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5-year overall survival (OS) in patients (pts) with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) treated with xevinapant + chemoradiotherapy (CRT) vs placebo + CRT in a randomized, phase 2 study

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On behalf of the GORTEC investigators

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Disclosures for Dr Bourhis

- Consulting or advisory role: AstraZeneca, BMS, Debiopharm, Merck, MSD, Nanobiotix, and Roche

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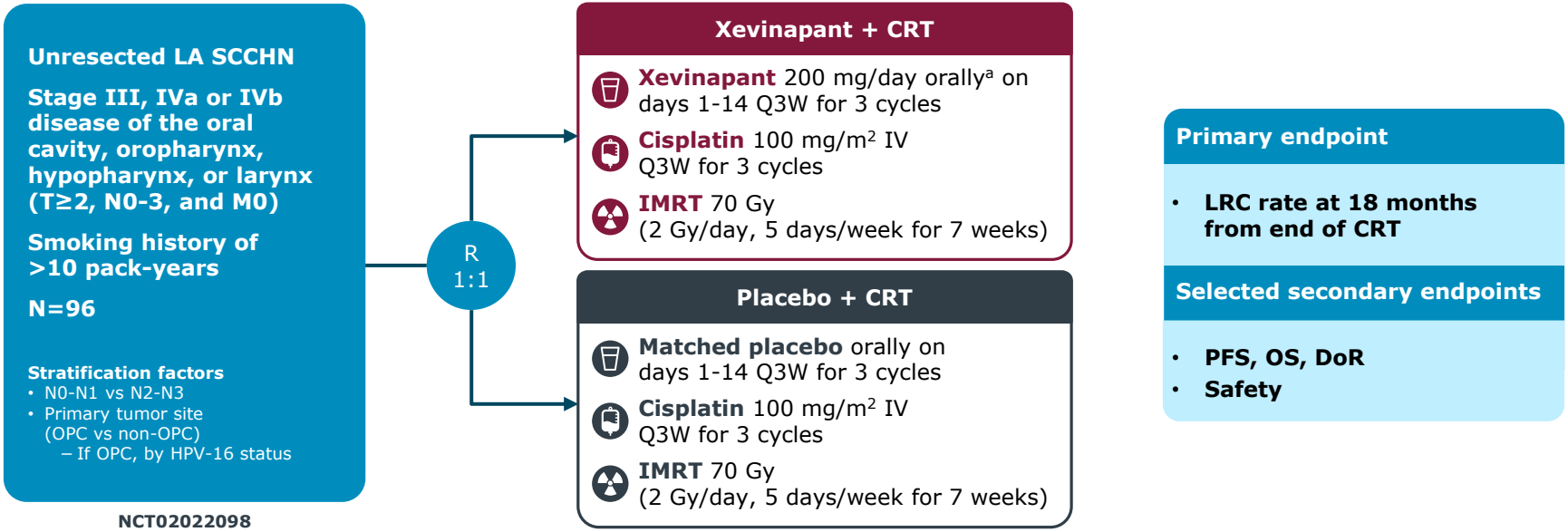
Randomized, double-blind, phase 2 study of xevinapant + CRT vs placebo + CRT in unresected LA SCCHN

- 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 effects of chemotherapy and radiotherapy[1]



[a]The recommended phase 2 dose of xevinapant (200 mg/day) was established in the phase 1 portion of the study[2]

CRT, chemoradiotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; IAP, inhibitor of apoptosis proteins; IMRT, intensity-modulated radiation therapy; IV, intravenous; LA, locally advanced; LRC, locoregional control; OPC, oropharyngeal carcinoma; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; SCCHN, squamous cell carcinoma of the head and neck.

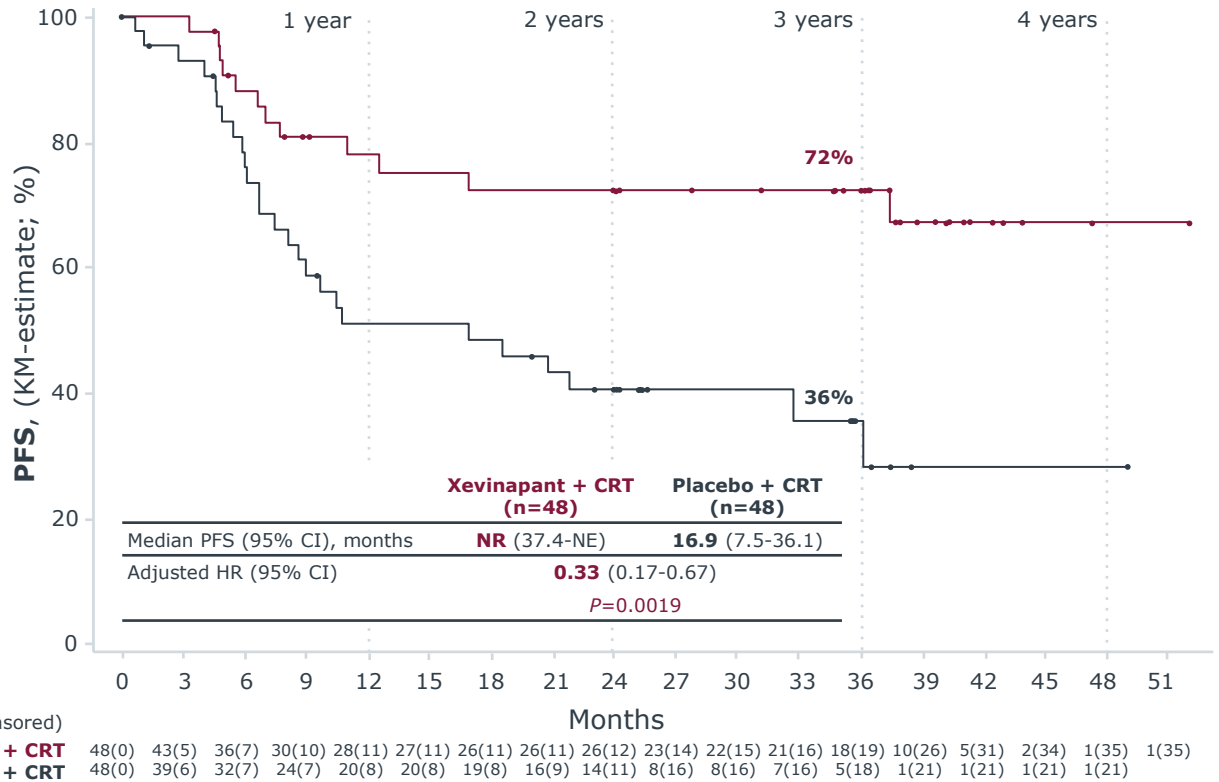
1. Sun XS, et al. *Lancet Oncol*. 2020;21:1173-87; 2. Le Tourneau C, et al. *Clin Cancer Res*. 2020;26(24):6429-36.

Previously reported efficacy results[1,2]

- **Primary endpoint was met:**
  LRC at 18 months after the end of CRT was significantly improved with **xevinapant** vs **placebo**:
  OR 2.74; 95% CI 1.15-6.53, *P*=0.0232

- **Key secondary endpoint:**
  PFS (3-year analysis) was markedly improved with **xevinapant** vs **placebo**

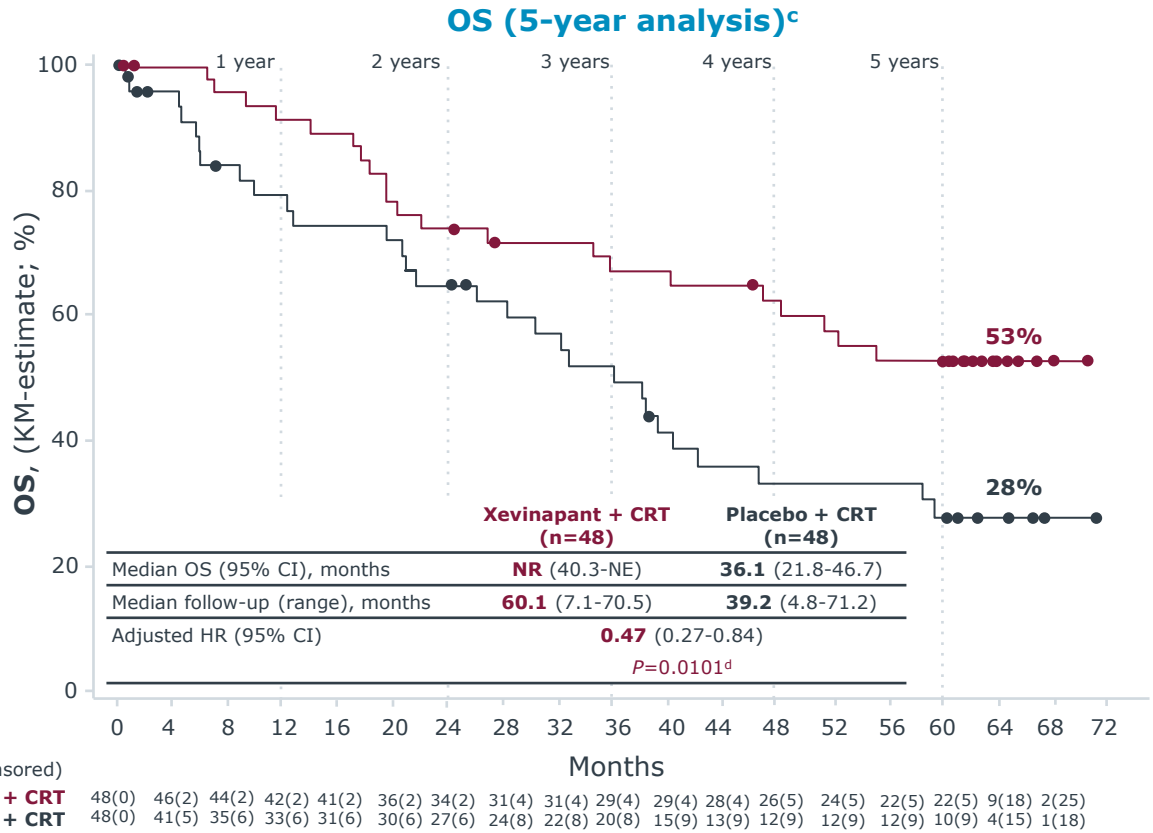
PFS (3-year analysis)[b]



[b]Analyzed 3 years after the last patient started treatment; not multiplicity-controlled (nominal p-value).
CRT, chemoradiotherapy; HR, hazard ratio; LRC, locoregional control; NR, not reached; PFS, progression-free survival.
1. Sun XS, et al. *Lancet Oncol*. 2020;21(9):1173-1187; 2. Bourhis J, et al. *Ann Oncol*. 2020;31:S1168 (abstract LBA 39; oral presentation).

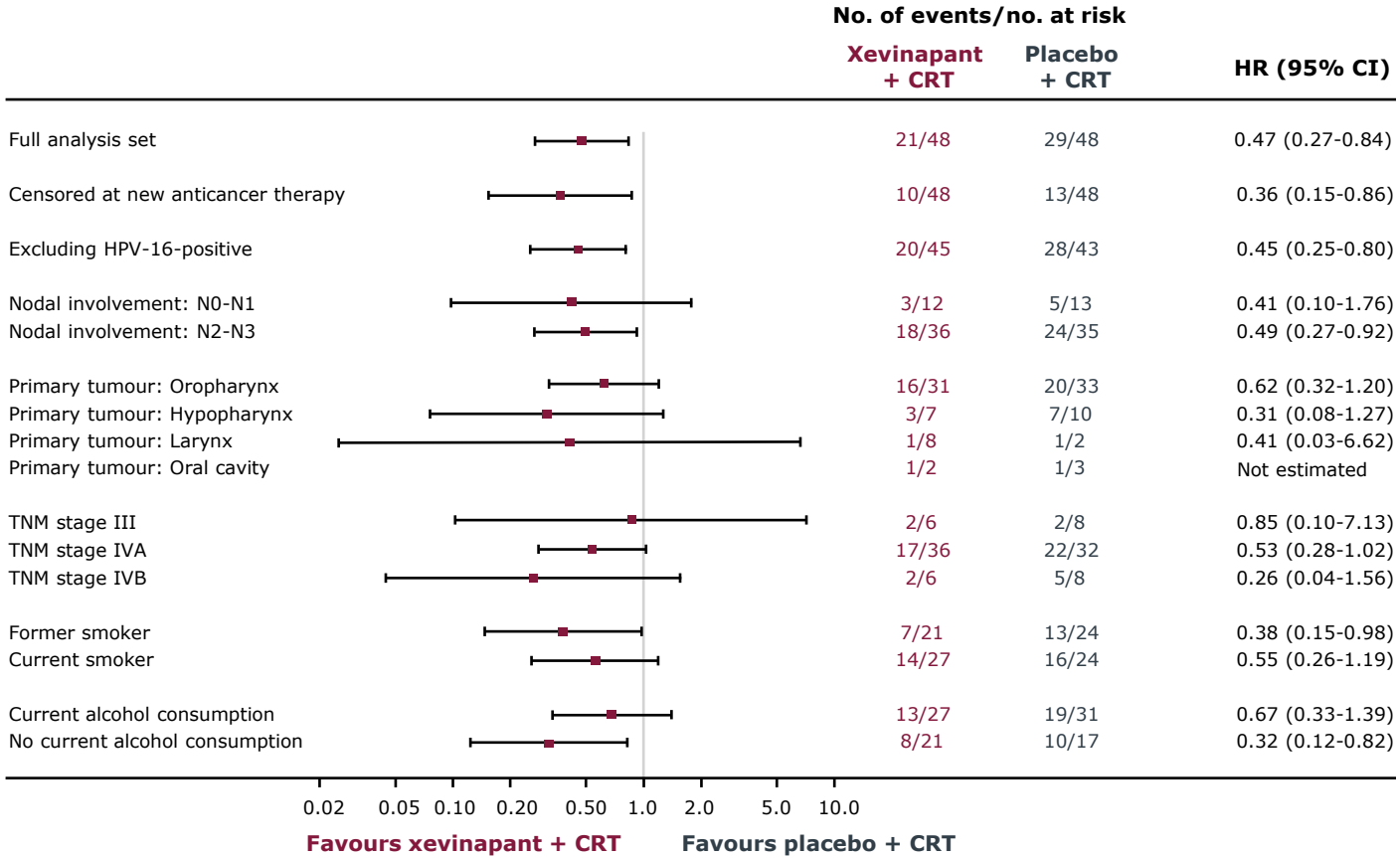
Addition of xevinapant to CRT nearly doubled 5-year OS*

- **The risk of death was more than halved** with **xevinapant** vs **placebo**
- **Median OS prolonged** with **xevinapant** vs **placebo**



*OS probability based on KM-estimate.
[c]Analyzed 5 years after the last patient started treatment; not multiplicity-controlled (nominal p-value). [d]Cox regression analysis adjusted for randomization stratification factors.
CRT, chemoradiotherapy; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival.

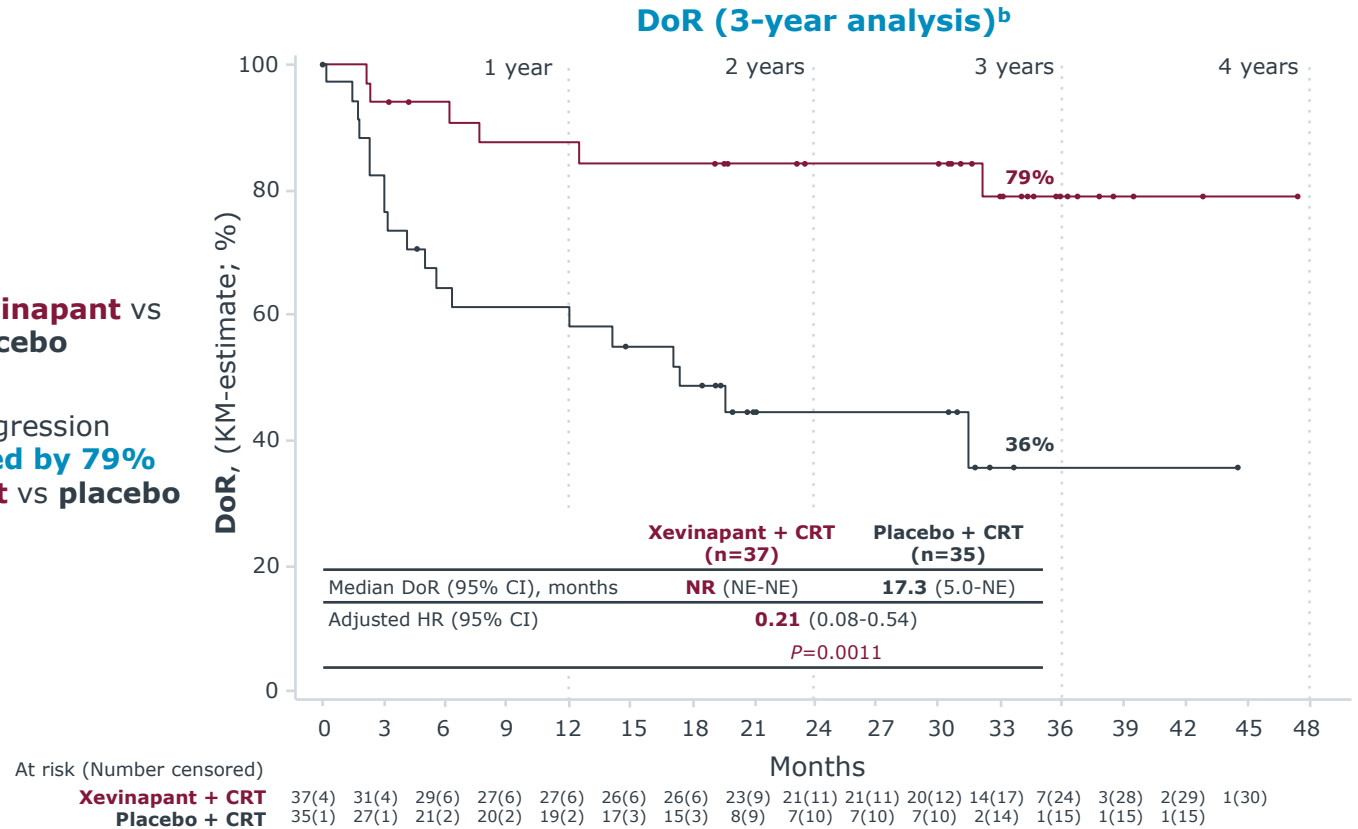
Xevinapant improved OS[c] across all prespecified subgroups



[c]Analyzed 5 years after the last patient started treatment.
CRT, chemoradiotherapy; HPV, human papillomavirus; HR, hazard ratio; OS, overall survival; TNM, tumor-node-metastasis.

DoR was prolonged with the addition of xevinapant to CRT

- **31 CRs** and **6 PRs** with **xevinapant** vs **26 CRs** and **9 PRs** with **placebo**
- Risk of death or disease progression after initial response **reduced by 79% (HR 0.21)** with **xevinapant** vs **placebo**



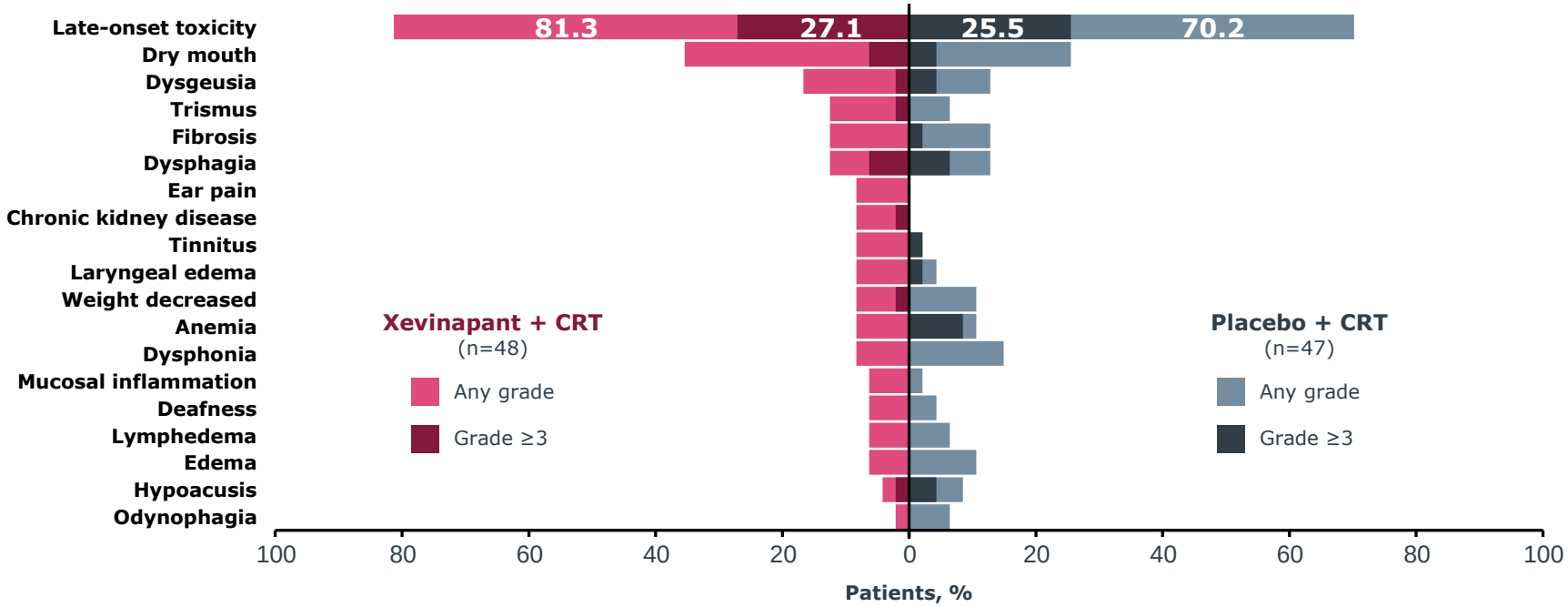
[b]Analyzed 3 years after the last patient started treatment; not multiplicity-controlled (nominal p-value).
CRT, chemoradiotherapy; DoR, duration of response; HR, hazard ratio; NE, not evaluable; NR, not reached.

Subsequent anticancer therapy was consistent with SoC in both arms[e]

	Xevinapant + CRT (n=48)	Placebo + CRT (n=47)
Received subsequent anticancer therapy, n (%)		
Yes	16 (33.3)	19 (40.4)
No	28 (58.3)	22 (46.8)
Unknown	4 (8.3)	6 (12.8)
Type of subsequent anticancer therapy, n (%)	**n=16**	**n=19**
Surgery	5 (31.3)	6 (31.6)
Radiotherapy	6 (37.5)	4 (21.1)
Systemic treatment	12 (75.0)	16 (84.2)
Type of subsequent anticancer medication, n (%)	**n=12**	**n=16**
Chemotherapy	8 (66.7)	8 (50.0)
Cetuximab with or without chemotherapy	8 (66.7)	11 (68.8)
Immune checkpoint inhibitor	5 (41.7)	10 (62.5)

CRT, chemoradiotherapy; SoC, standard of care.
[e]Analyzed in the safety population (all patients treated with ≥1 dose of study drug).

As previously reported, the safety profile, including late-onset AEs, was similar between arms[b,e]



- No patients in the **xevinapant** arm died due to TEAEs vs 2 (4.3%) in the **placebo** arm (asphyxia and multiple organ dysfunction syndrome)
- 8 patients (16.7%) discontinued study treatment prematurely in the **xevinapant** arm vs 7 (14.6%) in the **placebo** arm[b]

AE, adverse event; CRT, chemoradiotherapy; TEAE, treatment-emergent adverse event.
AEs that occurred in ≥5% of patients in either arm in the safety population (all patients treated with ≥1 dose of study drug) are shown.
[b]Analyzed 3 years after the last patient started treatment.
[e]Analyzed in the safety population (all patients treated with ≥1 dose of study drug).

Conclusions

- Adding xevinapant to standard of care CRT markedly improved efficacy outcomes without increasing toxicity
  - **OS** (5-year analysis): **HR, 0.47**; 95% CI, 0.27-0.84, *P*=0.0101
  - **DoR** (3-year analysis): **HR, 0.21**; 95% CI, 0.08-0.54, *P*=0.0011

- The first study in decades to improve the cure rate by adding a new treatment to SoC (cisplatin + RT)

- A confirmatory phase 3 trial is currently recruiting: TrilynX study in patients with unresected LA SCCHN (NCT04459715)[1]

CRT, chemoradiotherapy; DoR, duration of response; HR, hazard ratio; LA, locally advanced; OS, overall survival; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard of care.

1. Bourhis J, et al. *Future Oncol*. 2022;18(14):1669-1678.

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- The trial was sponsored by Debiopharm. In March 2021, Merck (CrossRef Funder ID: 10.13039/100009945) gained exclusive rights to develop and commercialize xevinapant worldwide, including in the United States[1]
- Medical writing support was provided by Sophie Saunders of Clinical Thinking and funded by Merck (CrossRef Funder ID: 10.13039/100009945)
- Merck reviewed the presentation for medical accuracy

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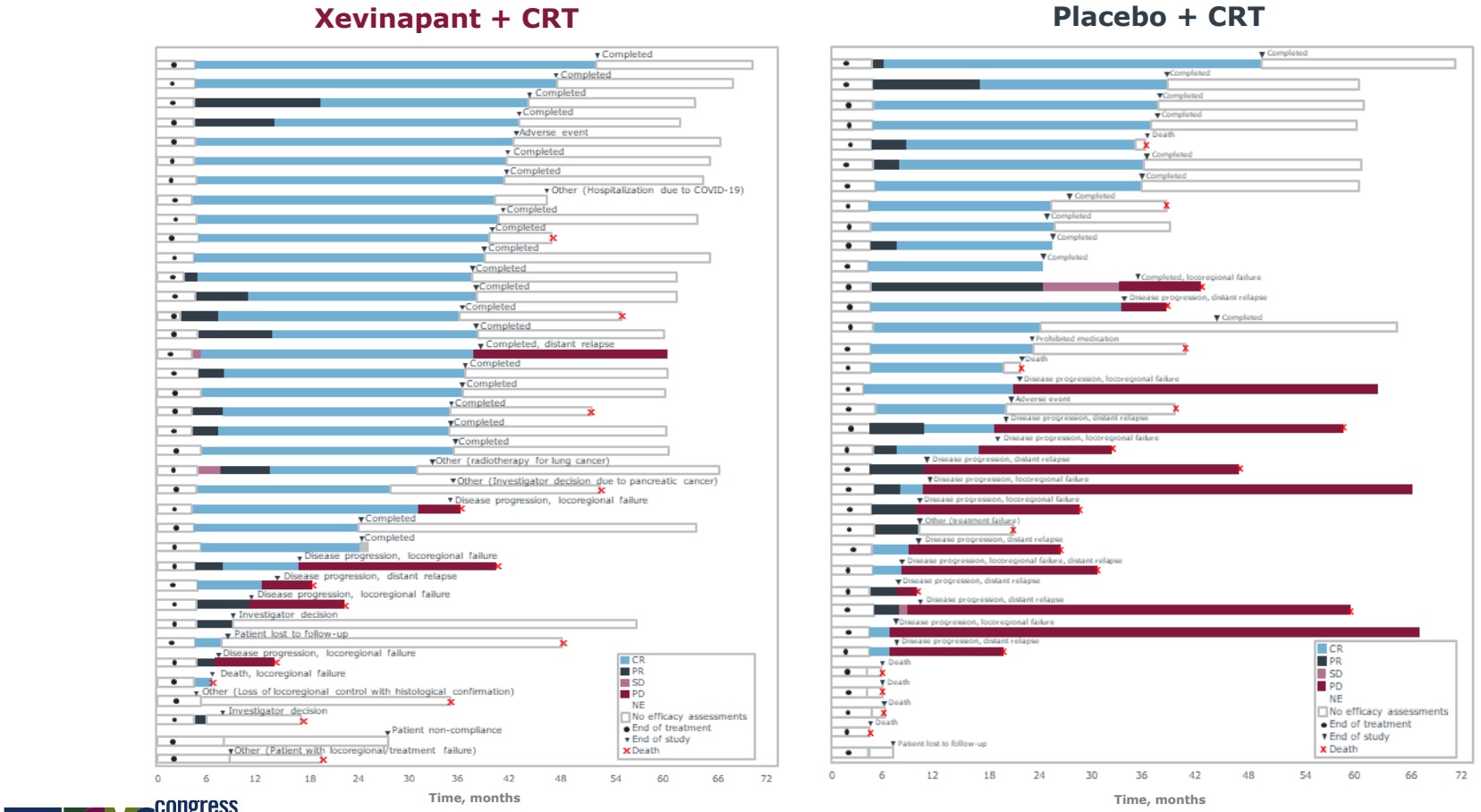
1. Merck Builds on Leadership in Head and Neck Cancer Through Worldwide Licensing Agreement with Debiopharm for Pivotal-Stage Xevinapant. Available at: https://www.merckgroup.com/en/news/xevinapant-01-03-2021.html. Accessed August 2022.

Additional slides

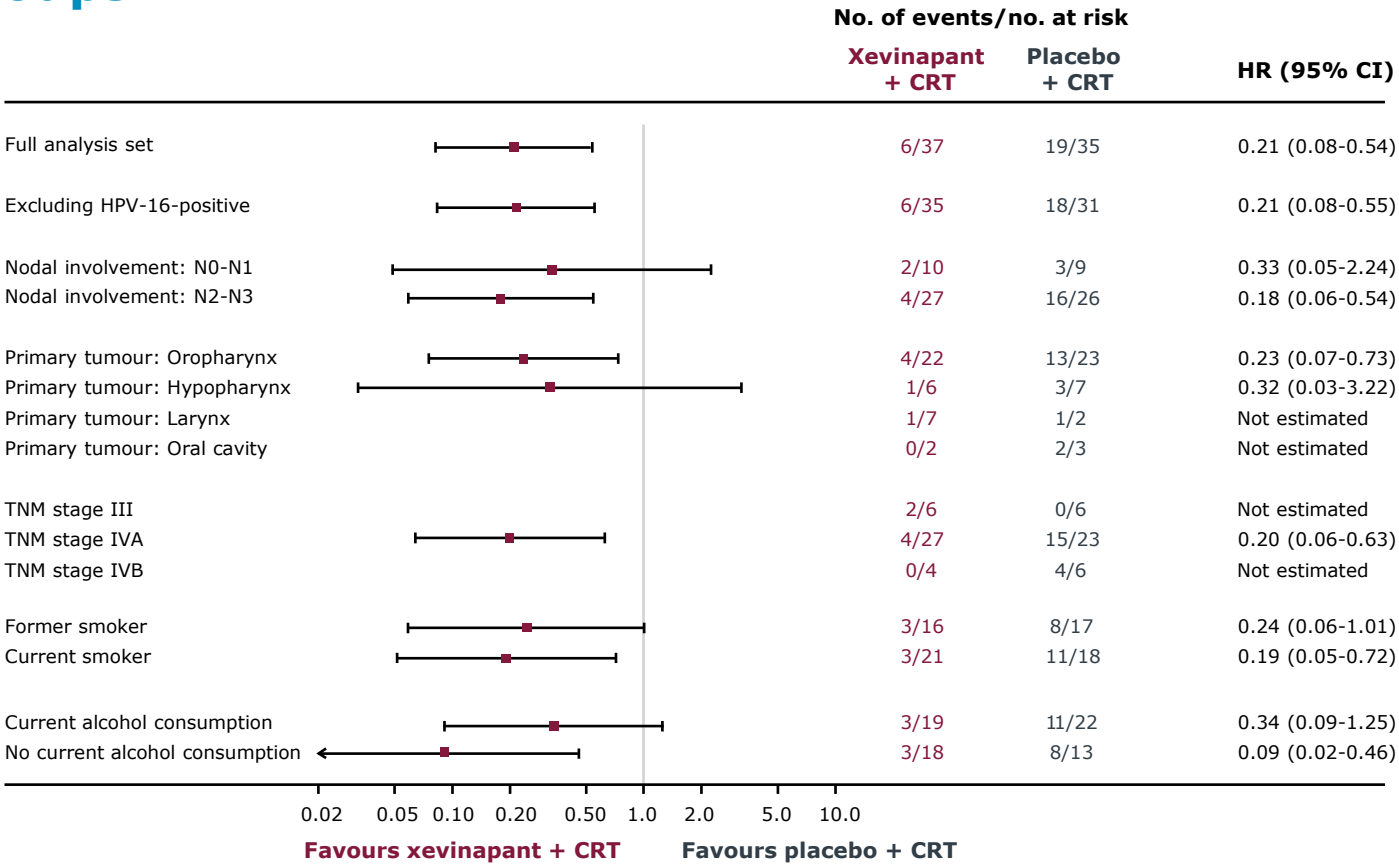
Objective tumor response over time[b]



[b]Analyzed 3 years after the last patient started treatment

CR, complete response; CRT, chemoradiotherapy; ITT, intention-to-treat; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

DoR[b] was prolonged with xevinapant across all prespecified subgroups



[b]Analyzed 3 years after the last patient started treatment.
CRT, chemoradiotherapy; DoR, duration of response; HPV, human papillomavirus; HR, hazard ratio; TNM, tumor-node-metastasis.