Comparison of Progression-Based and Time-To-Death Health State Utility Modelling Using EQ-5D-5L Values: A Study in Endometrial Cancer Patients from the GARNET Trial

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Background

- In 2022, the World Cancer Research Fund International reported that endometrial cancer (EC) was the sixth most common cancer in women worldwide, with over 400,000 new cases per year[1]
- Health state utilities play a crucial role in assessing quality of life (QoL) and treatment outcomes and are essential components of cost effectiveness models and budget impact models in health technology assessment[2]
- Utility is a measure of the preference or value that patients assign to a particular health state, typically ranging from 0 (equal to death) to 1 (equal to perfect health).[3] It is used to quantify health-related quality of life (HRQoL) in patients with cancer, reflecting the physical, emotional, social and functional dimensions of health[2, 4]
- Instruments such as EQ-5D-3L,[5] EQ-5D-5L,[5] SF-6D[2] and EORTC QLQ-C30[4] collect patient-reported outcomes to derive utility values. EQ-5D-5L is available in more than 150 languages and is widely used for this purpose[5]
- Traditional utility analysis models often focus on disease progression, but recent evidence suggests that time-to-death (TTD) may also be a good predictor of QoL[2, 6]

Objective

- To compare health state utility prediction models based on progression status and/or TTD using EQ-5D-5L data from patients with EC enrolled in the dostarlimab monotherapy GARNET trial

Methodology

- The EQ-5D-5L questionnaire comprises five dimensions that include mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has five response levels: no problem, slight problem, moderate problem, severe problem or extreme problem
- The analysis examined data from the EQ-5D-5L questionnaire for patients with EC enrolled in the dostarlimab monotherapy GARNET trial (ClinicalTrials.gov identifier: NCT02715284)
- Data from EQ-5D-5L responses at the following timepoints were utilised: baseline, every 3 to 6 weeks during treatment, at end-of-treatment visit, safety follow-up and every 90 days during the post-treatment follow-up period
- Health state utilities were derived based on the Netherlands reference value set
- Health states were partitioned by disease progression and TTD
- Different models (**Table 1**) were fitted to predict health utilities using data from patients with EC
- Among the baseline covariates, only histology was significant and used in the final model
- Models were compared using quasi-likelihood information criteria (QIC), generalised R^2, mean absolute error (MAE), root mean square error (RMSE) and significance of regression coefficients

Table 1. **Model scenarios**

Model 1	Model 2	Model 3	Model 4
Baseline utility + progression	Baseline utility + TTD	Baseline utility + progression + TTD + (progression x TTD)	Baseline utility + progression + TTD + (progression x TTD) + significant baseline covariate (histology)

Statistical estimation of utilities

- Post-baseline EQ-5D-5L utility values were modelled using the generalised estimating equations (GEE) adjusted for baseline utility values and other covariates as per the model scenarios
- The GEE approach models a known function of the marginal expectation of the dependent variable as a linear function of the explanatory variables, resulting in parameter estimates that are population averaged

$$G(E(y_i)) = g(\mu_i) = x_i'\beta$$

where y_i is a response variable (i=1,…,n), $\mu_i = E(y_i)$, g is a link function, x_i is a vector of independent variables and β is a vector of regression parameters to be estimated

- GEE methodology to estimate β:

$$\sum_{i=1}^{n} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1}(Y_i - \mu_i(\beta)) = 0$$

where $\mu_i = \mu_i(\beta)$ is the corresponding vector of means $\mu_i = (\mu_{i1},\ldots,\mu_{iti})$, response $Y_i = (y_{i1},\ldots,y_{iti})$, t_i were repeated measurements, $1 \le t_i \ge t$ from each of n patients, and V_i is an estimator of the covariance matrix of Y_i, $\frac{\partial \mu_i'}{\partial \beta}$ is the working correlation matrix

Results

- Patient demographics are shown in **Table 2**
- Patients experienced reduction in utilities post-progression and at times closer to death (**Figure 1**)
- Based on QIC, Model 2 with TTD alone showed the best fit (**Table 3**)
- Model 3 showed a statistically significant interaction between progression and TTD (**Table 3**)
- Based on R^2, MAE and RMSE, Model 4 with progression, TTD and baseline covariate showed the best predictive power (**Table 3**)
- Model 4 performance data is shown in **Figure 2**

Table 2. Demographic characteristics

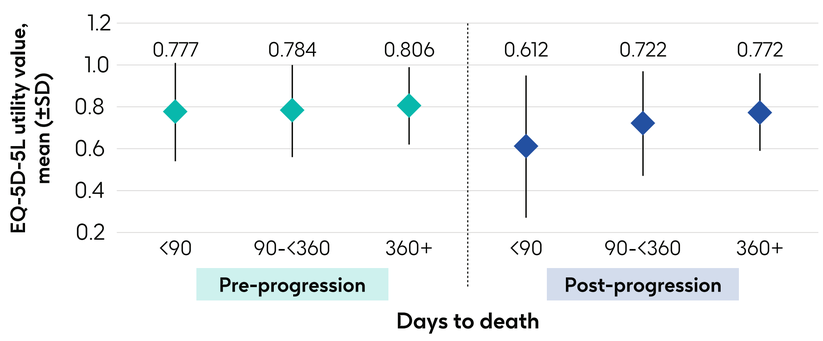
Parameter	N=117
Population	
EC: MSI-H/dMMR	116 (99)
EC: unknown MSI-H/MMR status	1 (1)
Health state	
Disease progression	56 (48)
Death	44 (38)
Baseline characteristics	
Age, years, mean (SD)	63.5 (8.8)
BMI, kg/m², mean (SD)	29.3 (7.8)
Baseline ECOG performance status	
0	48 (41)
1	69 (59)
Histology category at first diagnosis	
Endometroid carcinoma type 1	75 (64)
Other*	42 (36)
Prior radiation	83 (71)

Values are n (%) unless otherwise stated. *Other include clear cell carcinoma, endometrial carcinoma type 2, grade 3 endometrioid, mixed carcinoma, serous carcinoma, undifferentiated carcinoma, other and unknown. BMI, body mass index; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; SD, standard deviation.

Table 3. GEE model estimation and model performance

	Model 1	Model 2	Model 3	Model 4
	Progression model	TTD model	Progression + TTD	Progression + TTD + baseline covariate
GEE model estimation				
Intercept	−1.02 (0.11), P<0.0001	−1.02 (0.11), P<0.0001	−1.01 (0.11), P<0.0001	−0.95 (0.10), P<0.0001
Baseline utility	0.99 (0.13), P<0.0001	0.98 (0.13), P<0.0001	0.97 (0.12), P<0.0001	0.95 (0.12), P<0.0001
Progression	−0.040 (0.03), P=0.177		−0.004 (0.02), P=0.871	−0.003 (0.02), P=0.908
TTD (<90 days)		−0.043 (0.02), **P=0.023**	−0.007 (0.01), P=0.576	−0.007 (0.01), P=0.581
Progression x TTD				
Progression, <90 days			−0.134 (0.06), **P=0.026**	−0.131 (0.06), **P=0.027**
Histology (endometrioid carcinoma)				−0.079 (0.03), P=0.004
Model performance				
QIC (smaller is better)	1437.5	**1433.2**	1438.1	1446.1
R^2 (larger is better)	0.312	0.310	0.321	**0.340**
MAE (lower is better)	0.128	0.129	0.128	**0.126**
RMSE (lower is better)	0.178	0.178	0.177	**0.174**
Model performance by utility interval				
MAE				
All values	0.128	0.129	0.128	0.126
EQ-5D-5L < 0.65	0.245	0.247	0.246	0.237
0.65 ≤ EQ-5D-5L < 0.75	0.095	0.093	0.094	0.093
0.75 ≤ EQ-5D-5L < 0.85	0.082	0.081	0.081	0.084
0.85 ≤ EQ-5D-5L < 0.95	0.093	0.094	0.093	0.096
0.95 ≤ EQ-5D-5L ≤ 1	0.148	0.148	0.147	0.141
RMSE				
All values	0.178	0.178	0.177	0.174
EQ-5D-5L < 0.65	0.309	0.310	0.308	0.300
0.65 ≤ EQ-5D-5L < 0.75	0.121	0.121	0.120	0.116
0.75 ≤ EQ-5D-5L < 0.85	0.117	0.117	0.115	0.118
0.85 ≤ EQ-5D-5L < 0.95	0.122	0.122	0.122	0.123
0.95 ≤ EQ-5D-5L ≤ 1	0.174	0.174	0.172	0.170

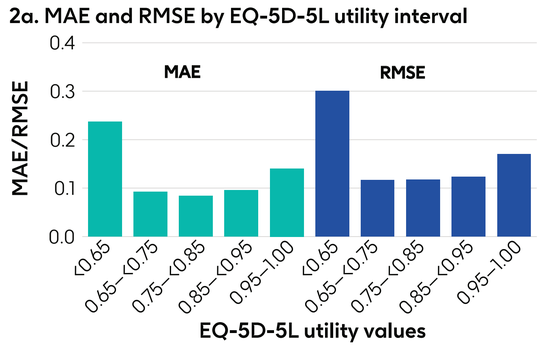
Figure 1. EQ-5D-5L utility value by progression status and TTD



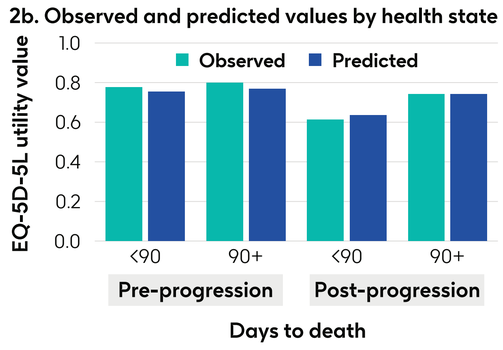
TTD was defined as the duration from date of EQ-5D-5L completion to date of death. For those alive, date of last follow-up was used as date of death.

Figure 2. Model 4 performance

2a. MAE and RMSE by EQ-5D-5L utility interval



2b. Observed and predicted values by health state



Conclusions

- The model that included baseline utility and TTD (Model 2) showed the best fit based on quasi-likelihood information criteria
- The model that included baseline utility, progression status, TTD, interaction of progression and TTD and baseline covariate histology (Model 4) was found to be the better fit based on R^2, RMSE and MAE and may improve cost effectiveness evaluation
- Mean utility values in Model 4 showed a decrease in utility in the final 90 days before death for patients who progressed compared to progression-free patients
- HRQoL data must be carefully analysed prior to constructing economic models; clinical measures such as disease progression alone may not explain QoL changes, and an event-based approach may be more suitable

Abbreviations

BMI, body mass index; dMMR, deficient mismatch repair; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30; EQ-5D-3L, EuroQoL 5-Dimensions 3-Levels; EQ-5D-5L, EuroQoL 5-Dimensions 5-Levels; GEE, generalised estimating equations; HRQoL, health-related quality of life; MAE, mean absolute error; MSI-H, microsatellite instability-high; QIC, quasi-likelihood information criteria; QoL, quality of life; RMSE, root mean square error; SD, standard deviation; SF-6D, short-form 6-dimension; TTD, time-to-death.

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