Improving External Validity of Trial Outcomes when Estimating Subgroup QALY Gains: A Case Study of Pembrolizumab ± Chemotherapy vs Cetuximab + Platinum-Based Chemotherapy (EXTREME) in Squamous Cell Carcinoma of the Head and Neck

Bullement A[1], Naik J[1], Schlichting M[2], Pescott CP[2]

[1]Delta Hat, Nottingham, UK; [2]Merck KGaA, Darmstadt, Germany

ORCID iDs
Bullement A, https://orcid.org/0000-0001-7091-0972; Naik J, https://orcid.org/0000-0002-6581-350X; Schlichting M, https://orcid.org/0000-0002-1649-5867; Pescott CP, https://orcid.org/0000-0002-7763-9326

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CONCLUSIONS

- **Considering clinical data from multiple trials shows that incremental quality-adjusted life year (QALY) estimates for the combined positive score (CPS) 1-19 subgroup for both pembrolizumab + chemotherapy (P+CT) and pembrolizumab (P), versus EXTREME yields substantial variability**
- **Consequently, incorporating external data should be considered when making decisions based on QALY estimates**

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]
- The EXTREME trial (NCT00122460) demonstrated improved overall survival (OS) for cetuximab plus platinum-fluorouracil chemotherapy (the EXTREME regimen) compared with platinum-based chemotherapy (PBT) plus fluorouracil alone[2]
- KEYNOTE-048 (KN-048, NCT02358031) trial demonstrated improved outcomes with pembrolizumab -/+ chemotherapy (P and P+CT, respectively) versus EXTREME in the total population.[3] Notably, combined positive score (CPS) status appeared to be an effect modifier for pembrolizumab treatment. Improved outcomes with P ± CT versus EXTREME were reported in two subgroups of CPS ≥20 and CPS ≥1.[3] Further exploratory analyses suggested limited or no benefit for pembrolizumab in the CPS 1-19 subgroup, and advantageous outcome for EXTREME in CPS <1[4]
- CPS is not expected to influence outcomes for patients treated with the EXTREME regimen, and the post-hoc CPS 1-19 subgroup analysis of KN-048 should be interpreted with caution
- We investigate differences in progression-free survival (PFS) and OS between patients with recurrent/metastatic (R/M) SCCHN receiving P/P+CT or EXTREME by utilizing external trial data
- We also present the findings from a modeling exercise to compare outcomes from KN-048 with other studies that provide results for cetuximab-containing regimens in R/M SCCHN, with findings expressed as life-years (LYs) and quality-adjusted life years (QALYs)

METHODS

Study identification

- Three representative published trials (EXTREME [NCT00122460], TPEXTREME [NCT02268695], and GORTEC [NCT01289522]) reporting on the EXTREME regimen, and no additional trials reporting on P/P+CT, were identified. These trials reported OS and PFS outcomes for at least one group of R/M SCCHN patients treated with the EXTREME regimen
- The Kaplan-Meier (KM) curves of PFS and OS were digitized (using WebPlotDigitizer[5]) and used to generate pseudo patient-level data (PLD, using the approach of Guyot et al., 2012)[6]
- A graphical depiction of recreated KM estimates of PFS and OS from each of the four trials analyses is provided in **Figure 1**

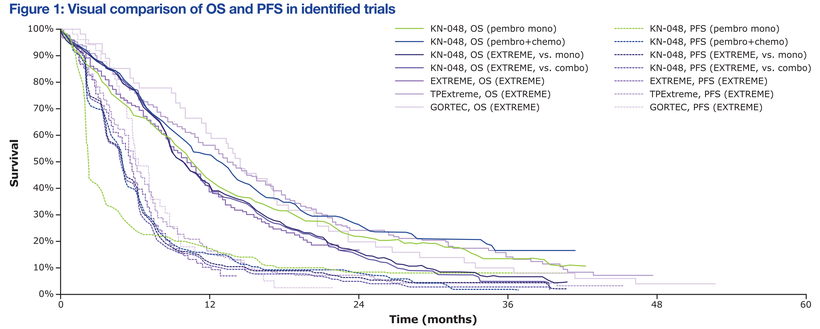
Statistical analysis and model parameterization

- Using the recreated PLD, parametric survival models were fitted to produce extrapolations of PFS and OS over a lifetime horizon; parametric survival models were generated using the *flexsurv* package in R
- Six standard parametric models were produced for each trial for both OS and PFS: exponential, generalized gamma, Gompertz, log-logistic, log-normal, and Weibull
- Models were selected for each outcome and trial based on statistical goodness-of-fit scores (Akaike and Bayesian Information Criteria; AIC and BIC, respectively), visual fit, and plausibility of long-term projections
- Health state utility values were identified from the National Institute for Health and Care Excellence (NICE)[7]
- The nonprogressed health state was associated with a utility value of 0.8192, whereas the progressed health state was associated with a utility value of 0.7046
- Utility values were age-adjusted based on the general population equation by Ara & Brazier (2010)[8]

Modeling

- The outputted survival models were incorporated within a partitioned-survival analysis, where health state occupancy was defined according to nonprogressed disease, progressed disease, or death
- Within the model, estimates of OS and PFS were capped based on age- and sex-adjusted general population mortality. In addition, PFS was not permitted to exceed OS, so if a combination of PFS and OS curves crossed, the PFS curve was capped by the OS curve
- To estimate QALYs, the area under the PFS and OS curves were used to estimate the time spent in each health state, and these were multiplied by the utility values
- QALYs were discounted at 3.5% per annum (in accordance with NICE standards[9]), whereas LYs were not discounted for ease of interpretation
- We compared incremental QALYs for KN-048 (results for P/P+CT) with estimates for each alternative trial (results for the EXTREME regimen)

Figure 1: Visual comparison of OS and PFS in identified trials



Note: Survival outcomes are associated with CPS 1-19 subgroup (KN-048) and overall population (other studies)

RESULTS

Study identification

- Full results of LYs and QALYs based on the comparisons explored, including clarification on the choice of parametric models for OS and PFS in each comparison, are provided in **Table 1**
- A summary of the extrapolations produced when selecting specific sources of data for the EXTREME regimen are provided in **Figure 2** (based on the results presented in **Table 1**)

Within KN-048 comparisons

- Results were first generated using data for the CPS 1-19 subgroup from KN-048, with curves selected for each comparison according to statistical goodness-of-fit scores
- The best-fitting OS models were log-logistic for the EXTREME regimen (both comparisons), Gompertz for P+CT, and log-normal for P
- The best-fitting PFS models were log-logistic (versus P+CT) and generalized gamma (versus P) for EXTREME regimen, and log-logistic for both P+CT and P
- For simplicity, the Gompertz model was selected for OS for both P+CT and P since there was little difference in the AIC and BIC scores. This allowed for using the same models across the comparisons of EXTREME against P and P+CT, for both OS and PFS
- Applying these models yielded +0.05 and +0.18 QALYs for P and P+CT, respectively, versus EXTREME

External data comparison

- For the external data, three sets of results were produced using each data source to replace the EXTREME arm of KN-048, irrespective of CPS
- Across the three sets of results using best-fitting models, QALY gains ranged from -0.12 to +0.27 (P) and -0.01 to +0.38 (P+CT)
- In some exploratory analyses, QALY gains were positive (i.e., favoring P/P+CT), while life-year gains were negative (i.e., favoring EXTREME); for example, if generalized gamma is used for OS and PFS for P, versus log-logistic for OS and PFS for EXTREME. This finding illustrates how the combination of choices of models can lead to results showing little difference in outcomes

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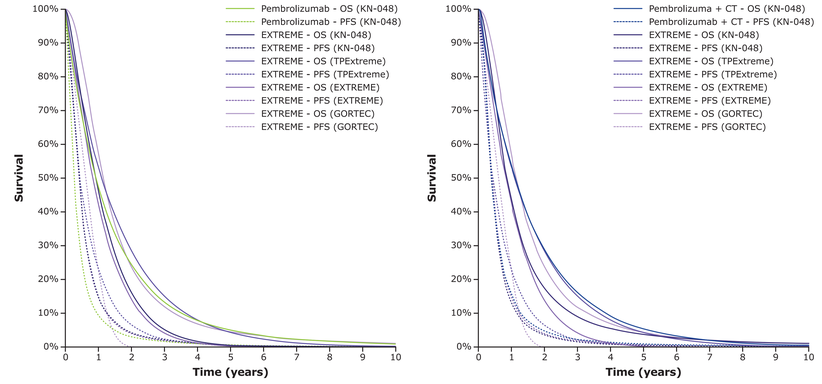
Table 1: LYs and QALYs based on comparisons explored

Results for pembrolizumab + chemotherapy versus EXTREME regimen					
Source		Models		Outcomes gained	
P+CT	EXTREME	OS	PFS	QALYs	LYs
KN-048 (2019)	KN-048 (2019)	P+CT: Gompertz EXTREME: Log-logistic	P+CT: Log-logistic EXTREME: Log-logistic	+0.18	+0.23
	EXTREME (2008)	P+CT: Gompertz EXTREME: Weibull	P+CT: Log-logistic EXTREME: Log-logistic	+0.38	+0.60
	GORTEC (2015)	P+CT: Gompertz EXTREME: Log-logistic	P+CT: Log-logistic EXTREME: Gompertz	-0.01	-0.04
	TPExtreme (2021)	P+CT: Gompertz EXTREME: Exponential	P+CT: Log-logistic EXTREME: Gompertz	+0.04	+0.08
Results for pembrolizumab monotherapy versus EXTREME regimen					
Source		Models		Outcomes gained	
P	EXTREME	OS	PFS	QALYs	LYs
KN-048 (2019)	KN-048 (2019)	P: Gompertz EXTREME: Log-logistic	P: Log-logistic EXTREME: Generalized gamma	+0.05	+0.09
	EXTREME (2008)	P: Gompertz EXTREME: Weibull	P: Log-logistic EXTREME: Log-logistic	+0.27	+0.50
	GORTEC (2015)	P: Gompertz EXTREME: Log-logistic	P: Log-logistic EXTREME: Gompertz	-0.12	-0.13
	TPExtreme (2021)	P: Gompertz EXTREME: Exponential	: Log-logistic EXTREME: Gompertz	-0.07	-0.01

Note: Survival outcomes are associated with CPS 1-19 subgroup (KN-048) and overall population (other studies)

Figure 2: Comparison of extrapolations: pembrolizumab monotherapy versus EXTREME



DISCUSSION

- A key strength of our analysis is that by making use of data collected outside of the KN-048 trial we incorporated further evidence of the efficacy of the EXTREME regimen that was available after marketing authorization
- It was not possible to adjust for population-level imbalances across the studies, because patient-level data were not readily available. Results were also not adjusted to account for different types of subsequent therapies administered after disease progression
- While CPS is expected to have little bearing on outcome for patients receiving EXTREME, another limitation of our analysis is that historic trials did not report outcomes by CPS to explore similar subgroups
- Further work is planned to explore more recent data for the EXTREME regimen made available from the CheckMate-651 trial, and to consider different combinations of survival extrapolation methods
- Further research is also required to conclusively determine the relative effectiveness of P/P+CT versus EXTREME for patients with CPS 1-19, given that outcomes for P/P+CT are based on a small, post-hoc subgroup analysis from KN-048

ABBREVIATIONS: CPS, combined positive score; **CT,** chemotherapy; **KM,** Kaplan-Meier; **KN-048,** KEYNOTE-048; **LYs;** life-years; **NICE,** National Institute for Health and Care Excellence; **OS**. overall survival; **P,** pembrolizumab; **PFS,** progression-free survival; **PLD,** patient-level data; **QALY,** quality-adjusted life year; **R/M,** recurrent/metastatic; **SCCHN,** squamous cell carcinoma of the head and neck.

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CORRESPONDENCE: abullement@deltahat.com

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