Poster No.
P8

Cost-effectiveness of lenvatinib in the treatment of hepatocellular carcinoma in the UK

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BACKGROUND

- Hepatocellular carcinoma (HCC) accounts for 85% of primary liver cancers [1, 2], and approximately 5,000 people are diagnosed each year in the UK [3]
- The prognosis for advanced HCC is poor, with a median survival of less than 1 year [4] and limited treatment options – sorafenib was previously the only first-line advanced-stage treatment option
- Lenvatinib, an oral multikinase inhibitor, was evaluated in the Phase III REFLECT trial (NCT01761266) versus sorafenib in individuals with untreated advanced/unresectable HCC
- REFLECT met the primary endpoint of non-inferiority for overall survival (OS; hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.79, 1.06), with a median OS in the lenvatinib arm of 13.6 months (95% CI 12.1, 14.9), compared with 12.3 months (95% CI 10.4, 13.9) in the sorafenib arm [5]
- However, baseline imbalances in certain key prognostic variables (i.e. the proportion of patients with alpha fetoprotein [AFP] levels ≥ 200 ng/mL and in hepatitis C virus aetiology) may have favoured the sorafenib arm. After adjustment for baseline imbalances, the HR for OS was nominally superior in favour of lenvatinib at 0.82 (95% CI 0.70, 0.96)
- Additionally, lenvatinib was superior versus sorafenib in all secondary endpoints – progression-free survival (PFS), time to progression and objective response rate
- In 2018, the National Institute for Health and Care Excellence (NICE) recommended lenvatinib as a treatment option for untreated, advanced, unresectable HCC in adults [6]

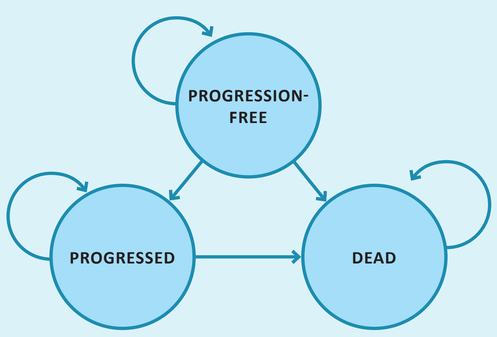
OBJECTIVE

- To perform an economic analysis to assess whether lenvatinib can be considered a cost-effective use of NHS resources compared with sorafenib in the treatment of adults with untreated advanced/unresectable HCC

METHODS

- A partitioned survival model (PSM) was developed, using data from the REFLECT trial to extrapolate costs and quality-adjusted life-years (QALYs) over a lifetime time horizon in adults with untreated advanced or unresectable HCC and Child-Pugh Class A liver function (the population of REFLECT)
- The model includes three health states – progression-free, progressed and dead – defined by survival curves for PFS and OS **(Figure 1)**

Figure 1: Model structure



- Survival curves for PFS and OS were based on multivariable parametric models adjusting for imbalances in baseline characteristics and other key prognostic variables; clinical experts provided candidate prognostic baseline characteristics, with the final variables included based on a backwards stepwise selection
  - Variables adjusted for included: baseline AFP (concentration ≥ or <200 ng/ml); body weight (<60 kg, ≥60 kg); Child-Pugh score (A, B); Eastern Cooperative Oncology Group performance status (0,1); factor of carcinogenesis (hepatitis B virus only); involved disease sites (liver, lung, bone, other); macroscopic portal vein invasion, extrahepatic spread, or both (yes, no); and region (Asia-Pacific, Western regions)
  - A scenario was considered in which no adjustment was made for baseline characteristics
- The log-logistic and log-normal distributions were selected for OS and PFS, respectively, based on statistical measures of goodness of fit and clinical plausibility
- The model adopted the perspective of the NHS and personal social services in England and Wales, with costs and QALYs discounted at an annual rate of 3.5% as per NICE guidance [7]
- Utility values for the progression-free and progressed states were derived from EQ-5D-3L data collected in REFLECT, and were estimated to be 0.75 and 0.68, respectively
- Costs were taken from published sources, and time-to-discontinuation data from REFLECT were used to calculate total drug costs
- The model used list prices for lenvatinib and sorafenib; however, confidential patient access schemes (PAS) are available for both therapies
  - Scenario analyses were therefore performed in which PAS discounts between 20% and 80% were considered for each of lenvatinib and sorafenib
- Uncertainty was explored using univariate sensitivity analysis, probabilistic sensitivity analysis (PSA) and scenario analysis

RESULTS

- Using list prices, the incremental costs and QALYs associated with lenvatinib are £8,541 and 0.18, respectively, resulting in an incremental cost-effectiveness ratio (ICER) of £48,494 per QALY gained **(Table 1)**

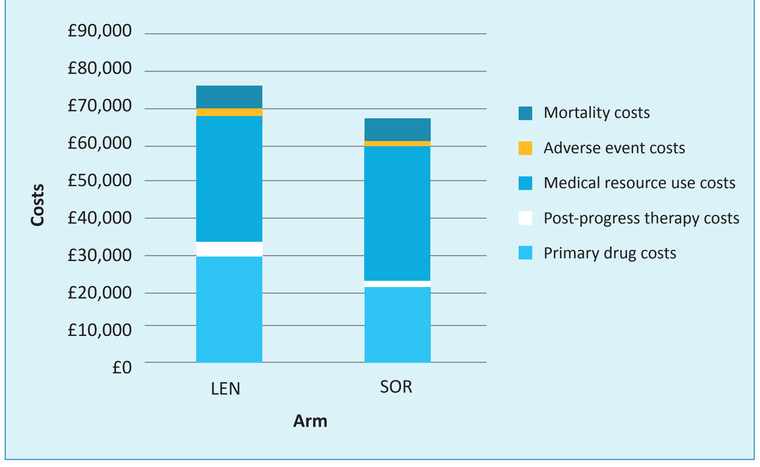
Table 1: Base-case results

	Sorafenib	Lenvatinib	Incremental
Total costs	£67,666	£76,207	£8,541
Total QALYs	1.03	1.20	0.18
Life expectancy (months)†	18.7	21.8	3.1
ICER	-	-	£48,494

† Undiscounted
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

- Total costs in the lenvatinib arm were £76,207, compared with £67,666 in the sorafenib arm; this difference was mainly driven by an increase in primary drug costs **(Figure 2)**

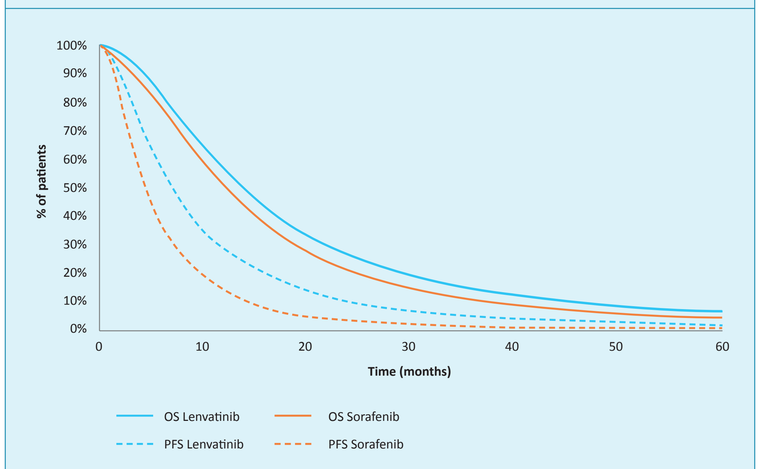
Figure 2: Breakdown of costs



Abbreviations: LEN, lenvatinib; SOR, sorafenib.

- The model estimates a mean life extension of 3.1 months with lenvatinib versus sorafenib **(Figure 3)**

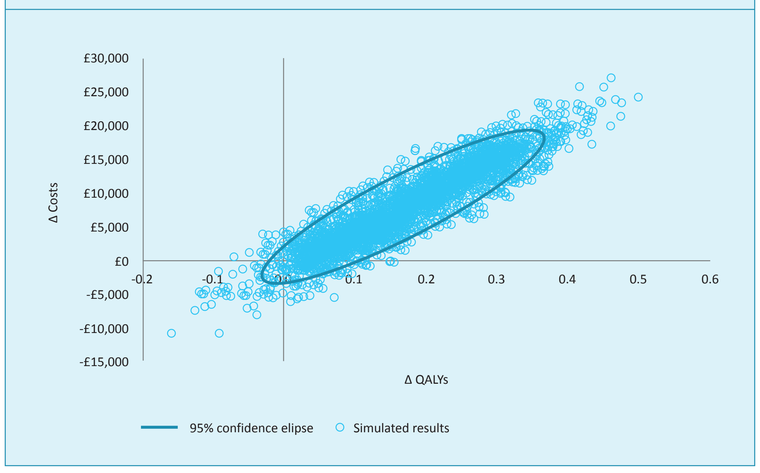
Figure 3: Modelled progression-free and overall survival



Abbreviations: OS, overall survival; PFS, progression-free survival.

- Across 10,000 PSA simulations **(Figure 4)**, average incremental costs were £8,450 and average incremental QALYs were 0.18, giving a probabilistic ICER of £48,125; this is highly congruent with deterministic changes in costs and QALYs of £8,541 and 0.18

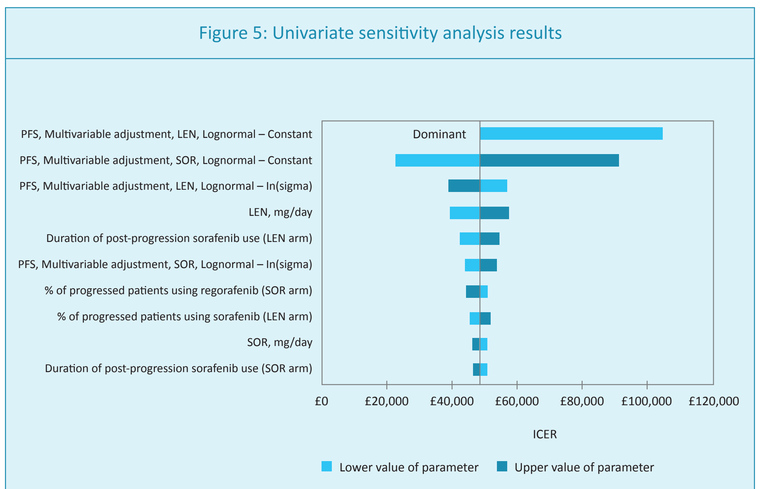
Figure 4: Cost-effectiveness plane



Abbreviations: QALYs, quality-adjusted life-years.

- The proportion of simulations considered cost-effective at a threshold of £50,000 per QALY was 56%
- Four of the ten most influential parameters identified in univariate sensitivity analysis are those describing the PFS curves for each of sorafenib and lenvatinib **(Figure 5)**; however, this result should be treated with some caution given that the highly correlated coefficients for this model are being varied as if they are independent from one another

Figure 5: Univariate sensitivity analysis results



Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; PFS, progression-free survival; SOR, sorafenib.

- The scenario analysis in which no adjustment is made for baseline characteristics resulted in a modest change in the ICER of 7% (£51,895)
- Results when considering alternative PAS discounts for lenvatinib and sorafenib ranged from dominant to an ICER of £101,470 **(Table 2)**

Table 2: Results of PAS discount scenario analysis

ICER for lenvatinib vs sorafenib†		Sorafenib PAS discount			
		20%	40%	60%	80%
Lenvatinib PAS discount	**20%**	**£36,970**	£58,470	£79,970	£101,470
	40%	**£3,945**	**£25,445**	**£46,945**	£68,445
	60%	**Dominant**	**Dominant**	**£13,921**	**£35,421**
	80%	**Dominant**	**Dominant**	**Dominant**	**£2,396**

† Results highlighted in bold indicate scenarios in which lenvatinib would be considered cost-effective at a WTP threshold of £50,000 per QALY; a 'dominant' result indicates scenarios in which lenvatinib is associated with lower costs and better outcomes (i.e. more QALYs) compared with sorafenib
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

CONCLUSIONS

- The HR for OS was nominally superior in favour of lenvatinib following adjustment for baseline imbalances. The model accounted for these imbalances, and predicted a mean survival gain of 3.1 months for lenvatinib patients
- The results incorporating PAS discounts used for decision making remain confidential to NICE and NHS England. It is expected that the true ICER incorporating these discounts for lenvatinib and sorafenib falls below £30,000 per QALY, as NICE have stated that, before the application of end-of-life criteria, "cost-effectiveness estimates for lenvatinib compared with sorafenib are within the range NICE normally considers acceptable" [6]
- Given that life expectancy for advanced HCC patients is less than 24 months [8], and the estimated life extension for lenvatinib patients exceeds 3 months, lenvatinib meets both NICE end-of-life criteria, and therefore a willingness-to-pay threshold of £50,000 per QALY can be applied
- Lenvatinib is associated with an ICER of £48,494, and so may be considered a cost-effective use of NHS resources at list price under the assumption that end of life criteria are met
- A key limitation of PSMs is the assumption of independence for highly correlated clinical outcomes (i.e. PFS and OS), which may have implications for the reliability of extrapolation; however, in this instance the implications are modest as trial follow-up data are relatively complete
- The model had good internal validity, with little difference between modelled OS and PFS outcomes and those observed in REFLECT
- The economic evaluation was considered highly relevant to the population of patients with HCC in England and Wales, as the core assumptions were informed and validated by UK-based clinical experts, and the overall trial population in REFLECT is considered to align with the UK population with HCC

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