Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase 3 study design

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INTRODUCTION

Xevinapant is a first-in-class, potent, small-molecule antagonist of **IAPs**, formulated as an **oral solution**

Xevinapant is designed to **restore sensitivity of cancer cells to apoptosis** and to **enhance the effects of other anticancer treatments**, such as chemotherapy and radiotherapy

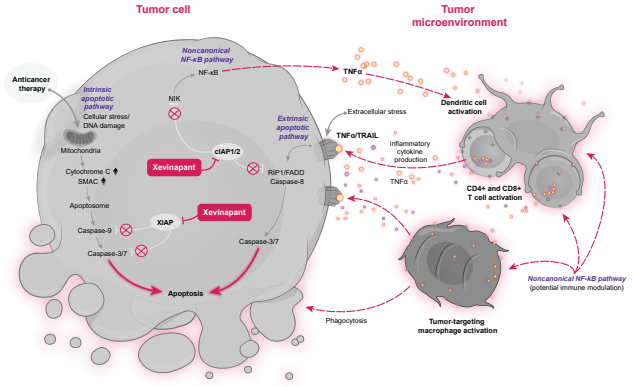

Figure. Xevinapant is a first-in-class, oral, small-molecule antagonist of IAPs that is thought to (1) restore apoptosis in cancer cells by blocking XIAP and cIAP1/2 leading to activation of caspases downstream of the intrinsic mitochondrial and the extrinsic TNF receptor pathway, respectively (2): enhance the inflammatory antitumor response in immune cells of the tumor microenvironment by activating noncanonical NF-κB signaling through blocking of cIAP1/2 downstream of the TNF receptor

CLINICAL EVIDENCE

In a randomized phase 2 study of 96 patients with unresected LA SCCHN, **xevinapant** (previously designated Debio 1143) + CRT significantly increased LRC at 18 months vs **placebo** + CRT[1]

54% in the xevinapant arm had LRC

33% in the placebo arm had LRC

At **3 years of follow-up**, median OS and PFS were significantly improved with **xevinapant** vs **placebo**:[2]

51% **Reduction in risk of death with xevinapant (HR, 0.49; 95% CI, 0.26-0.92; *P*=.0271)**

67% **Reduction in risk of disease progression or death with xevinapant (HR 0.33; 95% CI, 0.17-0.67; *P*=.0019)**

At 3 months, CR rates were ~35% for both arms; at 6 months after completing CRT, the CR rate was **52% for xevinapant** and **38% for placebo[1]**

TRILYNX: STUDY DESIGN AND PATIENTS

TrilynX is a phase 3 trial comparing the efficacy and safety of **xevinapant** + CRT vs **placebo** + CRT in patients with **unresected LA SCCHN**

The TrilynX trial design includes **additional treatment** with **xevinapant** or **placebo** monotherapy for 3 cycles **after the completion of CRT-based treatment**

Histologically confirmed unresected LA SCCHN

Stage III, IVa, or IVb tumor of the oropharynx (HPV-negative), hypopharynx, or larynx

ECOG PS 0-1

N≈700

R 1:1*

Combination treatment
- **Xevinapant** 200 mg/day (days 1-14, Q3W for 3 cycles)
- **Cisplatin** 100 mg/m² Q3W for 3 cycles (day 2)
- **IMRT** 70 Gy (2 Gy/day, 5 days/week for 7 weeks)

Monotherapy
- **Xevinapant** 200 mg/day (days 1-14, Q3W for 3 cycles)

Combination treatment
- **Matched placebo** (days 1-14, Q3W for 3 cycles)
- **Cisplatin** 100 mg/m² Q3W for 3 cycles (day 2)
- **IMRT** 70 Gy (2 Gy/day, 5 days/week for 7 weeks)

Monotherapy
- **Matched placebo** (days 1-14, Q3W for 3 cycles)

Endpoints	
1ary	EFS, defined as time from randomization to the occurrence of death, clinical or radiological progression, primary treatment failure, radiological or clinical relapse after achieving a loco-regional CR, or the occurrence of secondary cancers†
2ary	OS, DOR†, PFS†, ORR†, LRC, safety, HRQOL

*Stratification factors: region (North America vs Western Europe vs rest of the world); primary tumor site (larynx vs other); lymph node involvement (N0-1 vs N2 vs N3); and tumor size (T4 vs other). †Per blinded independent central review according to RECIST 1.1.

Glossary terms: cIAP1/2, cellular IAPs 1 and 2; **CR,** complete response; **CRT,** chemoradiotherapy; **DOR,** duration of response; **ECOG PS,** European Cooperative Oncology Group performance status; **EFS,** event-free survival; **FADD,** fas-associated protein with death domain; **HR,** hazard ratio; **HRQOL,** health-related quality of life; **IAPs,** inhibitor of apoptosis proteins; **IHC,** immunohistochemistry; **IMRT,** intensity-modulated radiotherapy; **LA SCCHN,** locally advanced squamous cell carcinoma of the head and neck; **LRC,** locoregional control; **NF-κB,** nuclear factor kappa-light-chain-enhancer of activated B cells; **NIK,** NF-κB-inducing kinase; **ORR,** objective response rate; **OS,** overall survival; **PFS,** progression-free survival; **Q3W,** every 3 weeks; **RECIST,** Response Evaluation Criteria in Solid Tumors; **RIP1,** receptor interacting serine/threonine kinase 1; **SMAC,** second mitochondria-derived activator of caspase; **TNF,** tumor necrosis factor; **TRAIL,** TNF-related apoptosis-inducing ligand; **XIAP,** X-linked IAP.

References: 1. Sun X-S, et al. Lancet Oncol 2020;21:1173–8. **2.** Tao Y, et al. [Unpublished].