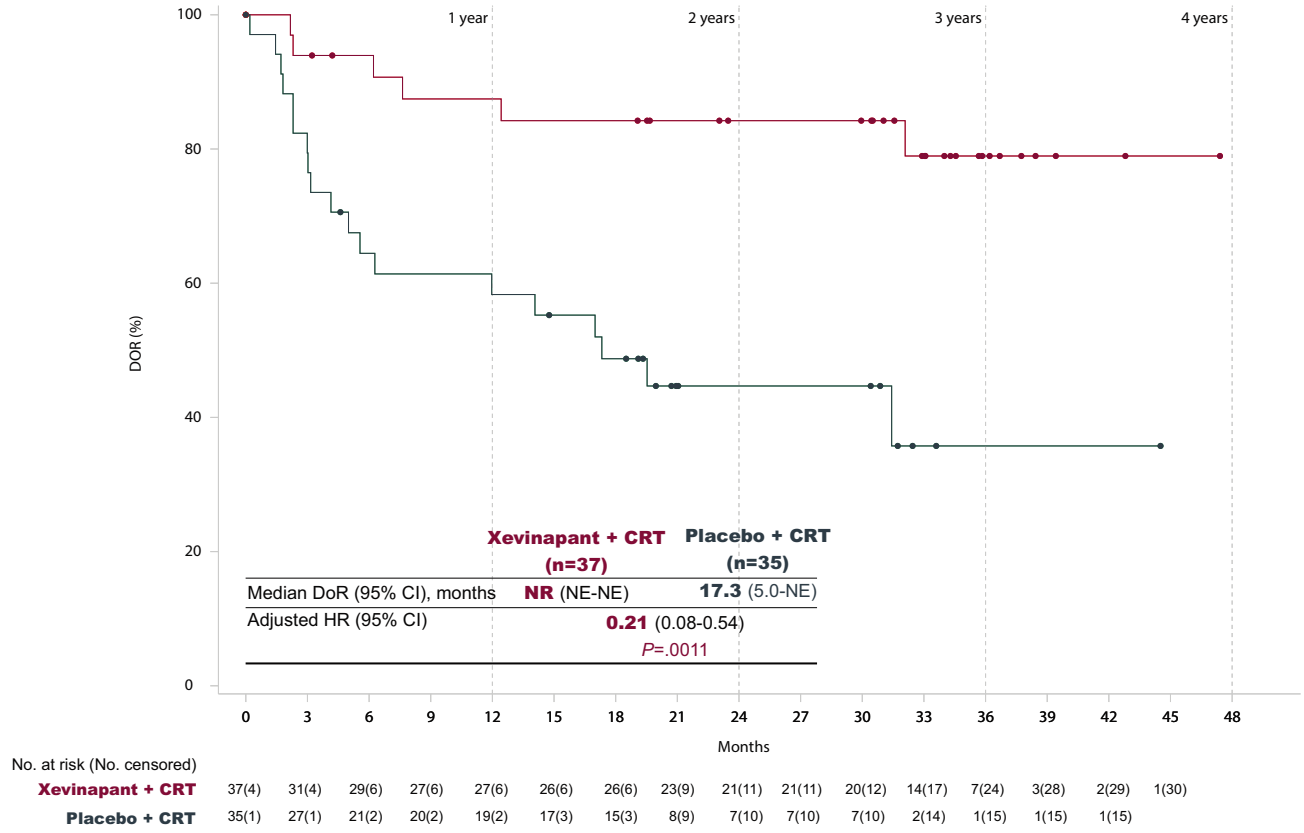

Fig. 2. (Continued).

CRT (Fig. 2). The risk of locoregional failure during the follow-up period was reduced by 54% in the xevinapant plus CRT arm vs. the placebo plus CRT arm, but this did not reach statistical significance (adjusted HR 0.46; 95% CI, 0.19–1.13, $P = .0893$). The probability of LRC at 3 years after the end of CRT was 78% (95% CI, 61%–88%) for xevinapant plus CRT vs. 56% (95% CI, 34%–73%) for placebo plus CRT; median duration of LRC was not reached for either group. The risk of death or disease progression was reduced by 67% for patients receiving xevinapant (adjusted hazard ratio [HR] 0.33; 95% CI, 0.17–0.67; $P = .0019$). Median PFS was not reached (95% CI, 37.4 months–not estimable [NE]) for the xevinapant plus CRT arm vs. 16.9 months (95% CI, 7.5–36.1 months) for the placebo plus CRT arm; the probability of PFS at 3 years was 72% (95% CI, 56%–84%) vs. 36% (95% CI, 20%–51%), respectively. At 3 years, 12 patients (25.0%) had events for PFS in the xevinapant plus CRT arm (4 locoregional, 7 distant relapse, and 1 death) vs. 26 (54.2%) in the placebo plus CRT arm (9 locoregional, 7 distant relapse, 2 locoregional and distant relapse, and 8 death). In patients who responded to treatment, median DoR was not reached for xevinapant plus CRT vs. 17.3 months (95% CI, 5.0 months-NE) for placebo plus CRT; 79% reduction in risk of death or disease progression after initial response for patients receiving xevinapant (adjusted HR 0.21; 95% CI, 0.08–0.54, $P = .0011$). The probability of a maintained response at 3 years after initial response was 79% (95% CI, 58%–90%) vs. 36% (95% CI, 16%–56%), respectively.

3.3. Long-term OS

The risk of all-cause mortality over the 5 years of follow-up was more than halved (adjusted HR 0.47; 95% CI, 0.27–0.84; $P = .0101$) for xevinapant plus CRT vs. placebo plus CRT (Fig. 3). OS was prolonged with

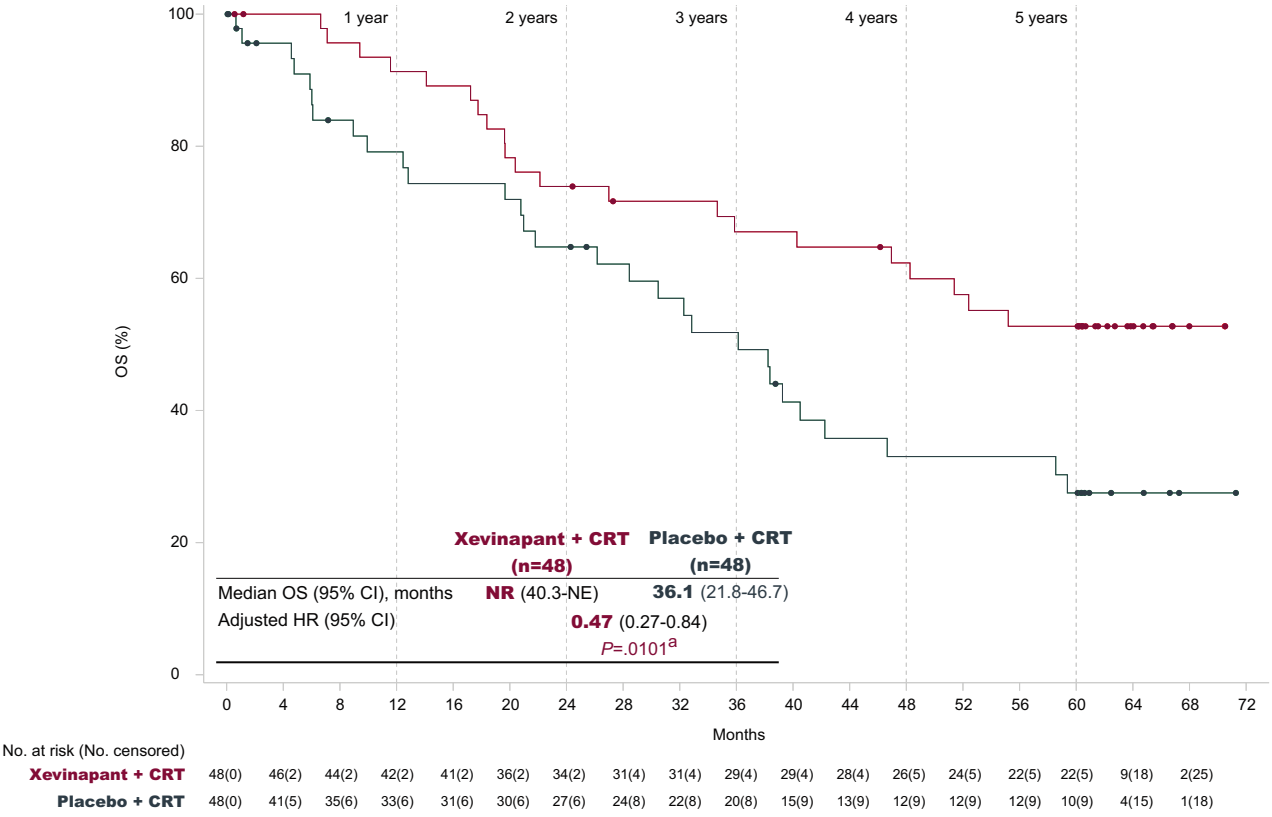

Fig. 3. Kaplan–Meier analysis of OS in the ITT population after 5 years of follow-up. CRT, chemoradiotherapy; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; NR, not reached; OS, overall survival. [a]Cox regression analysis adjusted for randomisation stratification factors.

xevinapant plus CRT vs. placebo plus CRT; median OS was not reached (95% CI, 40.3 months–NE) vs. 36.1 months (95% CI, 21.8–46.7 months). The probability of survival 5 years after randomisation was 53% (95% CI, 37%–66%) in the xevinapant plus CRT arm vs. 28% (95% CI, 15%–42%) in the placebo plus CRT arm.

3.4. OS sensitivity analysis

Sensitivity analyses were performed considering actual values of stratification factors (Supplementary Table 1). Results were in line with those obtained in the main OS analysis, showing a reduction in the risk of mortality from any cause in the xevinapant plus CRT arm compared with the placebo plus CRT arm (HR 0.48; 95% CI, 0.27–0.85; $P = .0121$).

3.5. Efficacy by subgroup analysis

PFS, duration of LRC, and DoR over 3 years of follow-up and OS over 5 years of follow-up were assessed in patient subgroups, including HPV status, smoking status, cancer localisation, nodal involvement, tumour node metastasis (TNM) stage, and alcohol consumption status. Efficacy benefits were comparable between subgroups and consistent with the benefit seen in the overall population (Fig. 4), with xevinapant plus CRT demonstrating improved efficacy benefits vs. placebo plus CRT.

3.6. Subsequent therapy in patients with disease progression

In the xevinapant plus CRT arm, 16 patients (33.3%) received subsequent antineoplastic therapy for progressive disease of the primary cancer compared with 19 patients (40.4%) in the placebo plus CRT arm (Supplementary Table 2); in both arms, most of these patients received subsequent systemic anticancer therapy, 12 (75.0%) vs. 16 patients (84.2%), respectively. Subsequent anticancer therapies included chemotherapy, immune checkpoint inhibitors, epidermal growth factor receptor inhibitors, or combinations of these treatments; fewer patients in the xevinapant plus CRT arm received immune checkpoint inhibitors as subsequent therapy vs. the placebo plus CRT arm (5 patients [41.7%] vs. 10 patients [62.5%], respectively; Supplementary Table 2).

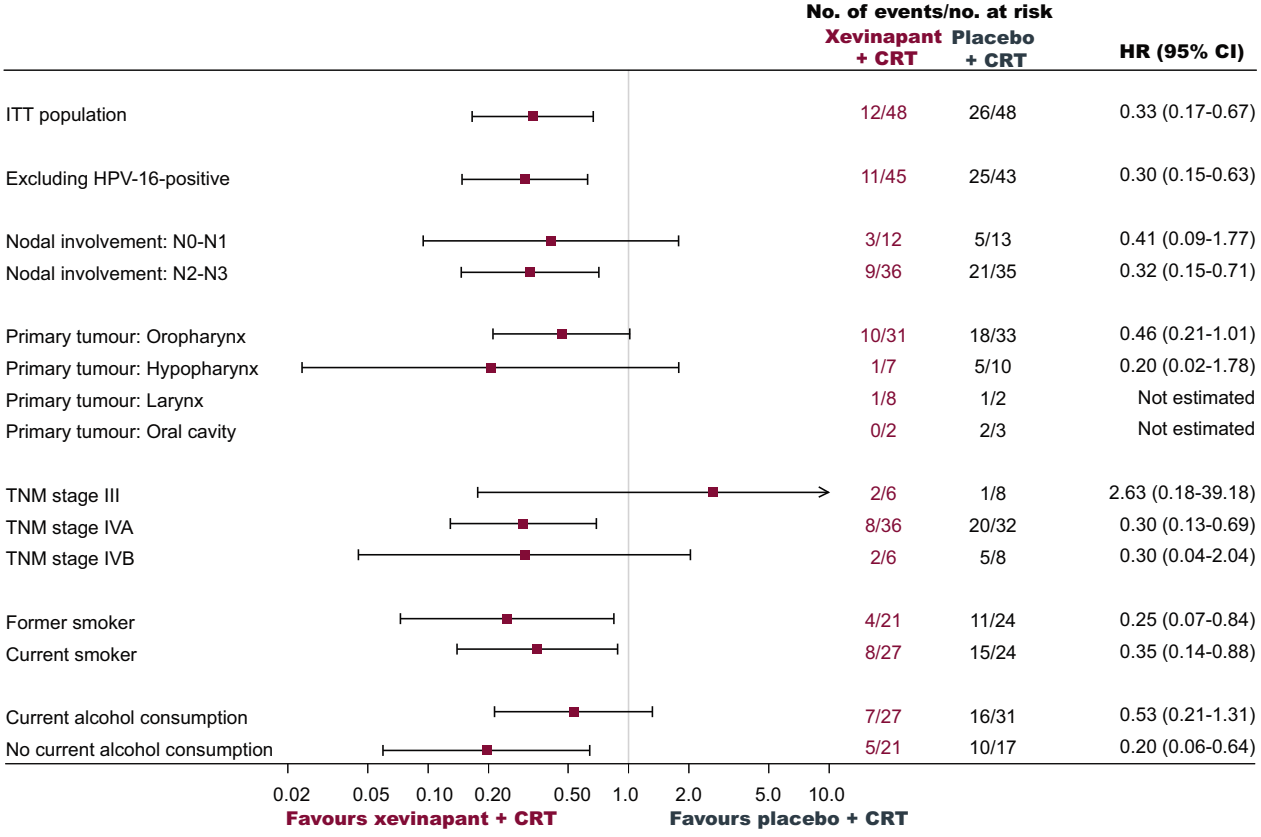

Fig. 4. Efficacy end-points. (A) PFS, (B) LRC, (C) DoR, and (D) OS by exploratory subgroup in the ITT population. CRT, chemo-radiotherapy; DoR, duration of response; HPV, human papillomavirus; ITT, intention to treat; LRC, locoregional control, OS, overall survival; PFS, progression-free survival; TNM, tumour node metastasis.

3.7. Long-term safety

Treatment-emergent adverse events (TEAEs) have been reported previously [33]. In the 3-year follow-up analysis, any-grade late-onset toxicities were reported for 39/48 patients (81.3%) in the xevinapant plus CRT arm and 33/47 patients (70.2%) in the placebo plus CRT arm, including late-onset toxicities of grade ≥3 in 13 (27.1%) and 12 patients (25.5%), respectively (Fig. 5). The most common late-onset toxicities of any grade were: dry mouth in 17 patients (35.4%) in the xevinapant plus CRT arm vs. 12 patients (25.5%) in the placebo plus CRT arm, dysgeusia in 8 (16.7%) vs. 6 patients (12.8%), respectively, and dysphagia and fibrosis, each reported in 6 patients (12.5% and 12.8%) in both arms.

As previously reported, by the end of the study, no patients in the xevinapant plus CRT arm had died due to TEAEs vs. 2 (4.3%) in the placebo plus CRT arm (asphyxia and multiple organ dysfunction syndrome) [33]. In total, 21 patients (43.8%) had died in the xevinapant plus CRT arm (14 due to disease progression, 3 from unknown cause, 1 from sepsis shock of pulmonary origin, 1 from pulmonary sepsis, 1 from leukaemia due to sideroblastic myelodysplasia, 1 from pancreatic cancer) vs. 29 (61.7%) in the placebo plus CRT arm (15 due to disease progression, 4 from unknown cause, 1 from pneumopathy, 1 from oral haemorrhage probably related to tumour progression, 1 from cardiac arrest, 1 after hospitalisation for respiratory distress and pulmonary infection, 1 due to a toxicity/adverse event deemed not related to study drug, 1 from oedemato-ascitic decompensation or septic shock, 1 from progression of lung cancer, 1 from oesophageal cancer, 1 from complications due to chemotherapy for secondary cancer of the bladder, 1 from unknown cause who died during sleep). None of these deaths were attributed to study treatment.

4. Discussion

The long-term efficacy and survival follow-up of this phase 2 study of 96 patients continues to show efficacy benefits with xevinapant plus CRT vs. placebo plus

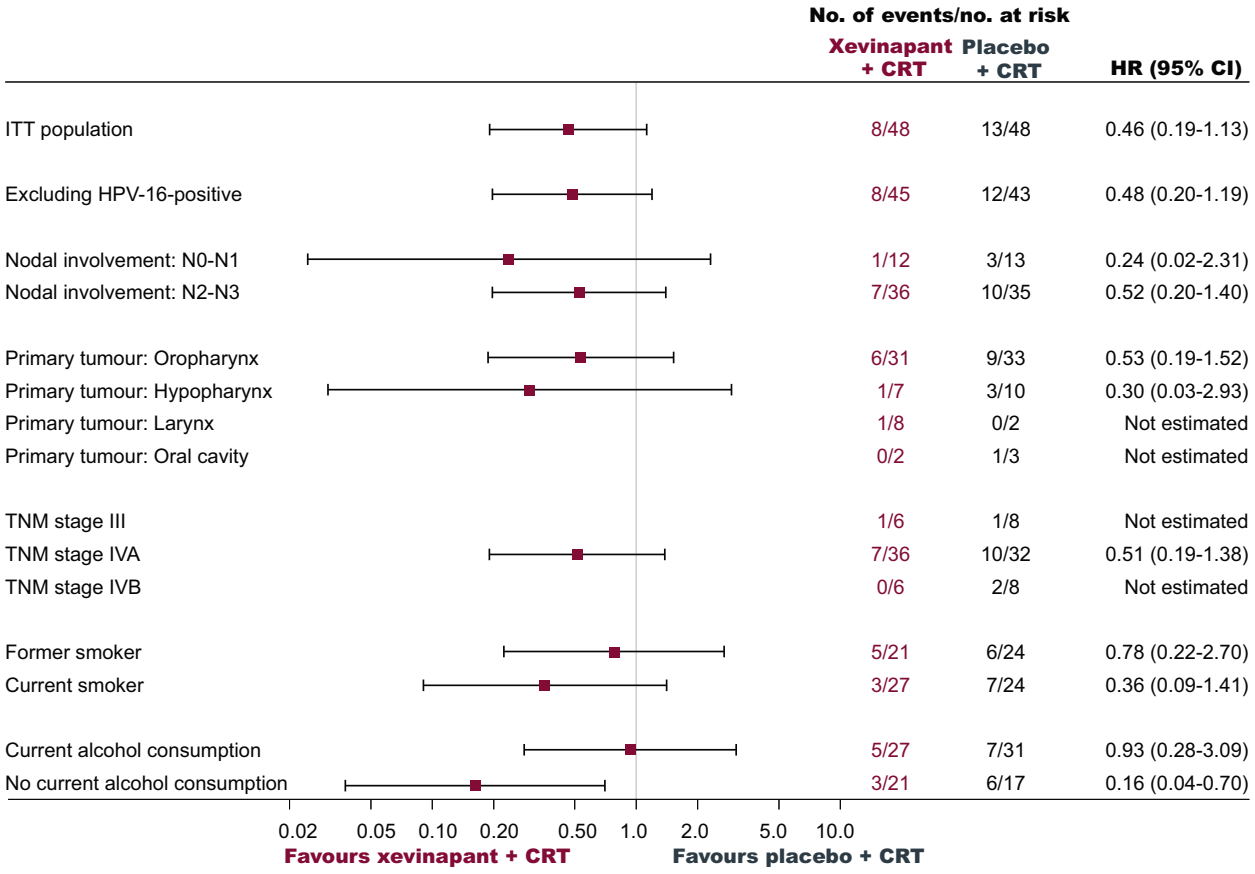

Fig. 4. (Continued).

CRT in patients with unresected LA SCCHN. PFS and DoR were markedly improved in the xevinapant plus CRT arm compared with placebo plus CRT in the 3-year follow-up analyses. Furthermore, the risk of all-cause mortality at 5 years was more than halved with xevinapant plus CRT vs. placebo plus CRT.

The probability of survival in the placebo plus CRT arm was lower than rates seen in some large phase 3 studies [34]. However, it is important to note that patients in this study had high-risk LA SCCHN; all patients were current or former smokers with a high number of pack-years, generally had high alcohol consumption, and a high percentage of patients were stage IVa at screening. Additionally, the majority of patients with oropharyngeal cancer enrolled into the study had HPV-negative disease; only three patients in the xevinapant arm and five patients in the placebo arm had HPV-positive oropharyngeal cancer [33]. The survival rates at 5 years in the placebo plus CRT arm are comparable with survival rates seen with CRT in previously published randomised phase 3 clinical trials of ≈400 patients in similar high-risk populations (5-year survival rates of ≈25%–32% estimated from the Kaplan–Meier curves) [35,36].

Exploratory subgroup analyses showed that the clinical benefit of xevinapant was generally maintained across patient subgroups, including HPV status, smoking status, cancer localisation, nodal involvement, TNM stage, and alcohol consumption status; however, as expected for any exploratory subgroup analysis, the power was insufficient to detect statistically significant differences in many subgroups. Clinical benefit was also demonstrated in patients with HPV-negative oropharyngeal cancer, who accounted for 58% of the patients in the overall study and are known to have a worse prognosis and to be more difficult to treat than patients with HPV-positive oropharyngeal cancer [37]. However, the sample size for this study was relatively small, and very few patients with HPV-positive oropharyngeal cancer were recruited. Therefore, based on the small number of patients with HPV-positive oropharyngeal cancer, it will

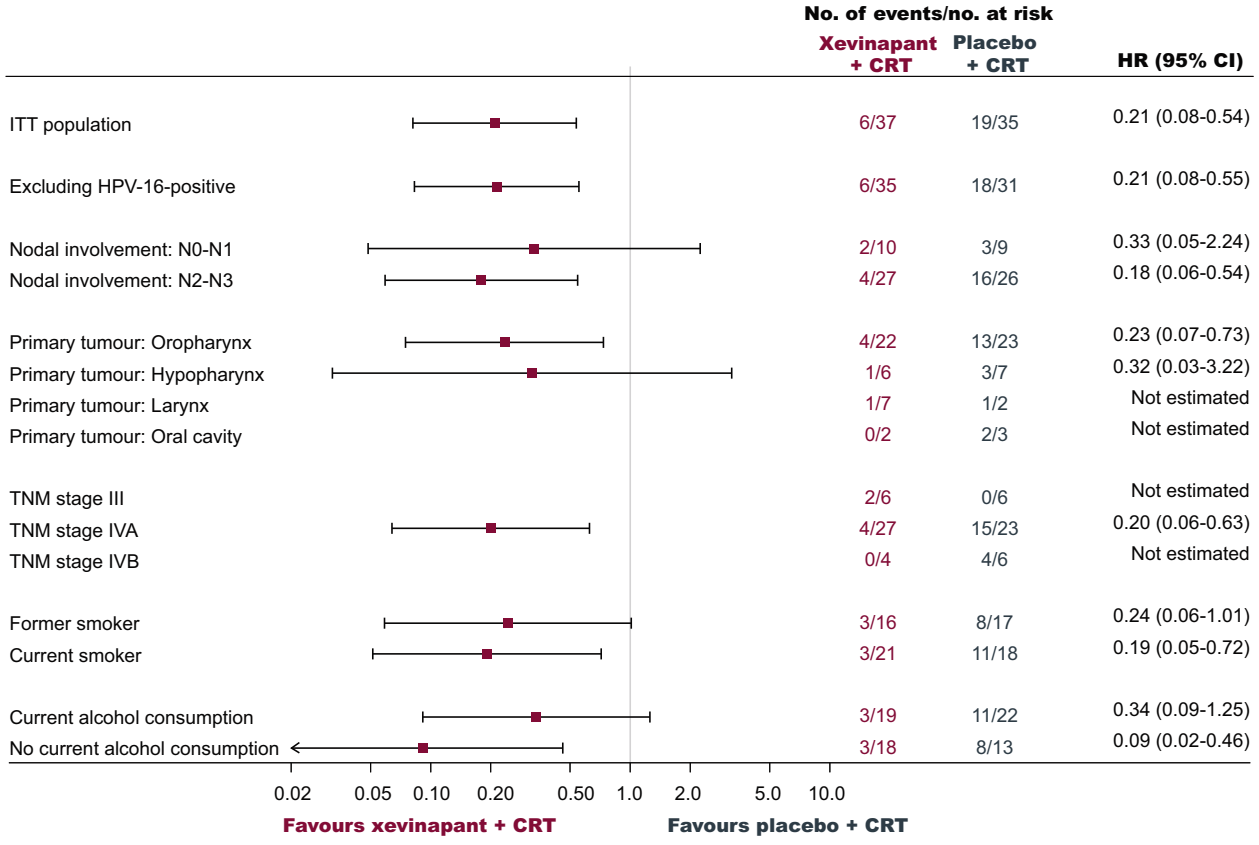

Fig. 4. (Continued).

not be possible to generalise the findings to all patients, and further study will be required to elucidate the effects of xevinapant in a broader population.

The use of xevinapant in combination with high-dose CRT was feasible, with a predictable and manageable safety profile in this patient population [33], and the incidence of late-onset grade ≥3 toxicities was similar across the treatment arms. The most common late toxicities included dry mouth, dysgeusia, and dysphagia, which were predominantly grade 1 or 2 in both treatment arms and are common in patients with SCCHN who receive CRT [38]. Subsequent anticancer therapy varied across the arms; however, it was consistent with SoC in both arms [2,5].

To our knowledge, xevinapant plus CRT is the first regimen to demonstrate superior efficacy vs. SoC CRT in patients with unresected LA SCCHN treated with curative intent, as well as the first to demonstrate proof of concept for the clinical effectiveness of targeting IAPs in a randomised, placebo-controlled phase 2 study. Phase 3 trials evaluating the combination of immune checkpoint inhibitors with CRT have failed to show improved efficacy in comparison with placebo plus CRT in patients with unresected LA SCCHN. Recently, the KEYNOTE-412 trial, evaluating pembrolizumab (anti−PD-1) plus CRT followed by pembrolizumab maintenance, failed to meet its primary end-point of improving event-free survival vs. placebo plus CRT [39]. Similarly, in the JAVELIN Head & Neck 100 trial, avelumab (anti−PD-L1) plus CRT did not improve PFS vs. placebo plus CRT [34]. Additionally, both the phase 3 REACH study (avelumab plus cetuximab and radiotherapy vs. SoC in patients with LA SCCHN fit and unfit for cisplatin) and the phase 2 PembroRad study (pembrolizumab plus radiotherapy vs. cetuximab plus radiotherapy in patients with unresected LA SCCHN) did not meet their primary end-points [40,41].

In conclusion, this randomised phase 2 study of 96 patients is the first in decades to show improved efficacy outcomes vs. SoC CRT in patients with unresected LA SCCHN, treated with curative intent. Xevinapant plus CRT demonstrated clinically meaningful benefits in relation to OS, PFS, and DoR, with no new safety signals, compared with placebo plus CRT. Based on these encouraging data, the addition of xevinapant to SoC may

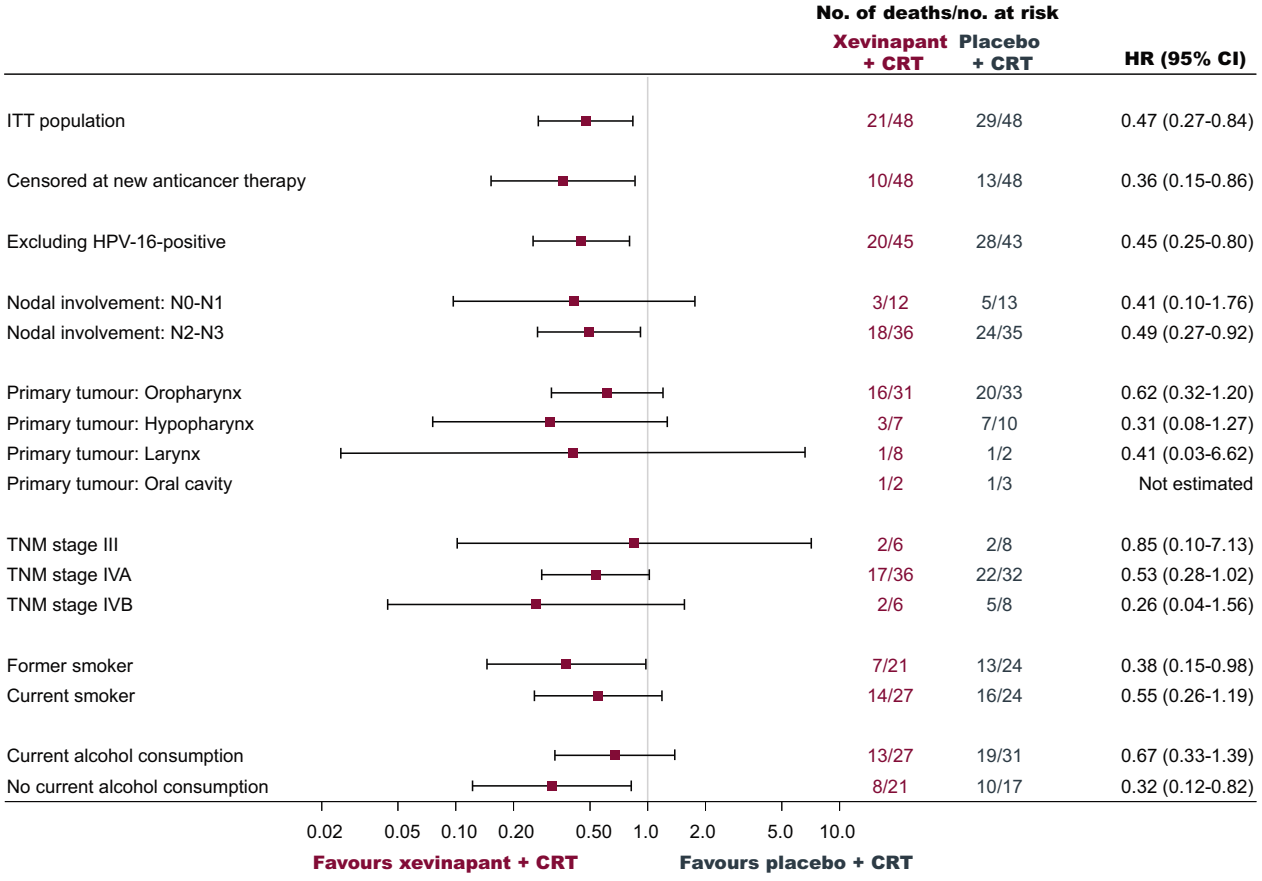

Fig. 4. (Continued).

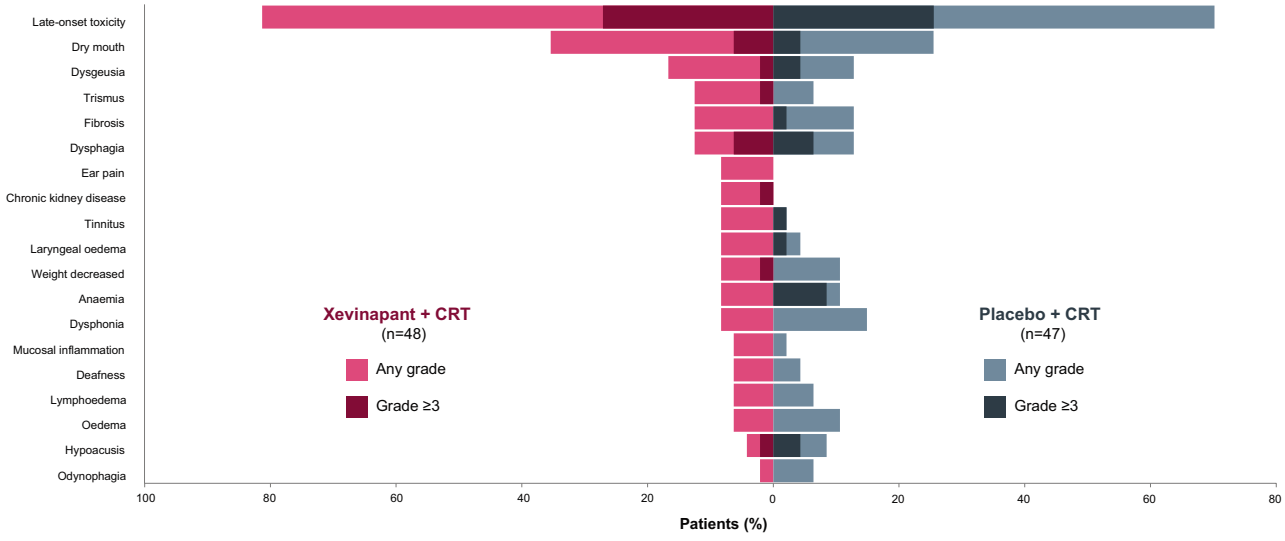

Fig. 5. Late-onset toxicities occurring in ≥5% of patients in the safety population. CRT, chemoradiotherapy.

have the potential to improve cure rates in patients with unresected LA SCCHN. The confirmatory, randomised phase 3 TrilynX study is now recruiting to confirm the efficacy of xevinapant plus CRT vs. placebo plus CRT in patients with unresected LA SCCHN (EudraCT Number: 2020-000377-25; NCT04459715) [42].

Author contributions

Y.T. Data curation, investigation, project administration, writing – original draft, writing – review and editing. X–S.S. Data curation, investigation, project administration, writing – original draft, writing – review and editing. Y.P. Data curation, investigation, project administration, writing – original draft, writing – review and editing. C.L.T. Data curation, investigation, project administration, writing – original draft, writing – review and editing. C.S. Data curation, investigation, project administration, writing – original draft, writing – review and editing. M-C.K. Data curation, investigation, project administration, writing – original draft, writing – review and editing. A.C. Data curation, investigation, project administration, writing – original draft, writing – review and editing. M.A. Data curation, investigation, project administration, writing – original draft, writing – review and editing. B.C. Data curation, investigation, project administration, writing – original draft, writing – review and editing. P.B. Data curation, investigation, project administration, writing – original draft, writing – review and editing. L.M. Data curation, investigation, project administration, writing – original draft, writing – review and editing. J.M. Data curation, investigation, project administration, writing – original draft, writing – review and editing. J-F.R. Data curation, investigation, project administration, writing – original draft, writing – review and editing. J-P.D. Data curation, investigation, project administration, writing – original draft, writing – review and editing. F.C. Data curation, investigation, project administration, writing – original draft, writing – review & editing. F.R. Data curation, investigation, project administration, writing – original draft, writing – review and editing. J.V. Data curation, investigation, project administration, writing – original draft, writing – review and editing. N.M. Data curation, investigation, project administration, writing – original draft, writing – review and editing. O.E. Data curation, investigation, project administration, writing – original draft, writing – review and editing. E.G. Data curation, investigation, project administration, writing – original draft, writing – review and editing. F.N. Data curation, investigation, project administration, writing – original draft, writing – review and editing. C.L. Data curation, investigation, project administration, writing – original draft, writing – review and editing. G.B. Data curation, investigation, project administration, writing – original draft, writing – review and editing. V.C. Data curation, investigation, project administration, writing – original draft, writing – review and editing. L.G. Data curation, investigation, project administration, writing – original draft, writing – review and editing. B.C. Data curation, investigation, project administration, writing – original draft, writing – review and editing. L.D. Project administration, resources, supervision, writing – original draft, writing – review and editing. P.C. Formal analysis, project administration, resources, software, supervision, validation, writing – original draft, writing – review and editing. A.E. Project administration, resources, supervision, writing – original draft, writing – review and editing. K.G. Project administration, resources, supervision, writing – original draft, writing – review and editing. H.N. Project administration, resources, supervision, writing – original draft, writing – review and editing. J.B. Conceptualisation, data curation, investigation, methodology, project administration, writing – original draft, writing – review and editing.

Data sharing statement

Availability of the data underlying this publication will be determined according to Debiopharm's commitment to the European Federation of Pharmaceutical Industries and Associations–Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing. This pertains to scope, timepoint, and process of data access. As such, Debiopharm commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and EU as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the USA and EU regulatory agencies on or after Jan 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help to advance medical science or improve patient care. Information on the Debiopharm criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Debiopharm is not involved in the decisions made by the independent review panel. Debiopharm will take all necessary measures to ensure that patient privacy is safeguarded.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Y.T. has an advisory/consultancy role with and has received honoraria from MSD, Merck and Ipsen; C.L.T. has an advisory/consultancy role with and has received honoraria from BMS, MSD, Merck, AstraZeneca, Nanobiotix, GSK and Roche, and has received honoraria from Rakuten; Y.P. has an advisory/consultancy role with and has received honoraria from MSD, Merck and

BMS; M.-C.K. has an advisory/consultancy role with and has received honoraria from Merck, and Novartis and has an advisory/consultancy role with Merck; P.B. has an advisory/consultancy role with and has received honoraria from Merck, and has an advisory/consultancy role with BMS and Roche; J.-P.D. has an advisory/consultancy role with BMS, Roche, MSD, Novartis and Merck; F.C. has an advisory/consultancy role with Merck, BMS, Lilly and MSD; F.R. has an advisory/consultancy role with Merck, BMS and MSD; N.M. has an advisory/consultancy role with MSD and Merck; L.D., K.C., P.C., A.E., K.G. and H.N. are employees of Debiopharm International; J.B. has an advisory/consultancy role with BMS, MSD, Merck, AstraZeneca, Debiopharm, Roche and Nanobiotix; X.-S.S., C.S., A.C., M.A., L.M., J.M., J.-F.R., J.V., O.E., E.G., F.N., C.L., G.B., V.C., L.G. and B.C. have declared no conflicts of interest.

Funding

This trial was sponsored by Debiopharm. Trial design, data collection, and data analysis were provided by a steering committee that included the authors and employees of the sponsor. Merck KGaA, Darmstadt, Germany, reviewed the manuscript for medical accuracy. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors. Funding for a professional medical writer who helped prepare the manuscript was provided by the healthcare business of Merck KGaA, Darmstadt, Germany. Debiopharm contributed to the design of the study and led the conduct of the study, monitored it, and provided the study drug. Debiopharm, with the authors, also participated in the collection, management, analysis, and interpretation of the data. Employees of Debiopharm are authors of this manuscript and were involved in reviewing and approving the manuscript as well as the decision to submit the manuscript for publication.

Acknowledgements

The authors would like to thank the patients, their families, study investigators, and study personnel across all sites for participating in this study. We also acknowledge contributions from Debiopharm employees Melanie Wirth, Florilene Bouisset, Ezilda Gruet Fagot, Oana Pop, Romain Perroteau, Francesca Peressotti, Nora Meskini, as well as members of the Efficacy and Safety Evaluation Committee. Merck KGaA, Darmstadt, Germany, reviewed the manuscript for medical accuracy. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

In March 2021, Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) gained exclusive rights to develop and commercialize xevinapant worldwide, including in the U.S (https://www.merckgroup.com/en/news/xevinapant-01-03-2021.html).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.12.015.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71:209–49.
[2] NCCN Clinical Practice Guidelines in Oncology. Head and neck cancer. v1. 2022.
[3] Ang KK. Multidisciplinary management of locally advanced SCCHN: optimizing treatment outcomes. Oncologist 2008;13:899–910.
[4] Lee Y-G, Kang EJ, Keam B, Choi J-H, Kim J-S, Park KU, et al. Treatment strategy and outcomes in locally advanced head and neck squamous cell carcinoma: a nationwide retrospective cohort study (KCSG HN13–01). BMC Cancer 2020;20:813.
[5] Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1462–75.
[6] Szturz P, Vermorken JB. Treatment of elderly patients with squamous cell carcinoma of the head and neck. Front Oncol 2016;6:199.
[7] Ionna F, Bossi P, Guida A, Alberti A, Muto P, Salzano G, et al. Recurrent/metastatic squamous cell carcinoma of the head and neck: a big and intriguing challenge which may be resolved by integrated treatments combining locoregional and systemic therapies. Cancers (Basel) 2021;13.
[8] Chow LQM. Head and neck cancer. N Engl J Med 2020;382:60–72.
[9] Argiris A, Harrington KJ, Tahara M, Schulten J, Chomette P, Ferreira Castro A, et al. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. Front Oncol 2017;7:72.
[10] Denaro N, Merlano MC, Russi EG. Follow-up in head and neck cancer: do more does it mean do better? A systematic review and our proposal based on our experience. Clin Exp Otorhinolaryngol 2016;9:287–97.
[11] Ahn JS, Cho SH, Kim OK, Lee JK, Yang DH, Kim YK, et al. The efficacy of an induction chemotherapy combination with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiotherapy in advanced head and neck cancer. Cancer Res Treat 2007;39:93–8.
[12] Porceddu SV, Scotte F, Aapro M, Salmio S, Castro A, Launay-Vacher V, et al. Treating patients with locally advanced squamous cell carcinoma of the head and neck unsuitable to receive cisplatin-based therapy. Front Oncol 2019;9:1522.
[13] Choong N, Vokes E. Expanding role of the medical oncologist in the management of head and neck cancer. CA Cancer J Clin 2008;58:32–53.
[14] Cohen EEW, Bell RB, Bifulco CB, Burtness B, Gillison ML, Harrington KJ, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). J Immunother Cancer 2019;7:184.
[15] Samra B, Tam E, Baseri B, Shapira I. Checkpoint inhibitors in head and neck cancer: current knowledge and perspectives. J Invest Med 2018;66:1023–30.

[16] Ortiz-Cuaran S, Bouaoud J, Karabajakian A, Fayette J, Saintigny P. Precision medicine approaches to overcome resistance to therapy in head and neck cancers. Front Oncol 2021:11.
[17] Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. Cancers 2014;6:1769–92.
[18] Neophytou CM, Trougakos IP, Erin N, Papageorgis P. Apoptosis deregulation and the development of cancer multi-drug resistance. Cancers 2021;13:4363.
[19] Obexer P, Ausserlechner MJ. X-linked inhibitor of apoptosis protein – a critical death resistance regulator and therapeutic target for personalized cancer therapy. Front Oncol 2014;4.
[20] Abbas R, Larisch S. Targeting XIAP for promoting cancer cell death-the story of ARTS and SMAC. Cells 2020;9.
[21] Vucic D. Targeting IAP (inhibitor of apoptosis) proteins for therapeutic intervention in tumors. Curr Cancer Drug Targets 2008;8:110–7.
[22] Schimmer AD. Inhibitor of apoptosis proteins: translating basic knowledge into clinical practice. Cancer Res 2004;64:7183–90.
[23] Dougan SK, Dougan M. Regulation of innate and adaptive antitumor immunity by IAP antagonists. Immunotherapy 2018;10:787–96.
[24] Graber TE, Holcik M. Distinct roles for the cellular inhibitors of apoptosis proteins 1 and 2. Cell Death Dis 2011;2:e135–.
[25] Fulda S, Vucic D. Targeting IAP proteins for therapeutic intervention in cancer. Nat Rev Drug Discov 2012;11:109–24.
[26] Lawrence MS, Sougnez C, Lichtenstein L, Cibulskis K, Lander E, Gabriel SB, et al. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517:576–82.
[27] Rathore R, McCallum JE, Varghese E, Florea A-M, Büsselberg D. Overcoming chemotherapy drug resistance by targeting inhibitors of apoptosis proteins (IAPs). Apoptosis 2017;22:898–919.
[28] Vucic D, Fairbrother WJ. The inhibitor of apoptosis proteins as therapeutic targets in cancer. Clin Cancer Res 2007;13:5995–6000.
[29] Fulda S. Targeting IAP proteins in combination with radiotherapy. Radiat Oncol 2015;10:105.
[30] Cai Q, Sun H, Peng Y, Lu J, Nikolovska-Coleska Z, McEachern D, et al. A potent and orally active antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer treatment. J Med Chem 2011;54:2714–26.
[31] Matzinger O, Viertl D, Tsoutsou P, Kadi L, Rigotti S, Zanna C, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, is TNFα-mediated in head and neck squamous cell carcinoma. Radiother Oncol 2015;116:495–503.
[32] Thibault B, Genre L, Le Naour A, Broca C, Mery E, Vuagniaux G, et al. DEBIO 1143, an IAP inhibitor, reverses carboplatin resistance in ovarian cancer cells and triggers apoptotic or necroptotic cell death. Sci Rep 2018;8:17862.
[33] Sun X-S, Tao Y, Le Tourneau C, Pointreau Y, Sire C, Kaminsky M-C, et al. Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study. Lancet Oncol 2020;21:1173–87.
[34] Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2021;22:450–62.
[35] Geoffrois L, Martin L, De Raucourt D, Sun XS, Tao Y, Maingon P, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: results of the GORTEC 2007-02 phase III randomized trial. J Clin Oncol 2018;36:3077–83.
[36] Tao Y, Auperin A, Sire C, Martin L, Khoury C, Maingon P, et al. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. J Clin Oncol 2018;36:3084–90.
[37] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[38] Ramaekers BL, Joore MA, Grutters JP, van den Ende P, Jong J, Houben R, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. Oral Oncol 2011;47:768–74.
[39] Machiels J, Tao Y, Burtness B, Tahara M, Rischin D, Alves GV, et al. Primary results of the phase III KEYNOTE-412 study: Pembrolizumab (pembro) with chemoradiation therapy (CRT) vs placebo plus CRT for locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). Ann Oncol 2022;33:S808–69.
[40] Bourhis J, Sire C, Tao Y, Martin L, Alfonsi M, Prevost JB, et al. Pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC): results of the GORTEC 2015-01 "PembroRad" randomized trial. Ann Oncol 2020;31(LBA38):S1168.
[41] Bourhis J, Tao Y, Sun X, Sire C, Martin L, Liem X, et al. Avelumab-cetuximab-radiotherapy versus standards of care in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN): randomized phase III GORTEC-REACH trial. Ann Oncol 2021;32(LBA35):S1310.
[42] Bourhis J, Burtness B, Licitra LF, Nutting C, Schoenfeld JD, Omar M, et al. Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase III study design. Future Oncol 2022;18:1669–78.