PCN449

PHMR

AN ANALYSIS OF EQ-5D ADJUSTING FOR TREATMENT SWITCHING: THE CASE OF PATIENTS WITH EGFR T790M POSITIVE NSCLC TREATED WITH OSIMERTINIB

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Objectives

Treatment switching, from control to treatment arm, following disease progression is common in trials of novel, targeted oncology therapies. If the control group accrues benefits from the new treatment, standard 'intention to treat' (ITT) analyses will underestimate the benefit of the treatment. To address this, statistical methods have been developed to account for treatment switching for the analysis of overall survival data[1]; however, such approaches are rarely used in the analysis of health-related utility or quality adjusted life years (QALYs).

The aim of the study is to examine the impact of adjusting for treatment switching using EQ-5D-5L data collected in a randomised clinical study, the AURA 3 trial.

Methods

AURA 3 is a phase III, open-label, randomised study assessing osimertinib (Tagrisso®, 80 mg, orally administered once daily) versus platinum-based doublet in patients with locally advanced or metastatic EGFR T790M positive non-small cell lung cancer (NSCLC) whose disease has progressed with previous EGFR TKI Therapy. 419 patients were randomised in a 2:1 ratio: 279 patients assigned to osimertinib and 140 to chemotherapy. At data cut-off, two-thirds of patients in the chemotherapy arm switched to treatment with osimertinib post- disease progression. EQ-5D-5L[2] data were collected every 6 weeks, across 25 time-points. A cross-walk developed by van Hout et al was applied, and the English EQ-5D-3L value set applied to generate utilities.[3,4]

Descriptive analyses, including pareto classification of health change (PCHC), were conducted.[5] PCHS assessed change in health states from baseline, 6 weeks (T1) and 12 weeks (T2). The primary analysis used two-stage least squares instrumental variable regression to estimate the treatment effect adjusting for treatment switching.[6] The analysis included randomised treatment group as the instrumental variable, treatment switching as an indicator variable, QALYs as the outcome measure. Baseline characteristics and randomised treatment allocation were included in the second step regression.

Multiple imputation was applied at the QALY level using mean predictive matching to account for missing data. QALYs were calculated using the 'area under the curve' method up to week 60. This cut-off was chosen as it represented one-year post enrolment into the trial, minimised the amount of missing data (35%) and 78% of patients had crossed over by this follow-up time point. Sensitivity analyses included data up to week 150 and imputation at the EQ-5D index level. Time to deterioration (TTD), defined by minimally important difference (MID) of 0.8 in EQ-5D-5L values[7], was also assessed after adjusting for crossover using a rank preserving structural failure time model (RPSFTM).

Results

The PCHC results showed a trend in a greater proportion of osimertinib patients reporting improvement compared to chemotherapy from baseline to 6 weeks (Figure 1). A greater proportion of patients in the osimertinib arm reported maintenance of health (no change) from 6 weeks to 12 weeks.

The analysis adjusting for treatment switching using the two-stage least squares regression) estimated a higher incremental QALY gain of 0.52 at week 60, compared to the analyses that did not account for treatment switching: 0.16 (complete case) and 0.23 (ITT) analysis. This trend was also reflected in the sensitivity analysis using data up to 150 weeks, but the impact was less when missing data were imputed at the EQ-5D index level (Table 1).

Patients treated with osimertinib had a longer time to deterioration of 12.76 weeks compared with those treated with standard chemotherapy; however, the difference in TTD was on the borderline of statistical significance (φ=−0.275, 95% CI: -0.50 to 0.00) (Table 2).

Conclusions

This study demonstrates methods to adjust for treatment switching in the analysis of EQ-5D from clinical trials. Failure to account for crossover significantly underestimated the QALY gain for osimertinib.

Figure 1: Change in EQ-5D health status (Pareto classification of health change)

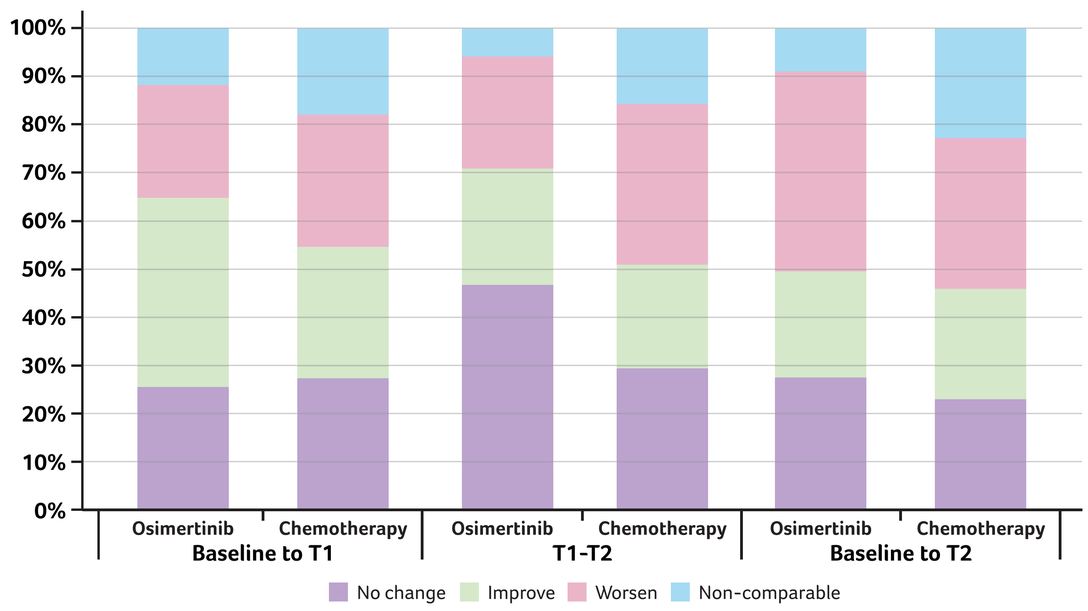


Table 1: Results of analysis adjusting for treatment switching using two-stage least squares regression (mean incremental QALY and 95% confidence interval)

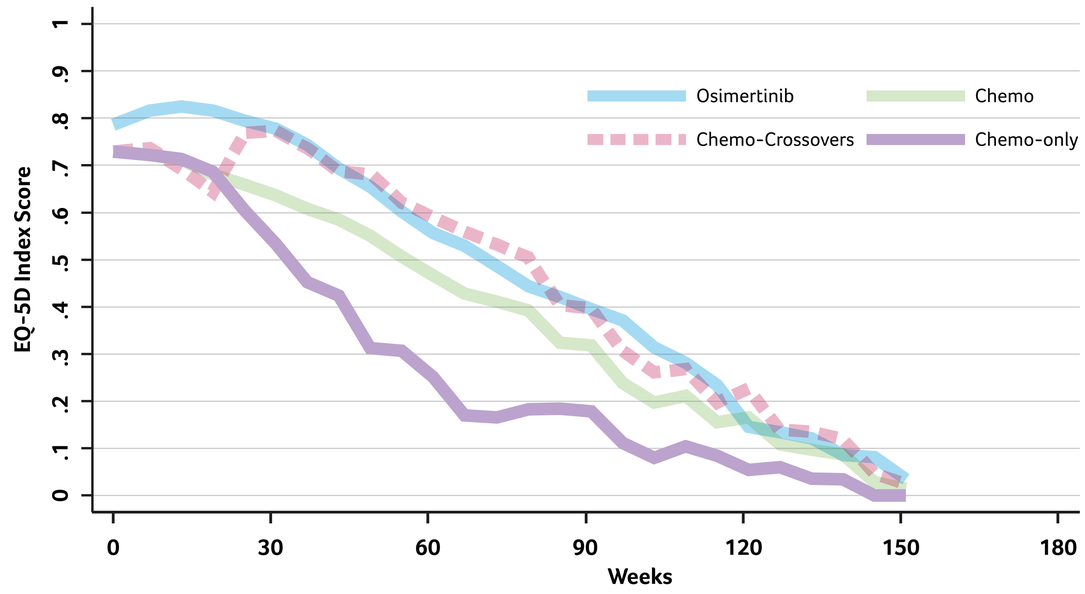
Complete case analysis†	ITT analysis	2 stage regression analysis
Primary analysis, up to 60 weeks		
0.16* (95%CI; 0.05 0.28)	0.23* (95% CI;0.17 0.29)	0.52* (95% CI (0.37, 0.68))
Sensitivity analysis: Imputed at QALY level, till week 150		
0.29* (95%CI -0.13 0.73)	0.40* (95% CI; 0.27 0.52)	0.63* (95% CI (0.36, 0.90))
Sensitivity analysis: Imputed at EQ-5D index level, till week 60		
0.16* (95%CI; 0.05 0.28)	0.11 (95% CI;0.5 0.17)	0.18* (95% CI-0.05, 0.31)

**Significant at the 95% confidence level; †Data was not imputed*

Table 2: Time to deterioration in weeks in EQ-5D-5L values, adjusting for treatment switching (RPSFTM analysis)

Variable	Mean	Standard deviation	Min	Max
Chemotherapy	52.80	8.01	19.65	75.43
Osimertinib	65.56	10.34	20.13	77.13

Figure 2. EQ-5D over time by arm (including zero values)



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Acknowledgements

Financial support for this study was provided by a contract with AstraZeneca. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The following author(s) is/are employed by the sponsor: Matthew Dyer. Louise Longworth and Nancy Devlin are members of the EuroQol Group, a not-for-profit organisation responsible for the development of the EQ-5D.

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