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Cost-effectiveness of pembrolizumab + chemotherapy versus cetuximab-containing regimens EXTREME and TPEx, for R/M SCCHN patients with a CPS between 1 and 19, in Italy

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CONCLUSIONS

- **For recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) patients with combined positive score (CPS) 1–19, our analyses demonstrate that cetuximab-containing regimens (CCRs) can represent more effective treatment options, which are likely cost-effective in Italy as opposed to pembrolizumab + chemotherapy (P+CT). Across all scenarios, CCRs demonstrated cost savings, and in some scenarios CCRs yielded more quality-adjusted life years (QALYs)**
- **Further research could establish a more accurate estimate of the relative effectiveness of the aforementioned treatment regimens for R/M SCCHN patients with CPS 1–19, while the robustness of the current analyses indicate that the overall cost-effectiveness (CE) results would not change**

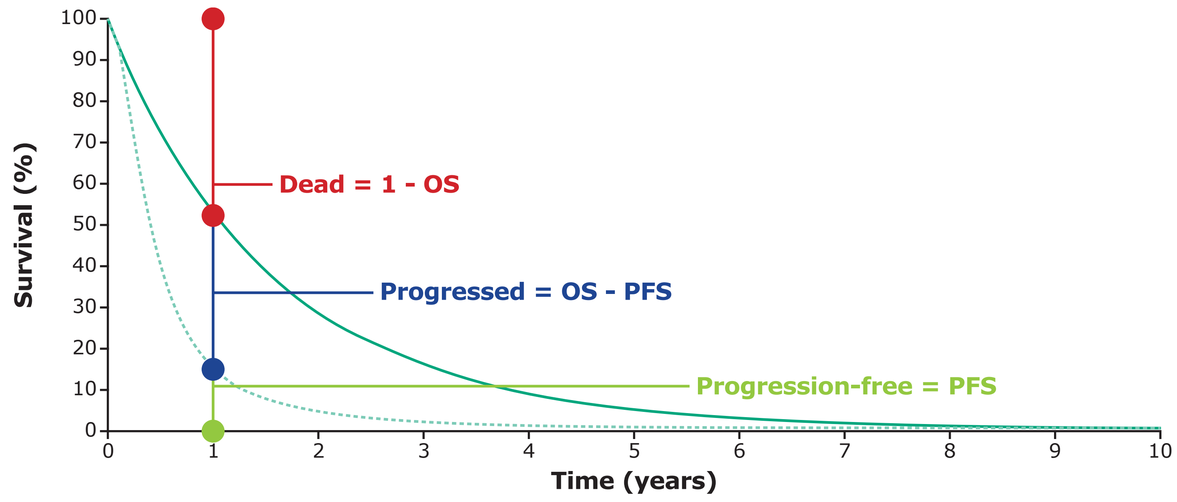
INTRODUCTION & OBJECTIVES

- Squamous cell carcinoma of the head and neck (SCCHN) is a group of cancers derived from the mucosal epithelium in the oral cavity, pharynx, and larynx[1]
- Treatment options for patients with recurrent/metastatic (R/M) SCCHN in Italy include targeted therapy (such as the epidermal growth factor receptor inhibitor cetuximab) or immunotherapy, in combination with chemotherapy[2]
- The EXTREME trial (NCT00122460) demonstrated improved overall survival (OS) for cetuximab plus platinum and 5-Fluorouracil (5-FU; the EXTREME regimen) compared with platinum and 5-FU alone[3]
- Following the EXTREME trial, the TPExtreme trial (NCT02268695) compared the EXTREME regimen with the TPEx regimen (cetuximab plus platinum and docetaxel), which suggested improved OS for TPEx over EXTREME, but the difference in OS did not reach statistical significance[4]
- Cetuximab and platinum-based chemotherapy (i.e., EXTREME or TPEx) are treatment options for patients with R/M SCCHN in Italy[2]
- More recently, the KEYNOTE-048 trial (KN-048, NCT02358031) demonstrated improved OS with pembrolizumab + chemotherapy (P+CT) versus EXTREME in the total population, as well as in the combined positive score (CPS) ≥20 and CPS ≥1 subgroups.[5] P+CT did not provide a benefit versus EXTREME in the CPS <1 subgroup[5,6]
  - A *post hoc* analysis showed that the survival benefit in the CPS 1–19 subgroup was less pronounced than in the CPS ≥20 subgroup (median OS: 12.7 months versus 14.7 months, respectively)[5,6]
  - In Italian practice, P+CT is the recommended immunotherapy-based regimen for patients with R/M SCCHN with CPS ≥1[2]
- It remains unclear which treatment option (P+CT versus EXTREME) offers the optimal clinical benefit to patients with R/M SCCHN and a CPS 1–19, as the overall response rate and median progression free-survival (PFS) were not superior for P+CT versus EXTREME.[6] The quality-adjusted life year (QALY) estimates require more data for differentiation between regimens[7]
- **In this study, we estimated the cost-effectiveness (CE) of P+CT versus cetuximab-containing regimens (CCRs) for patients with R/M SCCHN and CPS 1–19 in Italy, making use of external trial data to increase external validity of results. The CE analysis was developed from an Italian National Health Service perspective, QALY and life-year (LY) estimates, one previously presented and the other accepted for presentation[7,8]**

METHODS

- A three-state partitioned-survival model was developed to estimate the CE of P+CT versus EXTREME and TPEx. The model included health states based on progression-free disease (informed by fitted PFS models) and progressed disease (informed by the difference between fitted PFS and OS models). The model schematic is presented in Figure 1
- We incorporated previously published comparative efficacy results in the intention-to-treat (ITT) population, and, where available, the CPS 1–19 subgroup for the CCRs from four trials. These included the EXTREME and TPExtreme trials, as well as two additional trials of relevance with EXTREME or TPEx trial arms (GORTEC 2008-03 [NCT01289522] and CheckMate-651 [NCT02741570]).[3,4,9,10] These extrapolations were also the focus of our previous research presented at ISPOR US 2023,[7] where we found that by considering clinical data from multiple trials, incremental QALY estimates had substantial variability; therefore, when making decisions based on QALY estimates, incorporating external data is warranted[7]
- For P+CT, CPS 1–19 subgroup data of KN-048 (NCT02358031) were used to inform the model. The KN-048 data were the only source for which specific CPS 1–19 data were available for analysis. This was as expected because CPS was not a relevant biomarker at the time the EXTREME, TPExtreme, and GORTEC 2008-03 studies were conducted. While CheckMate-651 presented results according to CPS, no results are available in the public domain specifically for the CPS 1–19 subgroup
- Survival models were applied according to their statistical goodness-of-fit (i.e., Akaike and Bayesian information criteria [AIC and BIC] scores). The range of models fitted covered those described in the Technical Support Document 14 by Latimer (2011),[11] namely: exponential, generalized gamma, Gompertz, log-logistic, log-normal, and Weibull. Models were fitted separately to each treatment arm, allowing for different models to be specified for each outcome (i.e., PFS and OS), as well as for each treatment arm (i.e., P+CT, EXTREME, or TPEx)
- Costs inputs were included from the Italian National Healthcare Service. List prices of pharmaceutical agents were retrieved from the *Farmadati Italia* database.[12] Treatment administration costs and resource use were retrieved from the National Tariff Nomenclator,[13] as well as clinician inputs, if public sources were unavailable. Costs for the treatment of adverse events were retrieved from the corresponding Diagnosis Related Groups fee published by the Health Ministry[14]
- Outcomes were expressed as costs, QALYs, and the incremental cost-effectiveness ratio (ICER). Results were generated separately for P+CT versus EXTREME and P+CT versus TPEx

FIGURE 1: Cost-effectiveness model schematic



RESULTS*

- The base case results are presented in Table 1 (versus EXTREME) and Table 2 (versus TPEx). In these results, the TPExtreme trial is used to provide a comparison to P+CT for both CCRs. In both sets of results, P+CT is dominated by either EXTREME or TPEx (i.e., P+CT provides fewer QALYs at an increased overall cost)
- Across the four other alternative data sources for CCRs (i.e., indirect treatment comparisons), results ranged from an ICER of €384,550/QALY to P+CT being dominated by EXTREME and TPEx: both CCRs provided more QALYs at lower costs (Table 3)
- Using a CE analysis based solely on KN-048 data (i.e., a direct treatment comparison) generated an ICER of €132,359/QALY for P+CT versus EXTREME (above the informal benchmark of willingness-to-pay threshold of €60,000 per QALY gained for Italy, Table 3)
- Probabilistic sensitivity analyses (PSAs) were also performed to estimate the impact of parameter uncertainty on results (Figure 2). These results demonstrated substantial spread in estimates for both costs and QALYs, though generally suggested better outcomes and lower costs for CCRs versus P+CT

TABLE 1: Base case cost-effectiveness results (P+CT versus EXTREME)

Treatment	Total			Incremental			ICER (€ per QALY gained)
	Costs (€)	QALYs	LYs	Costs (€)	QALYs	LYs	
EXTREME	86,407	1.634	2.508				
P+CT	111,501	1.207	1.673	25,095	–0.428	–0.836	Dominated

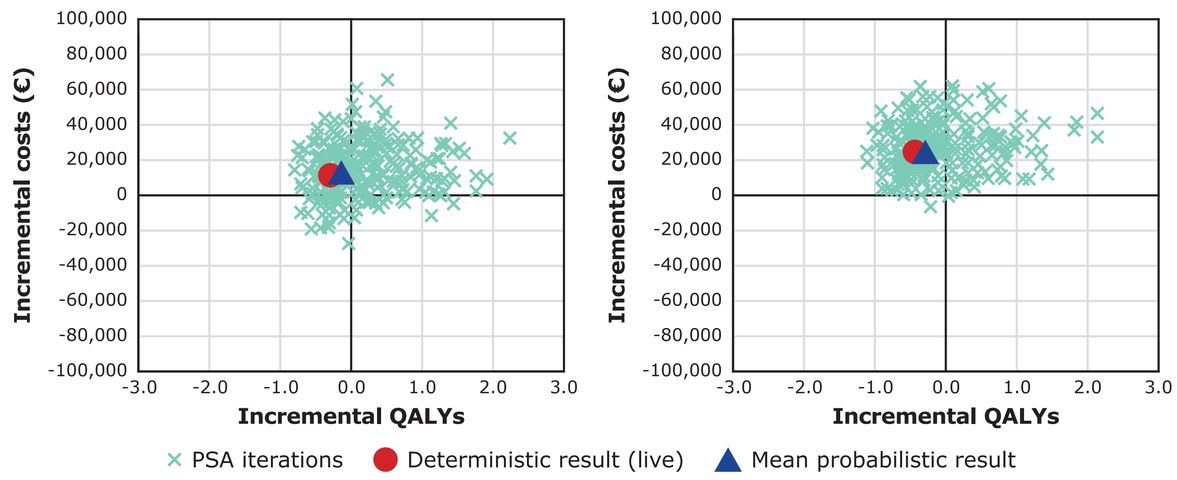
TABLE 2: Base case cost-effectiveness results (P+CT versus TPEx)

Treatment	Total			Incremental			ICER (€ per QALY gained)
	Costs (€)	QALYs	LYs	Costs (€)	QALYs	LYs	
TPEx	106,842	1.483	2.081				
P+CT	118,834	1.207	1.673	11,993	0.277	–0.409	Dominated

TABLE 3: Scenario analysis results (P+CT versus EXTREME and TPEx)

Scenario	ICER (€ per QALY gained)
Use EXTREME arm of TPExtreme trial for CCR efficacy	Dominated
Use EXTREME arm of EXTREME trial for CCR efficacy	€437,830
Use EXTREME arm of CheckMate-651 trial for CCR efficacy	Dominated
Use GORTEC 2008-03 trial for CCR efficacy (TPEx arm)	€384,550
Use EXTREME arm of KN-048 trial for CCR efficacy	€132,359

FIGURE 2: PSA scatterplots for base case analysis (P+CT versus EXTREME, left; and P+CT versus TPEx, right)



DISCUSSION

- **For patients with R/M SCCHN and CPS 1–19, our analyses demonstrate that CCRs can represent more effective treatment options, which are likely cost-effective in Italy, versus P+CT**
- Depending on the clinical trial source used to inform the efficacy of patients treated with a CCR, the QALY gain could plausibly be in favor of either treatment arm (P+CT or CCR). However, across all scenario analyses, costs were lower for CCRs, which supports the expectation that CCRs are a cost-effective treatment option for patients with a CPS of 1–19. These findings suggest that CCRs remain a relevant treatment option for patients with CPS 1–19, both from a clinical and economic perspective
- This analysis focuses on the subgroup of patients with CPS 1–19 for whom there is little evidence to support decision making in a clinical context.[6,7] This analysis is based on multiple cohorts of patients, rather than a single trial population, to inform CE for two CCRs in the Italian healthcare setting
- There are some limitations to the analysis presented. Efficacy results for the ITT population of EXTREME, TPExtreme, and GORTEC 2008-03 trials were assumed to adequately describe the efficacy results of the CPS 1–19 subgroup, because CPS stratification data were lacking in these trials. However, the CPS score is not expected to have a significant impact on treatment outcomes for patients treated with CCRs[15]
- Further research could establish a more accurate estimate of the relative effectiveness of the treatment regimens for patients with R/M SCCHN and a CPS of 1–19. However, the robustness of the current analysis does not indicate that the overall CE results would change substantially, should these data emerge in the future

*The results presented in the tables above differ slightly from the submitted abstract. This is due to the correction of a costing error for carboplatin and cisplatin.

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ABBREVIATIONS: CCR, cetuximab-based regimen; **CE,** cost effectiveness; **CPS,** combined positive score; **CT,** chemotherapy; **EXTREME,** cetuximab plus platinum and 5-FU; **5-FU,** 5-Fluorouracil; **ICER,** incremental cost-effectiveness ratio; **ITT,** intention-to-treat; **KN-048,** KEYNOTE-048 trial; **LY,** life-year; **OS,** overall survival; **P,** pembrolizumab; **PFS,** progression-free survival; **PSA,** probabilistic sensitivity analysis; **QALY,** quality-adjusted life year; **R/M,** recurrent/metastatic; **SCCHN,** squamous cell carcinoma of the head and neck **TPEx,** cetuximab plus platinum and docetaxel.

DISCLOSURES: AB and JN are employees of Delta Hat Limited. Delta Hat received consulting fees for performing the analyses described within this presentation. MS, AG and CPP are employees of Merck Healthcare KGaA, Darmstadt, Germany. PI has been an advisor/provided expert testimony for Bayer, Bristol Myers Squibb, ClinSol, Deciphera, Eisai, Merck, EUSA Pharma, H5-Oncology, Ipsen, Metaplan, Merck Sharp & Dohme, Onkowissen, Pfizer, Roche; owns stocks in BB-Biotech and has received honoraria from AIM, Apogepha, AstraZeneca, Astellas, Bayer, Bristol Myers Squibb, CORE2ED, Deciphera, DKG-Onkoweb, EISAI, EUSA Pharma, FoFM, ID-Institut, Ipsen, Merck, Merck Sharp & Dohme , MedKom, MTE-Academy, MedWiss and New Concept Oncology, Onkowissen-tv.de, Pharma Mare, Pfizer, Roche, ThinkWired, Schmitz-Communikation, StreamedUP, Solution Academy and Vivantis. He has also received funding support for scientific research from AIO, AstraZeneca, Bristol Myers Squibb, EUSA Pharma, Eisai, GlaxoSmithKline, Ipsen, Eli Lilly, Merck, Merck Sharp & Dohme, Niedersächsische Krebsgesellschaft, Novartis, Pfizer, Roche, Stiftung Immunonkologie, Wilhelm Sander Stiftung and also travel grants from Bayer, BB-Biotech, Bristol Myers Squibb, Deutsche Gesellschaft für Thoraxchirurgie, EUSA Pharma, Ipsen, Merck and Pharma Mare.

ACKNOWLEDGEMENTS: This analysis was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945). Medical writing support was provided by Nucleus Global, Asia Pacific, in September 2023, which was funded by Merck, in accordance with Good Publication Practice (GPP) guidelines (https://www.ismpp.org/gpp-2022).

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Presented at the Professional Society for Health Economics and Outcomes Research (ISPOR) Europe 2023 | November 12–15, 2023 | Copenhagen, Denmark