

Lenvatinib for untreated advanced hepatocellular carcinoma

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

- 1.1 Lenvatinib is recommended as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults, only if:
- they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and
 - the company provides it according to the [commercial arrangement](#).
- 1.2 This recommendation is not intended to affect treatment with lenvatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Advanced unresectable hepatocellular carcinoma is treated with sorafenib, but some people cannot tolerate it because of side effects.

Clinical trial evidence shows that lenvatinib slows disease progression and causes more tumours to shrink than sorafenib. The evidence also shows that people having lenvatinib live for about as long as those having sorafenib. Lenvatinib has different side effects to sorafenib and this would benefit some people.

Using the most plausible assumptions and including the commercial arrangement, the cost-effectiveness estimates for lenvatinib compared with sorafenib are within the range NICE normally considers acceptable. Therefore, lenvatinib is recommended for untreated, advanced, unresectable hepatocellular carcinoma in adults with Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

2 Information about lenvatinib

Marketing authorisation indication	Lenvatinib (Lenvima, Eisai) is indicated as monotherapy for 'the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy'.
Dosage in the marketing authorisation	The daily dose of lenvatinib in the summary of product characteristics is 8 mg (2×4 mg capsules) given orally for patients who weigh less than 60 kg, and 12 mg (3×4 mg capsules) orally for patients who weigh 60 kg or over (based on company submission). The summary of product characteristics advises that dose adjustments are not needed on the basis of hepatic function in people with Child–Pugh grade A liver impairment. It advises that the available data are not sufficient to make a dosing recommendation for people with Child–Pugh grade B liver impairment; safety should be closely monitored in these patients. Because lenvatinib has not been studied in patients with Child–Pugh grade C liver impairment, the summary of product characteristics does not advise use in these patients.
Price	<p>£1,437 for 30×4 mg capsules (excluding VAT; British national formulary [BNF] online [accessed May 2018]).</p> <p>The company has a commercial agreement (patient access scheme). This makes lenvatinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Eisai and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Unmet need

People with advanced hepatocellular carcinoma would welcome an alternative treatment option

- 3.1 Advanced unresectable hepatocellular carcinoma is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms, including pain, digestive problems and weight loss. The patient experts noted that people with advanced unresectable hepatocellular carcinoma consider improving their quality of life to be particularly important. Sorafenib is currently the only licensed option for people who have not already had systemic treatment. The committee understood that an alternative first-line treatment option would be valuable to patients with the condition.

Treatment pathway

Lenvatinib may offer benefits over current treatment options

- 3.2 The clinical experts explained that there is a low response rate with sorafenib and around 25% of patients stop treatment because they cannot tolerate it. They added that hand-foot syndrome is more common with sorafenib, which can be very unpleasant for patients. The committee was aware that lenvatinib also has common side effects, such as hypertension. It considered that lenvatinib and sorafenib have different side-effect profiles, and that tolerability of each drug would depend on the patient. A patient expert noted that lenvatinib offers a longer time to disease progression compared with sorafenib, although there is no evidence showing a difference in overall survival. The clinical experts indicated that they may use lenvatinib instead of sorafenib based on individual patient characteristics, but also because of the improvements it offers in side-effect profile, time to disease progression and response rates. The committee agreed that lenvatinib may offer improved

benefits for people with advanced unresectable hepatocellular carcinoma who have not had systemic treatment.

Population

The company positioned lenvatinib in line with the REFLECT trial

- 3.3 The company positioned lenvatinib in line with the REFLECT trial (that is, for adults with advanced unresectable hepatocellular carcinoma who have not already had systemic treatment and who have Child–Pugh grade A liver impairment). This was narrower than both the marketing authorisation and the final scope issued by NICE, but was in line with the REFLECT trial population and previous NICE technology appraisal guidance on [sorafenib for treating advanced hepatocellular carcinoma](#). The clinical experts explained that treatment may not be clinically effective in people with more impaired liver function (for example, people with Child–Pugh grade B liver impairment). The committee accepted the company's positioning of lenvatinib for adults with advanced unresectable hepatocellular carcinoma who have not already had systemic treatment and who have Child–Pugh grade A liver impairment.

Comparator

Sorafenib is the most relevant comparator

- 3.4 The company did not consider best supportive care to be an appropriate comparator because it is only used in clinical practice if systemic treatment is not appropriate. The company's clinical expert estimated that less than 5% of patients have best supportive care; most people instead have sorafenib. The clinical experts stated that most people would be eligible for systemic therapy and would have sorafenib. The committee concluded that sorafenib was the most relevant comparator.

Clinical evidence

REFLECT included a clinically appropriate population with Child–Pugh grade A liver impairment and ECOG performance status of 0 or 1

3.5 The clinical evidence came from a phase III, open-label randomised controlled trial (REFLECT) comparing lenvatinib with sorafenib for untreated, advanced hepatocellular carcinoma in 954 adults with Child–Pugh grade A liver impairment and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial excluded people with Child–Pugh grade B liver impairment or worse and people with an ECOG performance status of 2 or more, and the committee understood the results may not be generalisable to these groups. The clinical experts explained that lenvatinib may not be clinically effective in these groups, and that these criteria are also used in clinical practice to decide the most appropriate treatment options. The Cancer Drugs Fund clinical lead confirmed that the NHS England treatment criteria would reflect these eligibility criteria. The committee concluded that people with both Child–Pugh grade A liver impairment and ECOG performance status 0 to 1 was the most clinically appropriate population, and agreed to consider the trial inclusion criteria when making its recommendations.

Baseline characteristics were imbalanced but the clinical-effectiveness results are relevant to NHS practice

3.6 The company highlighted that in REFLECT, more people in the lenvatinib group had alpha-fetoprotein levels of 200 ng/ml or above compared with the sorafenib group, and there were differences in the pre-existing liver conditions associated with hepatocellular carcinoma (hepatitis C, hepatitis B or alcohol) across the 2 groups. The company explained that these variables were not included as randomisation stratification factors. It considered that these imbalances in baseline characteristics may affect the treatment benefit seen with lenvatinib because they were potentially important prognostic factors. However, the clinical experts explained that a similar treatment benefit was likely regardless of pre-existing liver conditions. The ERG's clinical expert agreed that although alpha-fetoprotein level was a prognostic factor, they did not consider the cut-off value of 200 ng/ml to be clinically relevant. The committee understood that the company had made adjustments to account for the imbalances in baseline

characteristics (see [section 3.12](#)) and that the difference in alpha-fetoprotein levels may not be clinically meaningful. The committee concluded that although there may be some imbalances in the baseline characteristics, the REFLECT trial was relevant to clinical practice in the NHS.

It is appropriate to use clinical data from the full trial population

3.7 Around two thirds of the trial population were from the Asia-Pacific region and the rest were from Western countries including the UK. The ERG noted important differences between the Western subgroup and the full trial population (the Western subgroup was heavier, had more heart disease, less underlying cirrhosis, less hepatitis B and more pre-existing hepatitis C or alcohol-related conditions), but explained that these differences may not have changed the relative treatment effect. The ERG also noted that baseline characteristics in the full population were more balanced than those in the Western subgroup, and the clinical experts agreed that the overall population reflected clinical practice in England. The committee was aware that the imbalance in post-progression treatment was larger in the Western subgroup compared with the full trial population. It understood that after adjusting for post-progression treatment (see [section 3.13](#)), the overall survival results were similar for both the Western subgroup and the full trial population. The committee agreed that there was no sufficient justification for using results from the Western subgroup instead of the full trial population because it was not more clinically relevant and had a relatively small sample size. It agreed that the baseline characteristics for the full trial population were generally in line with clinical practice in England, and it preferred to use these results.

The company's updated approach to censoring is appropriate

3.8 In the company's original submission, progression-free survival results were censored if there was no disease progression when treatment is stopped (because not all patients were followed up until the end of the trial). The ERG explained that this could be considered to be informative censoring (that is, reasons for drop-out may potentially be related to disease progression or survival time) and that it may lead to inaccurate conclusions about the size of the treatment difference between lenvatinib and sorafenib. Based on the clinical evidence presented, the ERG explained that the company's method of censoring would likely favour lenvatinib because more people stopped lenvatinib either through choice or because of adverse effects. More events may

therefore be missed because of censoring in the lenvatinib group. In response to consultation, the company updated its censoring approach to include all events in the analysis and only censored if there were missing assessments or no disease progression at the last assessment. Progression-free survival was lower with the updated censoring approach, but the results still showed a statistically significant improvement for lenvatinib compared with sorafenib. The committee concluded that the company's updated approach to censoring (that is, including all events in the analysis and only censoring missing assessments or patients with no disease progression at last assessment) was appropriate.

More patients had post-progression treatment in the sorafenib arm than in the lenvatinib arm and the overall survival results may favour sorafenib

3.9 In REFLECT, treatment after disease progression was allowed in both the lenvatinib and sorafenib arms. In the lenvatinib arm, patients could switch to sorafenib but were not eligible for trials using second-line treatment. In the sorafenib arm, patients could continue sorafenib and were eligible for trials using second-line treatments such as regorafenib. Regorafenib is not used in England because it is not currently recommended by NICE (see the NICE technology appraisal guidance on [regorafenib for previously treated advanced hepatocellular carcinoma](#)). The committee understood that 51% of patients in the sorafenib group had post-progression treatment compared with only 43% in the lenvatinib group. It noted that longer overall survival may be expected for people having post-progression treatment, so the overall survival results may favour patients randomised to sorafenib. The committee concluded that more patients having post-progression treatment in the sorafenib arm may affect the estimates of treatment effect for overall survival.

Overall survival with lenvatinib is non-inferior compared with sorafenib

3.10 The primary end point of REFLECT was overall survival and the study was powered to demonstrate non-inferiority. There was no statistically significant difference in overall survival (see [table 1](#)). However, the results for overall survival met the pre-specified criteria for non-inferiority (that is, the upper limit of the 95% confidence interval was less than 1.08). There was also a statistically significant improvement in median investigator-assessed progression-free

survival with lenvatinib (7.4 months) compared with sorafenib (3.7 months). Similar results were reported for independently assessed progression-free survival using standard response evaluation criteria in solid tumours (RECIST) to measure disease progression, and a modified version of RECIST that evaluates change more accurately in hepatocellular carcinoma. The committee understood that the proportional hazards assumption (that is, there is a constant treatment effect over time) was not met for the overall and progression-free survival results, so these should be interpreted with caution. The committee noted the consistency in the progression-free survival results using the 2 different censoring rules (see [section 3.8](#)), and agreed there was robust evidence of a progression-free survival benefit, although there is some uncertainty around the size of this benefit (see [section 3.15](#)). Lenvatinib also improved response rates compared with sorafenib. The committee concluded that overall survival with lenvatinib was non-inferior compared with sorafenib.

Table 1 Clinical-effectiveness results from REFLECT

Outcome	Lenvatinib – median (range)	Sorafenib – median (range)	Result – (95% CI)
Overall survival			
Unadjusted	13.6 (12.1 to 14.9)	12.3 (10.4 to 13.9)	HR 0.92 (0.79 to 1.06)
Adjusted for post-progression treatment	–	–	Confidential and cannot be reported here
Investigator-assessed progression-free survival			
Using modified RECIST	7.4 (6.9 to 8.8)	3.7 (3.6 to 4.6)	HR 0.66 (0.57 to 0.77)
Using modified RECIST and committee's preferred censoring rules	–	–	Confidential and cannot be reported here
Independently assessed progression-free survival			
Using modified RECIST	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.7)	HR 0.64 (0.55 to 0.75)
Using standard RECIST (1.1)	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.9)	HR 0.65 (0.56 to 0.77)

Response rate			
Objective response rate	24.1%	9.2%	OR 3.13 (2.15 to 4.56)
Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RECIST, response evaluation criteria in solid tumours.			

The company's model

The model structure is appropriate for decision-making

3.11 The company used a partitioned survival model with 3 health states (progression free, progressed disease and death). The committee noted that although progression-free and overall survival data were relatively mature in the REFLECT trial, extrapolations were needed for both to model effects over a lifetime horizon. The ERG considered the model structure to be appropriate but identified an inconsistency in the half-cycle correction because it was not fully applied to all costs and quality-adjusted life years (QALYs). The ERG corrected this in its own preferred base case. At clarification, the company did not consider this to be an error and so did not correct it. Ultimately these corrections had little effect on the cost-effectiveness estimates, and the committee concluded that the model structure was appropriate for decision-making.

Survival estimates in the model

The company's adjustment for baseline characteristics using the corrected group prognosis method is acceptable

3.12 In its original submission, the company adjusted the treatment estimates used in the model to account for imbalances in baseline characteristics of patients in REFLECT. The company fitted multivariable parametric survival models to the progression-free and overall survival data and adjusted for covariates using the mean of covariates approach. The committee was aware that the company's model contained categorical variables (such as Child–Pugh grade) and that interpreting these variables using the mean of covariates approach is problematic. The committee considered the corrected group prognosis method to be more appropriate for adjusting for categorical variables. In response to consultation, the company revised its analyses to use the corrected group

prognosis method to adjust for baseline imbalances. However, the committee considered that there was still some uncertainty in the revised analyses; proportional hazards were not tested for all potential covariates, and choice of adjustment covariates was based on the pre-consultation overall survival model. However, on balance, the committee concluded that the company's adjustment for baseline characteristics using the corrected group prognosis method was acceptable.

It is appropriate to include post-progression benefit in line with REFLECT

- 3.13 The company's base case included the clinical benefit of post-progression treatment. The committee recalled that in REFLECT, fewer people in the lenvatinib arm had post-progression treatment compared with the sorafenib arm (see [section 3.9](#)). The ERG explained that this may bias overall survival estimates in favour of sorafenib, because people who have post-progression treatment may have longer overall survival. The committee understood that the company used a simple binary adjustment for post-progression treatment (patients either had or did not have post-progression treatment). The committee considered that there was some uncertainty in the company's adjustment; there were missing data about the types of post-progression treatments people had, and the company did not explore alternative statistical adjustments for post-progression treatment (for example, by including post-progression treatment as a time-varying covariate). However, mindful of the risk of bias from the post-progression treatment distribution in the trial, the committee concluded that it could accept the inclusion of post-progression treatment benefit in line with REFLECT.

A log-logistic distribution is appropriate for extrapolating overall survival

- 3.14 The company used a log-logistic model in its base case to extrapolate overall survival for both lenvatinib and sorafenib. The committee understood that this model provided a good fit to data from both treatment groups and concluded that a log-logistic distribution was appropriate for extrapolating overall survival for both lenvatinib and sorafenib.

Gamma extrapolation of the progression-free survival data

predicts lower survival than log-normal extrapolation but both are reasonable

3.15 In its original base case, the company used a log-normal distribution to extrapolate progression-free survival for both lenvatinib and sorafenib. At the first meeting, the committee considered that the gamma distribution was a better fit to the treatment groups. However, the committee was aware that both extrapolations were based on Kaplan–Meier data that had not been adjusted or censored in line with its preferences. In response to consultation, the company presented updated progression-free survival analyses based on the committee's preferred censoring approach (see [section 3.8](#)) and the corrected group prognosis method of adjusting for baseline characteristics (see [section 3.12](#)). In its updated base case, the company extrapolated progression-free survival using a gamma distribution and presented a log-normal distribution as an exploratory analysis. However, the company did not provide statistical indications of goodness of fit for the updated models. The committee visually assessed the model fit of both extrapolations compared with the updated Kaplan–Meier data and noted that both distributions appeared to be a reasonable fit to the adjusted trial data. However, it considered that evaluating the models without a statistical assessment of fit introduced some uncertainty about the choice of extrapolation. The committee concluded that both the gamma and log-normal extrapolations of progression-free survival were reasonable.

Costs in the model

Including drug wastage does not have a large effect on total costs

3.16 The company did not include drug wastage costs in its base-case analysis. The committee understood that in a previous NICE technology appraisal on [sorafenib for treating advanced hepatocellular carcinoma](#), it was considered appropriate to include drug wastage for up to 7 days. However, in a more recent NICE technology appraisal on [regorafenib for previously treated advanced hepatocellular carcinoma](#), the committee considered 7 days to be arbitrary and associated with some uncertainty. The ERG did a scenario analysis using drug costs based on the planned number of capsules and tablets needed each day. This led to only a modest reduction in total costs. The committee concluded that drug wastage did not have a large effect on the total costs.

It is acceptable to include the costs of post-progression treatment in line with REFLECT

3.17 In its original submission, the company's base case only included the costs of sorafenib and regorafenib after disease progression because these are the only licensed treatments for advanced hepatocellular carcinoma. The committee was aware that other treatments and procedures were also used after disease progression in REFLECT, but these costs had not been included in the company's base case. In response to consultation, the company included in its model the costs of all post-progression treatments and procedures used in REFLECT. The committee considered that because the model included the benefit of post-progression treatments, it was also appropriate to include the costs. Because of this, the committee concluded that the company's updated modelling of post-progression treatment costs was acceptable.

Utility values in the economic model

Utility values in the progressed state are acceptable

3.18 In its base case, the company used utility values from the full population in REFLECT for both lenvatinib and sorafenib because there was only a small difference in mean utility values. The company used a value of 0.745 in the progression-free state and 0.678 in the progressed state, although the company's clinical experts noted that the utility value in the progressed state was higher than would be expected given that advanced hepatocellular carcinoma can severely affect functioning and wellbeing. The committee noted that the final measurement in the post-progression stage was 30 days after the final dose of lenvatinib or sorafenib so these measurements may not include the full effect of disease progression on health-related quality of life. The ERG did a scenario analysis using a utility value of 0.50 in the progressed disease state. The committee observed that this led to only a small increase in the cost-effectiveness estimates, and concluded that the utility values used in the company's analysis were acceptable.

Cost-effectiveness estimate

The company's updated base-case ICER is above the range normally considered to be an acceptable use of NHS resources

3.19 The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's updated base case after consultation. This was recalculated by the ERG to include the confidential commercial arrangements for lenvatinib and sorafenib. The company's model assumptions included:

- a larger discount as part of the patient access scheme
- updated censoring rules for progression-free survival that include all events in the analysis and only censor missing assessments or patients with no disease progression at last assessment
- adjustment for baseline characteristic imbalances using the corrected group prognosis method
- progression-free survival extrapolated using the gamma distribution
- post-progression treatment costs and benefits modelled in line with REFLECT.

The committee concluded that the company's base-case ICER for lenvatinib compared with sorafenib was higher than the range normally considered to be an acceptable use of NHS resources.

The most plausible ICER for lenvatinib compared with sorafenib is within the range normally considered to be an acceptable use of NHS resources

3.20 The committee considered that the company's updated model had captured its preferred assumptions. However, it was aware that there was still some uncertainty in the model because there was no statistical goodness-of-fit assessment of the progression-free survival extrapolation, and no exploration of alternative statistical adjustments for post-progression treatment. The committee recalled that the log-normal extrapolation gave substantially lower ICER estimates than the gamma extrapolation. It also recognised that although it had accepted the company's modelling of post-progression treatment costs and benefits, there were still flaws with the company's method of adjustment,

and uncertainty from missing data on post-progression treatment (see [section 3.13](#)). Having considered all these factors, the committee concluded that the most plausible ICER for lenvatinib compared with sorafenib (including the confidential commercial arrangements for both drugs) is within the range normally considered to be an acceptable use of NHS resources (the exact ICER is confidential and cannot be reported here). The committee concluded to recommend lenvatinib for untreated, advanced, unresectable hepatocellular carcinoma in adults with Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

End of life

End-of-life considerations are not relevant because lenvatinib is recommended for routine commissioning

3.21 In the first committee meeting, the committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [guide to the methods of technology appraisal](#). It concluded that lenvatinib met the short life expectancy criterion, but that it was uncertain whether lenvatinib met the extension to life criterion. In the second committee meeting, the committee considered that the end-of-life considerations were no longer relevant to the appraisal decision because the most plausible ICER was within the range normally considered to be an acceptable use of NHS resources.

Equality

There are no equality issues relevant to the recommendations

3.22 The committee considered whether its recommendations were associated with any potential issues related to equality. The committee noted comments from patient and clinical expert submissions that hepatocellular carcinoma is more common in men and people of some ethnicities. The committee did not consider this to be an equality issue because its recommendations apply to everyone with advanced, unresectable hepatocellular carcinoma.

Innovation

There is no evidence of any additional benefits with lenvatinib

- 3.23 The company considered lenvatinib to be innovative because there is an unmet need for treatment options other than sorafenib that delay disease progression and improve survival without decreasing health-related quality of life. The clinical experts acknowledged that lenvatinib is the only alternative first-line treatment option for advanced hepatocellular carcinoma in over 10 years, and they were not aware of any benefits that were not already captured in the model. The committee concluded that lenvatinib would be beneficial for patients (see [section 3.2](#)) but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

4 Implementation

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated, advanced, unresectable hepatocellular carcinoma and the doctor responsible for their care thinks that lenvatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation

