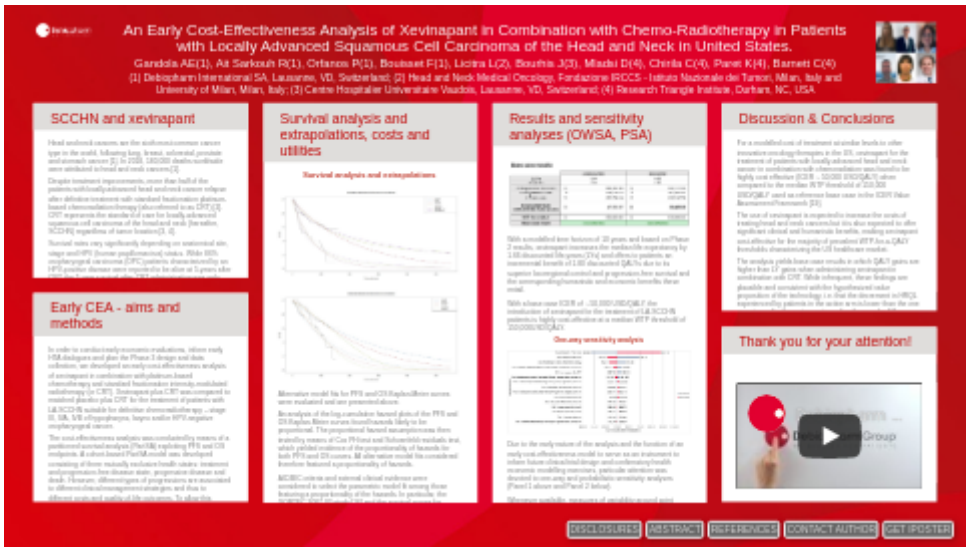
An Early Cost-Effectiveness Analysis of Xevinapant in Combination with Chemo-Radiotherapy in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck in United States.



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PRESENTED AT:

SCCHN AND XEVINAPANT

Head and neck cancers are the sixth most common cancer type in the world, following lung, breast, colorectal, prostate and stomach cancer [1]. In 2018, 180,000 deaths worldwide were attributed to head and neck cancers [1].

Despite treatment improvements, more than half of the patients with locally-advanced head and neck cancer relapse after definitive treatment with standard fractionation platinum-based chemoradiation therapy (also referred to as CRT) [2]. CRT represents the standard of care for locally-advanced squamous cell carcinoma of the head and neck (hereafter, SCCHN) regardless of tumor location [3, 4].

Survival rates vary significantly depending on anatomical site, stage and HPV (human papillomavirus) status. While 86% of oropharyngeal carcinoma (OPC) patients characterized by an HPV-positive disease were reported to be alive at 5-years after CRT, the 5-year survival after CRT administration was only 11% for HPV-negative OPC patients [5].

In addition to an important clinical burden, head and neck cancer is considered as one of the most debilitating types of cancer due to the impact both the disease and available treatments exert on quality of life: patients are impaired in their ability to chew, swallow, talk and breathe due to the surgical resection of their tumors, the administration of chemoradiation therapy or both [6-8].

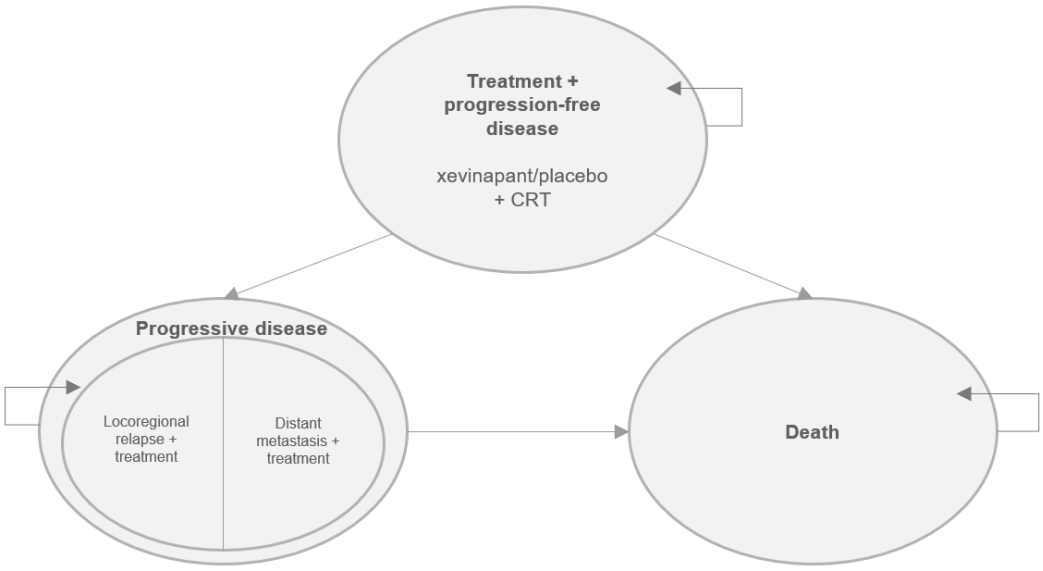
The economic burden associated with SCCHN is substantial and was estimated at 3.64 billion USD in direct medical costs in 2010 in the United States [9], with associated productivity losses reaching a comparable magnitude [10]. The total cost of care for SCCHN has increased significantly since the introduction of PD(L)-1 agents for the treatment of recurrent/metastatic disease [11].

Xevinapant is a first-in-class oral IAP antagonist with the potential to enhance the antitumour activity of chemotherapy and radiotherapy [12]; in a randomized Phase 2 study with LA-SCCHN patients with poor prognosis, the combination of xevinapant with CRT was shown to increase disease control, extend remission and prolong survival compared to CRT alone [12-14], providing the rationale for the ongoing Phase 3 TrilynX study (NCT04459715 (https://clinicaltrials.gov/ct2/show/NCT04459715.)) [15].

EARLY CEA - AIMS AND METHODS

In order to conduct early economic evaluations, inform early HTA dialogues and plan the Phase 3 design and data collection, we developed an early cost-effectiveness analysis of xevinapant in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy (or CRT). Xevinapant plus CRT was compared to matched placebo plus CRT for the treatment of patients with LA-SCCHN suitable for definitive chemoradiotherapy – stage III, IVA, IVB of hypopharynx, larynx and/or HPV-negative oropharyngeal cancer.

The cost-effectiveness analysis was conducted by means of a partitioned survival analysis (PartSA) exploiting PFS and OS endpoints. A cohort-based PartSA model was developed consisting of three mutually exclusive health states: treatment and progression-free disease state, progressive disease and death. However, different types of progressions are associated to different clinical management strategies and thus to different costs and quality-of-life outcomes. To allow this differentiation in utilities and costs, a discrete (time-invariant) split in the patterns of relapse was retrieved from trial data and applied to the overall probability of progressing to obtain conditioned probabilities for locoregional relapses and distant metastases.

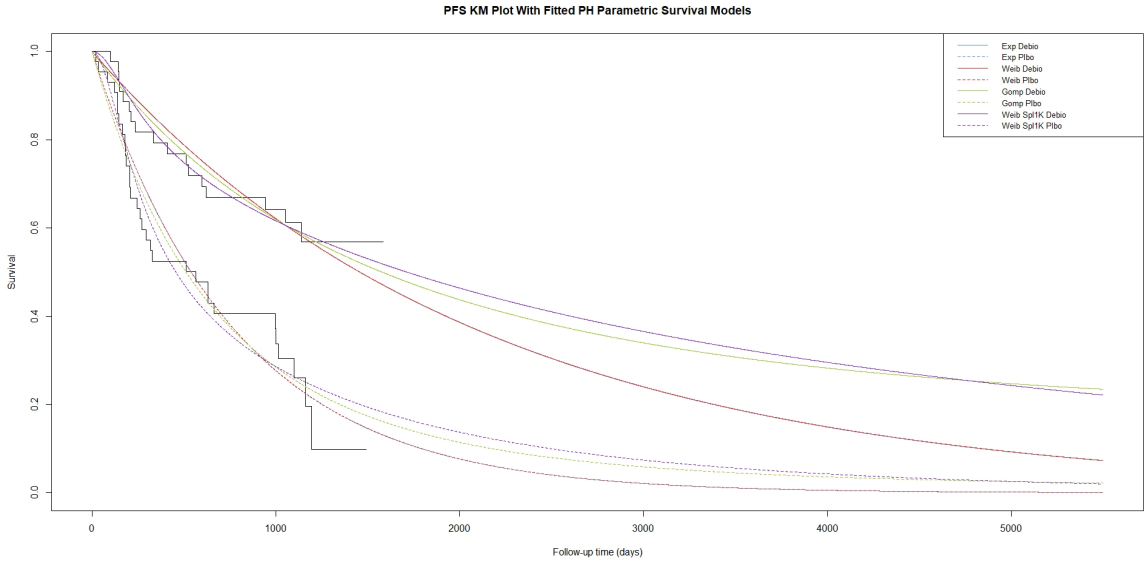


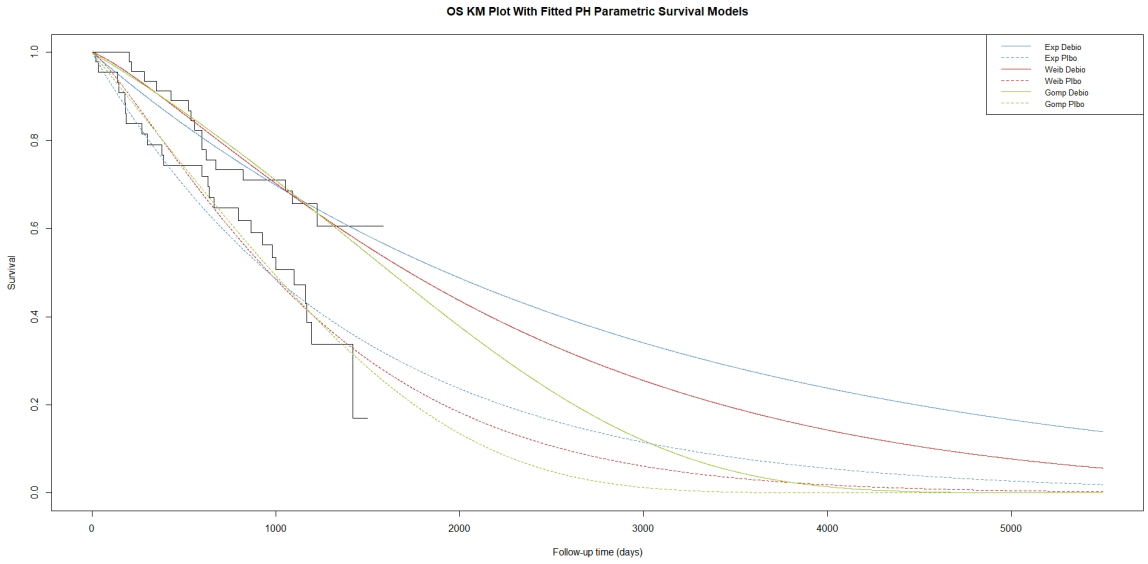
The modelled time horizon chosen was 10 years in order to capture appropriately costs and outcomes characterizing the course of the disease for head and neck cancer patients and their average life expectancy.

Costs in the model were included from the perspective of a US-based third-party payer; model results included incremental costs, LYs, QALYs and incremental costs per QALY gained.

SURVIVAL ANALYSIS AND EXTRAPOLATIONS, COSTS AND UTILITIES

Survival analysis and extrapolations





Alternative model fits for PFS and OS Kaplan-Meier curves were evaluated and are presented above.

An analysis of the log-cumulative hazard plots of the PFS and OS Kaplan-Meier curves found hazards likely to be proportional. The proportional hazard assumption was then tested by means of Cox PH test and Schoenfeld residuals test, which yielded evidence of the proportionality of hazards for both PFS and OS curves. All alternative model fits considered therefore featured a proportionality of hazards.

AIC/BIC criteria and external clinical evidence were considered to select the parametric model fit among those featuring a proportionality of the hazards. In particular, the GORTEC 2007-02 study [16] and the survival curves for oropharyngeal cancer patients from the meta-analysis conducted by Blanchard et al [17] were considered to inform long-term model extrapolations for PFS and OS, respectively, of the control arm.

Time	OS, external evidence [17]	OS, modelled (exponential)	OS, modelled (Weibull)	PFS, external evidence [16]	PFS, modelled (exponential)	PFS, modelled (Weibull)
3y (156W)	~40%	45.53%	44.60%	~35%	24.61%	24.63%
4y (208W)	~35%	35.02%	31.65%	~25%	15.42%	15.44%
5y (260W)	~30%	26.94%	22.01%	~20%	9.67%	9.69%

The Weibull model was selected as the preferred fit for both the within-trial and extrapolated portion of the survival curves; the choice of Weibull fits is also conservative in character, which we consider particularly appropriate for an early model.

Cost and utilities

Future streams of costs and outcomes were discounted at an annual rate of 3% [18]. The base case WTP for a QALY was set at 150,000 USD [19].

HCPCS, CPT and DRG codes billed to the Centers for Medicare and Medicaid Services (CMS) were used to retrieve cost estimates of treatments, medical procedures and hospitalizations in the US, respectively [20, 21]. Due to the early nature of the model, cost items included were limited to cost drivers and expert opinion was sought to confirm their appropriate selection. Costs retrieved in the literature were adjusted to 2020 US dollars by means of the US cumulative inflation rate relative to consumer prices [22].

LA-SCCHN treatment and progression-free disease: probabilities, costs and utility inputs

Probabilities	Frequency		Point estimate	Reference
END	one-off		15%	[23]
Treatment cost inputs	**Frequency**		**Point estimate**	**Reference**
Cisplatin cost	one-off (full treatment)		$ 33.38	J9060 [24]
IMRT[1]	one-off (full treatment)		$ 50,501.00	[22, 25, 26]
MRI[2]	staging, EOT, Q6M during 1-3y, QY thereafter		$ 301.35	CPT 70540 [20]
CT scan[2]	staging, EOT, Q6M during 1-3y, QY thereafter		$ 252.99	CPT 70491 [20]
PET scan (full body)	staging, EOT		$ 1,475.34	CPT 78816 [20]
HPV test[3]	one-off		$ 43.67	CPT Q0091 [20]
END	one-off		$ 1,499.52	CPT 38724 [20]
CVC installation	one-off		$ 1,552.81	CPT 36561 [20]
Cost of SAEs (Gr3-4):	**Frequency**		**Point estimate**	**Reference**
	Xevinapant + CRT	**Placebo + CRT**		
Nausea and vomiting	4.20%	8.50%	$ 2,631.05	Include medication therapy, outpatient visits, procedures and expected hospitalization costs
Anemia	35.40%	23.40%	$ 10,559.78	
Febrile neutropenia	6.30%	4.30%	$ 20,410.87	
Dysphagia and dry mouth	50.00% 2.10%	21.30% 0.00%	$ 13,231.00	
Mucosal inflammation	31.30%	21.30%	$ 16,010.43	
Utilities	**Duration (weeks)**		**Point estimate**	**Reference**
Utility from remission after CRT[4]	until progression		0.970	[51]
Utility from END	until death		0.763	[52]
Utility from nausea and vomiting	1.1		0.788	[53]
Utility for anemia	0.9		0.750	[54]
Utility for febrile neutropenia	1.1		0.990	[51]
Utility for dysphagia and dry mouth	38.0		0.750	[38, 39, 55]
Utility from mucosal inflammation	1.6		0.938	[56]

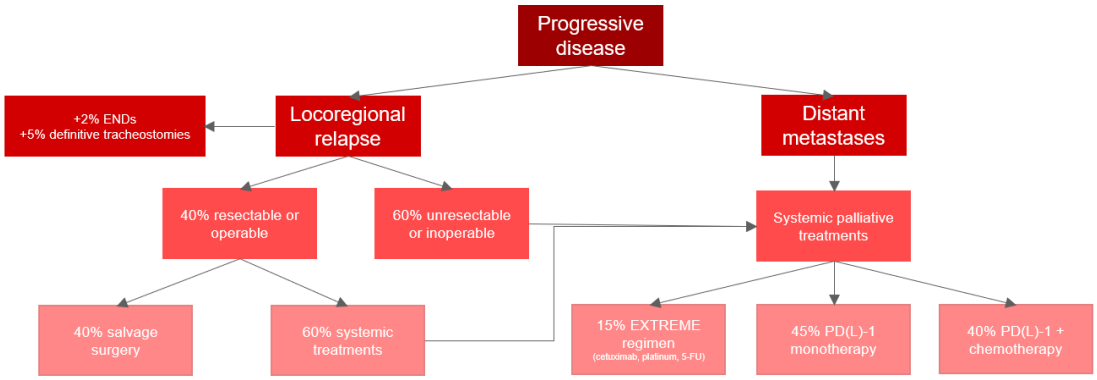
Notes: (1) Inflated to 2020 USD. (2) assumed distribution: 50% imaging using MRI, 50% using CT scans. (3) applies to 65% of patients (oropharyngeal carcinomas). (4) Remission-related scenarios in the vignette study by de Almeida et al. captured the long-term morbidity associated with treatment (some persistent dry mouth, skin thickening, some swallowing issue, occasional concerns about cancer returning)

The cost of toxicity was modelled by considering the incidence of frequent (≥ 20%) treatment-emergent serious adverse events (per CTCAE v4.03 Grade > 2) and corresponding median time to resolution below Grade 2 or recovery. Cost estimates were proposed based on two components: (1) relevant medication therapy, outpatient visits and procedures and (2) expected cost of hospitalization. Clinical management assumptions were retrieved from ESMO clinical guidance practices [35-38], CTCAE v4.03 guidelines [39] or expert opinion.

Utilities associated to SAEs were retrieved from the literature and applied multiplicatively for the median time to resolution below Grade 2 or recovery.

As the 1143-201 trial collected sparse data on the clinical management of patients once a progression was experienced, the different clinical management strategies for relapsing/progressing patients depending on their pattern of disease relapse/progression (loco-regional vs. distant) was retrieved from the literature and validated by expert opinion [41-43]. The conceptual model used to inform the model assumptions on the clinical management of progressive diseases and the corresponding costs and utilities is presented below.

Utility estimates were derived from the SCCHN-specific studies as much as possible [27-34, 44, 45]. Utility from remission after CRT and from elective neck dissections (END) were retrieved from a Vignette and a TTO study, respectively. Utility estimates for loco-regional relapses, distant relapses and definitive tracheostomies were derived from studies featuring EQ-5D administration. Utilities associated to definitive tracheostomies and ENDs are applied multiplicatively to the progressive disease states.



Progressive disease: probabilities, costs and utility inputs

Progression pattern split	xevinapant + CRT	Placebo + CRT	Reference
Loco-regional relapse, given a progression	40.0%	47.4%	trial data
Distant metastasis, given a progression	60.0%	52.6%	trial data
Frequency of medical procedures	**xevinapant + CRT**	**Placebo + CRT**	**Reference**
Salvage surgery following loco-regional relapse	17.2%	17.2%	[41-43]; Expert opinion
Subsequent systemic treatments following loco-regional relapse	22.8%	22.8%	[41-43]; Expert opinion
END following loco-regional relapse	2.0%	2.0%	[42]; Expert opinion
Definitive tracheostomy	5.0%	5.0%	Expert opinion
Cost inputs	**Frequency**	**Point estimate**	**Reference**
Laryngectomy (total)	one-off	$ 3,174.01	[20] (CPT 31365)
Laryngopharyngectomy (total)	one-off	$ 2,926.14	[20] (CPT 31390)
Pharyngectomy (total)	one-off	$ 1,471.73	[20] (CPT 42890)
Laryngo- and pharyngoplasty	one-off	$ 3,083.86	[20] (CPT 31395)
Subsequent systemic treatments	weekly, until death	$ 3,140.39	[24], (J9299, J9271, J9055)
END post-progression	one-off	$ 1,499.52	[20] (CPT 38724)
Definitive tracheostomy	one-off	$ 149.41	[20] (CPT 31500)
Utilities	**Duration of disutility (weeks)**	**Point estimate**	**Reference**
END	until death	0.763	[28]
Loco-regional relapse + salvage surgeries (all types)	until death	0.620	[44]
Distant metastasis + subsequent treatment	until death	0.642	[45]
Definitive tracheostomy	until death	0.780	[44]

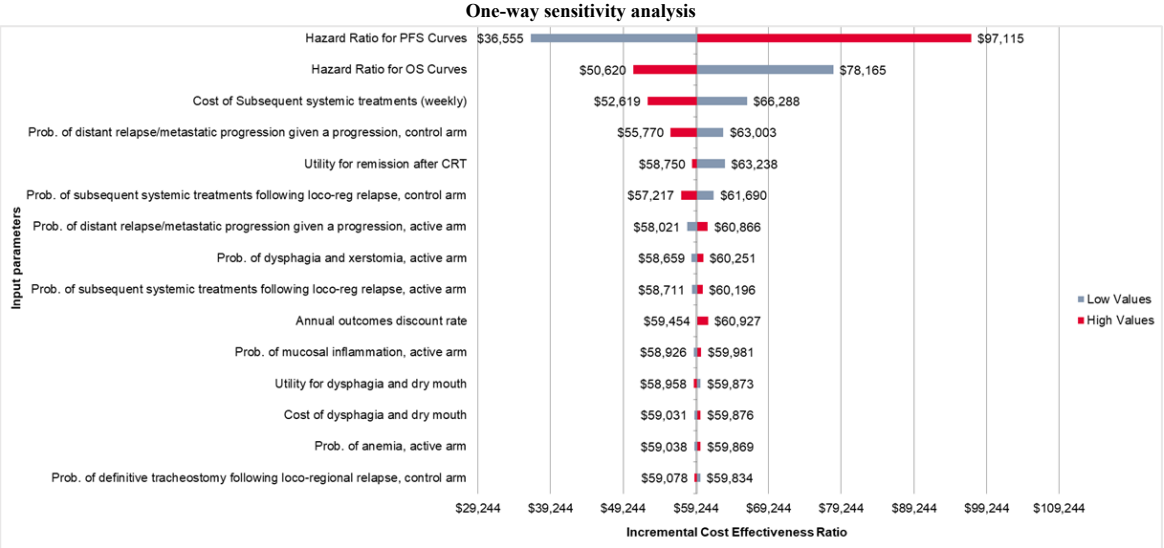
RESULTS AND SENSITIVITY ANALYSES (OWSA, PSA)

Base case results

	undiscounted	*discounted*
Δ LYs	1.94	1.66
Δ QALYs	2.09	1.80
Δ Progression-free costs	$ 168,384.89	$ 168,217.68
Δ Progression costs	$ -68,030.76	$ -61,400.95
Δ Total costs	$ 100,354.14	$ 106,816.74
Incremental Cost-Effectiveness Ratio (ICER)	$ 47,956.07	**$ 59,453.56**
WTP for a QALY	$ 150,000.00	$ 150,000.00
Base case result	cost-effective	cost-effective

With a modelled time horizon of 10 years and based on Phase 2 results, xevinapant increases the median life expectancy by 1.66 discounted life-years (LYs) and offers to patients an incremental benefit of 1.80 discounted QALYs due to its superior locoregional control and progression-free survival and the corresponding humanistic and economic benefits these entail.

With a base case ICER of ~50,000 USD/QALY, the introduction of xevinapant for the treatment of LA-SCCHN patients is highly cost-effective at a median WTP threshold of 150,000USD/QALY.



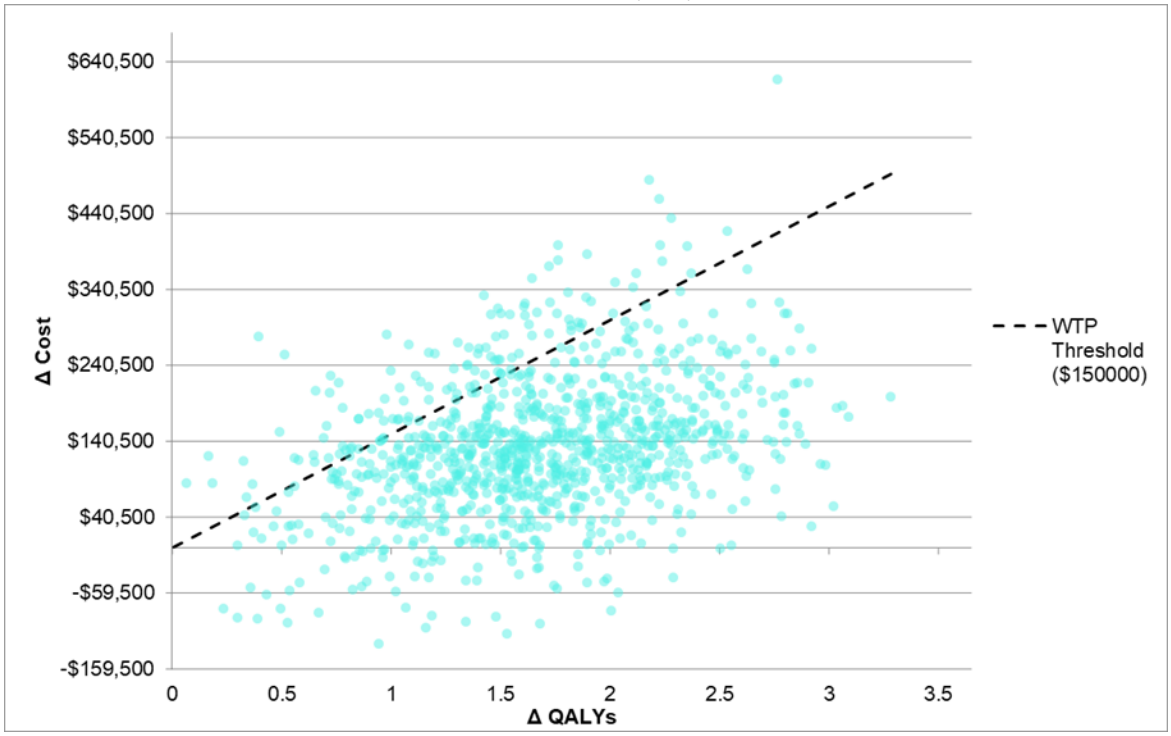
Due to the early nature of the analysis and the function of an early cost-effectiveness model to serve as an instrument to inform future clinical trial design and confirmatory health economic modelling exercises, particular attention was devoted to one-way and probabilistic sensitivity analyses (Panel 1 above and Panel 2 below).

Whenever available, measures of variability around point estimates reported in literature sources were used. Where unavailable, a 20% variation was assumed for all cost inputs and a 5-point variation was assumed for all probabilities and utility estimates.

Following measures of xevinapant efficacy, the third most important variable in terms of base case ICER impact is represented by the cost of subsequent systemic treatments. This finding is consistent with the literature and with the economic value proposition of xevinapant: by keeping patients in loco-regional control and avoiding disease progressions, xevinapant allows payers to avoid incurring the significant expenses generated by PD(L)-1 and EGFR agents. Such agents are used for the palliative treatment of SCCHN patients not eligible for salvage surgery or experiencing a distant relapse or metastatic progression.

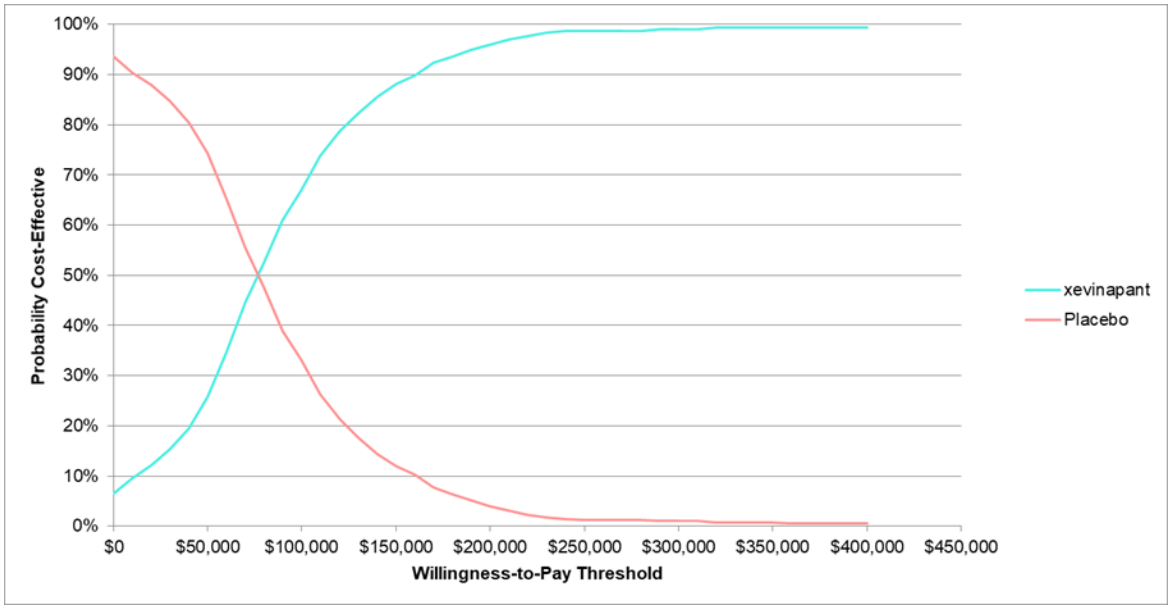
In addition, the cost-effectiveness of xevinapant critically depends on the quality of life experienced by patients who are progression-free after definitive treatment; a utility of 0.97 served as a base case estimate to reflect the long-term morbidity associated with treatment with chemoradiotherapy (notably xerostomia, skin thickening, swallowing issues and psychological concerns about a potential relapse) [27]. Ensuring that the HRQL experienced by patients who are progression-free after treatment with xevinapant + CRT will be non-inferior compred to standard CRT alone will play a paramount role in determining the cost-effectiveness profile of the drug on top of its importance for patients and societies at large.

Probabilistic sensitivity analysis



Gamma distributions were assumed for all cost inputs and SAE durations while beta distributions were assumed for probabilities, rates and utilities.

For 1,000 PSA iterations, 88% of ICERs continue to be below the median WTP of 150,000 USD/QALY, thereby reinforcing the robustness of the base case results obtained.



The cost-effectiveness acceptability curves (CEAC) are reported above. At the lowest WTP threshold of 50,000 USD/QALY for the US healthcare system, the probability of xevinapant to be cost-effective is 25.7%. The probability of cost-effectiveness increases to 67% for a WTP threshold of 100,000 USD/QALY and raises to 88.1% for the median WTP threshold of 150,000 USD/QALY. These results underline the potential of xevinapant to be a highly cost-effective treatment for the vast majority of US third party payers.

DISCUSSION & CONCLUSIONS

For a modelled cost of treatment at similar levels to other innovative oncology therapies in the US, xevinapant for the treatment of patients with locally-advanced head and neck cancer in combination with chemoradiation was found to be highly cost effective (ICER ~50,000 USD/QALY) when compared to the median WTP threshold of 150,000 USD/QALY used as reference base case in the ICER Value Assessment Framework [19].

The use of xevinapant is expected to increase the costs of treating head and neck cancers but it is also expected to offer significant clinical and humanistic benefits, making xevinapant cost-effective for the majority of prevalent WTP-for-a-QALY thresholds characterizing the US healthcare market.

The analysis yields base case results in which QALY gains are higher than LY gains when administering xevinapant in combination with CRT. While infrequent, these findings are plausible and consistent with the hypothesized value proposition of the technology, i.e. that the decrement in HRQL experienced by patients in the active arm is lower than the one experienced in the xevinapant arm (in other words: $LY_x - QALY_x < LY_{CRT} - QALY_{CRT}$ where x=xevinapant). While cure rates were not explored in order to maintain a conservative approach, a utility of 0.970 was hypothesized for patients remaining in the progression-free health state after treatment with CRT with or without xevinapant, thereby generating a limited HRQL adjustment for the high proportion of patients that remain progression-free in the active arm compared to the control arm. In addition, a higher proportion of patients in the control arm compared to the active arm experience progressions that are locoregional in nature, often requiring mutilating surgeries and characterized by a lower utility compared to systemic palliative treatments. This finding is thus consistent with the literature on the sizable humanistic burden characterizing head and neck cancer patients experiencing locoregional relapses.

Lastly, the use of xevinapant is expected to reduce progression costs because, by increasing locoregional control of the disease and progression-free survival, less patients would need to be treated with humanistically and economically burdensome palliative treaments (based on PD(L)-1 and EGFR agents) and/or radical salvage surgeries.

Strengths and limitations

- The main strength is represented by the conservative approach used in the model, reflected in the choice of Weibull functions as model fits, the modelled time horizon and the choice of progression cost inputs, limited to cost drivers. A lifetime horizon and exploitation of alternative fits (e.g., Gompertz or spline models) would enhance the relative benefit of xevinapant and demonstrate higher cost-effectiveness. Due to our conservative approach and length of trial follow-up, a 10-year horizon was considered as the most appropriate at this stage.
- An important limitation is represented by the use of a time-invariant split in the patterns of relapse used for utilities and costs attributions. The clinical complexity of progressive head and neck cancer calls for the flexibility provided by a Markov model, which would have allowed the inclusion of time-varying probabilities of different types of relapses and of different treatment choices depending on the disease and patient characteristics.
- An additional limitation of the model is represented by its extensive use of expert opinion, especially on the frequency of post-progression treatment strategies, which were assumed equivalent across treatment arms with a conservative intent. A thorough HRU research has been included as exploratory endpoint of the Phase 3 (TrilynX) study also with the purpose of overcoming the limitations of the current literature and produce trial-based data on the clinical management of progressive disease, their outcomes and capture any potential cross-arm differences in this respect.
- A similar limitation characterizes the utility estimates included in this analysis. The Phase II trial from which PFS and OS curves were derived did not feature the inclusion of PRO instruments and the available literature on preference-based measures and the range of health states described is scarce. To overcome this limitation, a thorough HRQL research strategy was included in the design of the Phase 3 (TrilynX) study.

Overall, the limitations featuring the current CEA are considered in line with its early nature as well as with the role of early models as instruments to signal HEOR evidence generation needs for future clinical development phases [46-48].

Conclusions

This early cost-effectiveness analysis based on Phase 2 efficacy evidence extrapolated to 10 years suggests that xevinapant can be classified as a high-value treatment with an ICER around 50,000 USD/QALY, thus offering superior cost-effectiveness potential compared to any other innovative therapy in this therapeutic area. Xevinapant has the potential to be a highly cost-effective treatment for the vast majority of US third-party payers.

THANK YOU FOR YOUR ATTENTION!

[VIDEO] https://www.youtube.com/embed/zRiNGq82WkQ?rel=0&start=4&fs=1&modestbranding=1&rel=0&showinfo=0

Acknowledgements

We thank the patients, their families, study investigators, and study personnel across all sites for participating in the Debio 1143-201 study.

The authors would also like to sincerely thank our colleagues from Debiopharm International SA who provided insights and expertise greatly supporting the research conducted, namely Nicolas Favre, Heidi Nauwelaerts, Abdallah Ennaji and Kathrin Gollmer.

Abbreviations

AIC: Akaike Information Criterion; BIC : Bayesian Information Criterion; CEAC: cost-effectiveness acceptability curves; CMS: Centers for Medicare and Medicaid Services; CPT: Common Procedural Terminology; CRT: chemoradiotherapy; CTCAE: Common Terminology Criteria for Adverse Events; DRG: Diagnosis-related groups; END: elective neck dissection; ESMO: European Society for Medical Oncology; HCPCS: Healthcare Common Procedure Coding System; HRQL: Health-related Quality of Life; HRU: Healthcare Resource Utilization; HPV: human papillomavirus; IAP: Inhibitor of apoptosis proteins; ICER: Incremental cost-effectiveness ratio; ICER: Institute for Clinical and Economic Review; LA-SCCHN: locally-advanced squamous cell carcinoma of the head and neck; LYs: life years; OS: overall survival; OWSA: one-way senstivity analysis; PD(L)-1: programmed death ligand-1; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; TTO: time trade-off; WTP: willigness to pay.

DISCLOSURES

This research was funded by Debiopharm International SA.

A.E.G.,R.A.S., P.O. and F.B. are employed by Debiopharm International SA.

L. L. recevied grants/research supports from Astrazeneca, BMS, Boehringer Ingelheim, Celgene International, Debiopharm International SA, Eisai, Exelixis inc, Hoffmann-La Roche ltd, IRX Therapeutics inc, Medpace inc, Merck–Serono, MSD, Novartis, Pfizer, Roche. L.L. recieved honoraria or consultation fees from Astrazeneca, Bayer, BMS, Eisai, MSD, Merck–Serono, Boehringer Ingelheim, Hoffmann-La Roche ltd, Novartis, Roche, Debiopharm International SA, Sobi, Ipsen, Incyte Biosciences Italy srl, Doxa Pharma, Amgen, Nanobiotics Sa and GSK.

J.N. recieved honoraria or consultation fees from Merck, MSD, Astra Zeneca, BMS, Debiopharm International SA

D.M., C.C., K.P. and C.B. received honoraria from Debiopharm International SA.

ABSTRACT

An EARLY Cost-Exectiveness Analysis of Xevinapant in Combination with Chemo-Radiotherapy in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck in United States.

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OBJECTIVES : To assess the cost-effectiveness of xevinapant in combination with cisplatin-based chemoradiotherapy (CRT) compared to CRT in the treatment of patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) from the perspective of a US third-party payer.

METHODS : A partitioned survival model including progression-free survival, progressive disease (segmented in locoregional or distant relapse) and death health states was used, to estimate the cost-effectiveness of xevinapant plus CRT compared to CRT alone, using time to event data from the Debio 1143-201 phase II, randomized, double-blind, placebo-controlled trial. Weibull distributions were chosen to model PFS and OS, based on optimal statistical and visual fit criteria as well as external
clinical evidence. Utility weights for each health state and prominent adverse events were derived from the literature. Disease management resource use estimates were retrieved from Centers for Medicare and Medicaid Services (CMS) data and epidemiological sources. The analysis assumed a 10-year time horizon and a 3% discount rate for both costs and effects. Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of results.

RESULTS : Xevinapant increases median life expectancy by 1.66 life years (LY) and offers to patients an incremental benefit of 1.80 discounted quality adjusted life years (QALY), due to its superior locoregional control and PFS. Assuming a cost of treatment at similar levels to other innovative oncology therapies in US, the estimated basecase incremental cost-effectiveness ratio (ICER) was approximately US$ 50,000/QALY. Sensitivity analyses confimed the robustness of the ICER variation.

CONCLUSIONS : Even with a conservative scenario featuring Weibull parametric survival extrapolations for both arms (rather than logarithmic) and a limited time horizon, xevinapant can be classified as a high-value treatment with an ICER around US$ 50,000 willingness-to-pay per QALY threshold range, thus offering superior cost-effectiveness potential compared to any other innovative therapy in this disease area.

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