NICE National Institute for Health and Care Excellence

NICE guidance

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

1 Recommendations

1.1 Ivosidenib is recommended, within its marketing authorisation, as an option for treating locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation in adults after 1 or more systemic treatments. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Usual treatment for locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation after systemic treatment is modified folinic acid plus fluorouracil and oxaliplatin (mFOLFOX), and best supportive care to manage symptoms.

Clinical trial evidence shows that ivosidenib increases how long people live and how long they have before their cancer gets worse compared with placebo.

Ivosidenib has not been directly compared with mFOLFOX in a clinical trial. An indirect comparison suggests that ivosidenib increases how long people live compared with mFOLFOX.

There is a considerable unmet need for treatments for locally advanced or metastatic cholangiocarcinoma. When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, ivosidenib is recommended.

2 Information about ivosidenib

Marketing authorisation indication

2.1 Ivosidenib (Tibsovo, Servier) monotherapy is indicated for 'the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ivosidenib.

Price

2.3 The list price of a 60-tablet pack of 250 mg ivosidenib is £12,500 (excluding VAT; BNF online, accessed October 2023).

2.4 The company has a commercial arrangement. This makes ivosidenib 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.

3 Committee discussion

The evaluation committee considered evidence submitted by Servier, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Unmet need

3.1 Cholangiocarcinoma is a rare cancer of the bile ducts. More than 90% of cholangiocarcinomas are adenocarcinomas that arise from the intrahepatic or extrahepatic epithelial cells of the biliary tract. A range of genetic alterations can promote cholangiocarcinoma, including mutations in the IDH1, IDH2, IDH3 and FGFR2 genes. The committee heard that cholangiocarcinoma often presents with non-specific symptoms, and is frequently diagnosed as cancer of an unknown origin. There are no specific screening methods for reliably detecting cholangiocarcinoma in its early stages. This regularly leads to people being diagnosed when the cancer is advanced or metastatic and incurable. There are very few treatment options available for cholangiocarcinoma. For some people a curative surgical resection may be an option, but for those with unresectable locally advanced or metastatic cancer, palliative chemotherapy is the primary treatment option. The patient expert explained that existing treatments can result in harmful side effects that have a considerable impact on people's quality of life and that of their families and carers. Patient and clinical experts commented that chemotherapy, including modified folinic acid plus fluorouracil and oxaliplatin (mFOLFOX), has a considerable negative impact on the physical and mental health of those who have the treatment. The patient expert noted that travelling to hospital to have mFOLFOX treatment was a substantial burden. They noted the benefit of ivosidenib being an oral treatment. They said that people with cholangiocarcinoma are often not well enough to travel to the hospital on their own to have chemotherapy. They said that an oral treatment at home is much more convenient. The patient expert also noted that, comparatively, ivosidenib is generally well tolerated. The committee acknowledged that there is a considerable unmet need in this treatment area.

Clinical management

Treatment pathway and comparators

3.2 First-line treatment of cholangiocarcinoma with an IDH1 R132 mutation is cisplatin–gemcitabine chemotherapy, followed by second-line modified folinic acid plus fluorouracil and oxaliplatin (mFOLFOX) or best supportive care (BSC) to manage symptoms. The marketing authorisation for ivosidenib is for people who have had at least 1 previous line of treatment, so it includes use beyond second line. The clinical experts explained that in NHS practice, people will have only had 1 line of treatment before moving onto mFOLFOX or BSC (described by the company as active symptom control). The clinical experts advised that only approximately 40% to 45% of people will go on to have mFOLFOX after cisplatin–gemcitabine chemotherapy. The experts reiterated that this is because mFOLFOX can be poorly tolerated (see section 3.1). The committee concluded that mFOLFOX and BSC were appropriate comparators.

Clinical effectiveness

Clinical-effectiveness evidence: ClarIDHy trial

3.3 The clinical-effectiveness evidence for ivosidenib came from the ClarIDHy clinical trial. This was a multinational, randomised, double-blind phase 3 trial that compared ivosidenib with placebo. Results from the placebo arm of the trial informed the BSC arm of the economic model. People in the trial were adults with a confirmed diagnosis of unresectable or metastatic cholangiocarcinoma with a mutated IDH1 gene who had had at least 1 and no more than 2 lines of previous treatment. The primary outcome was progression-free survival (PFS). Ivosidenib significantly improved PFS compared with placebo (hazard ratio 0.37, 95% confidence interval 0.25 to 0.54, $p< 0.0001$). People in the placebo arm were allowed to cross over into the ivosidenib arm when their cancer progressed. Most people in the placebo arm (43 out of 61) crossed over to the ivosidenib arm. The company used the rank preserving structural failure time (RPSFT) method to mitigate bias caused by treatment switching, which the EAG deemed appropriate. After adjustment, ivosidenib was shown to significantly improve overall survival

(OS) compared with placebo (hazard ratio 0.49, 95% confidence interval 0.34 to 0.70, p< 0.0001). The committee concluded that ivosidenib improved PFS and OS compared with placebo.

Indirect treatment comparison

3.4 The company did a Bucher indirect treatment comparison (ITC) to compare the OS of ivosidenib with mFOLFOX. The ABC-06 trial was a randomised, multicentre, open-label phase 3 study that compared a combination of folinic acid plus fluorouracil and oxaliplatin (FOLFOX, an unmodified version of mFOLFOX) and active symptom control (ASC, also known as BSC) with ASC alone. Data from the unmodified FOLFOX plus ASC arm in the ABC-06 trial informed the clinical outcomes for mFOLFOX. The people in the trial had locally advanced or metastatic biliary tract cancer previously treated with cisplatin–gemcitabine chemotherapy. The ABC-06 trial did not capture IDH1 mutation status. The ITC was done only for OS because the ABC-06 trial did not report PFS in the ASC alone arm. Rather than use the intention to treat (ITT) population from the ClarIDHy trial, the company used a subgroup for the ITC. The subgroup was of people who had had only 1 line of treatment. The company explained that this was done to better match the population of the ABC-06 trial, which only included people who had had only 1 line of treatment. The company said that this also better reflected NHS clinical practice (see section 3.2). The clinical experts agreed that the ClarIDHy subgroup used for the ITC reflected NHS clinical practice. They noted that the number of previous lines of treatment was unlikely to affect the overall response to ivosidenib treatment. The ITC results showed that ivosidenib improved OS compared with mFOLFOX (after RPSFT adjustment), but the result was not statistically significant (the company considers the exact results to be confidential, so they cannot be reported here). The EAG raised concerns over the reporting of the ITC, including a lack of justification and clarity about the ClarIDHy trial subgroup selection. It was concerned that there was a discrepancy in the numbers that the company reported it had used to inform the analyses. After the meeting, the company provided extra information to explain the discrepancy in the subgroup numbers, which the EAG was satisfied with. The EAG provided a scenario in which the hazard ratio was derived from ITT data from the ClarIDHy trial. This resulted in a large increase in the incremental cost-effectiveness ratio (ICER). The committee acknowledged the lack of clarity and

justification around the selection of the ClarIDHy subgroup and understood that this could have affected the overall results. The committee noted that there was uncertainty around the appropriateness of the company's ITC between ivosidenib and mFOLFOX and the subgroup used in the analysis. But it concluded that the ITC and subgroup results were sufficient for decision making.

Economic model

Company's model structure

3.5 The company developed a partitioned survival model with 3 discrete health states: progression free, progressed disease, and death. Progression-free and progressed states were further divided into on-treatment and off-treatment substates. The EAG agreed that the structure of the economic model was appropriate and consistent with NICE's technology appraisal guidance on pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. The committee concluded that the economic model was acceptable.

Extrapolation of overall survival curves

Ivosidenib overall survival

3.6 The company selected the log-normal survival curve to model OS data for ivosidenib over a lifetime horizon. This predicted that at 5 years 5.6% of people would be alive. It noted that the log-normal survival curve provided a good visual fit to the observed data. It noted that the log-normal survival curve also had the lowest Akaike's information criterion (AIC) and second lowest Bayesian information criterion (BIC) of all the fitted curves. The company also explored 5 other parametric curves and chose to use the log-logistic (more optimistic) and exponential (more pessimistic) curves in its scenario analyses. The EAG noted that the choice of survival curve used had a large impact on the ICER. It noted that the visual fit was similar for each of the 6 curves explored, and the statistical goodness of fits fell within a narrow range. It preferred the generalised gamma

curve to extrapolate ivosidenib OS data, noting that it had a good visual fit to the observed data and provided a middle ground in terms of extrapolated survival landmarks. The generalised gamma curve predicted that 3.6% of people would be alive at 5 years. The committee noted that the company's preferred log-normal curve predicted that 0.3% of people would be alive at 20 years. One of the clinical experts explained that some people may be alive 20 years after diagnosis. But they explained that this is unlikely to be because of treatment with ivosidenib and is likely to be through some other mechanism, such as the person having curative resection. The clinical expert emphasised that treatment with ivosidenib is not curative but aims to keep the cancer stable for as long as possible. The committee considered that both the company's and the EAG's preferred parametric survival curves could fit with expected survival (based on clinical expert opinion) at 5 years, 10 years and 20 years. The committee concluded that both the log-normal and generalised gamma curves were plausible, and considered this when determining its preferred ICER.

BSC overall survival

3.7 Both the company and the EAG agreed on using the Weibull curve to extrapolate OS data in the BSC arm. This curve predicted that there would be no people alive at 5 years. The committee heard from the clinical experts that for people who have progressed after first-line treatment, 5-year survival is approximately between 0% and 3%. The EAG noted that the Weibull curve predicted that 2.9% of people would be alive at 2 years and 0.0% would be alive at 5 years. The EAG agreed with the company that the log-logistic, log-normal and generalised gamma curves may have overestimated OS for BSC and should be excluded from the selection. But based on statistical and visual fit, and clinical plausibility of extrapolations, the exponential and Gompertz curves could provide potentially valid options. The committee noted that some survival curves, ruled out by both the company and EAG, also reflected expert opinion on survival at 2 years and 5 years. The committee highlighted that the log-normal curve predicted OS at 5 years to be 1.2% and was potentially valid. It noted that using a combination of a log-normal extrapolation for ivosidenib OS (see section 3.6) and the Weibull extrapolation for BSC OS may underestimate the ICER. The committee considered that the company's and the EAG's preferred Weibull curve was consistent with clinical expert opinion. It acknowledged that there was

uncertainty in this selection, because other curves were also potentially valid. The committee concluded that the Weibull curve was acceptable for decision making.

Ivosidenib treatment beyond disease progression

3.8 The summary of product characteristics for ivosidenib states that treatment should be continued until disease progression or until treatment is no longer tolerated. For this reason, in its economic model, the company capped time on treatment at disease progression and used the log-normal PFS extrapolation as a proxy for time on treatment. The EAG commented that treatment with ivosidenib beyond progression was allowed in the ClarIDHy trial when the investigator deemed that there was clinical benefit. The EAG suggested that this treatment beyond progression may have had a positive effect on OS for ivosidenib. It also noted that the company's choice of extrapolation for PFS (log-normal) may have underestimated PFS in the tail of the Kaplan–Meier data. It noted that this may further artificially reduce treatment costs if used to cap time on treatment. The EAG also noted that the company's chosen PFS extrapolation fell below the observed time-on-treatment data from the ClarIDHy trial. It noted that using a poorly fitted PFS curve as a proxy for time on treatment may artificially reduce extrapolated time on treatment compared with what might be expected in clinical practice. The EAG preferred to keep the log-normal PFS curve for ivosidenib but to allow time on treatment to follow the fitted generalised gamma curve. The committee heard from the clinical experts that in clinical practice it would be unlikely for ivosidenib to be used beyond disease progression. The experts noted that any treatment beyond progression in clinical practice was only likely to happen if there was difficulty confirming progression because of an unclear radiological presentation. The committee agreed that based on expert advice, treatment beyond progression would be unlikely in clinical practice. It also agreed with the EAG that allowing treatment with ivosidenib beyond progression when the investigator deemed that there was clinical benefit may have had a positive effect on OS. The committee noted that the company's chosen extrapolation for PFS (the log-normal) did underestimate PFS compared with the tail of the Kaplan–Meier data from the ClarIDHy trial. It noted that because the company capped time on treatment for ivosidenib at disease progression, and because this had been underestimated by the company's extrapolation, ivosidenib's costs

would likely be underestimated. The committee noted that the EAG's approach to modelling time on treatment using the generalised gamma curve helped to account for underestimated costs. The committee concluded that it preferred to model time on treatment using a generalised gamma extrapolation.

Modelling time on treatment for mFOLFOX

3.9 The company used unadjusted PFS from the ABC-06 trial to estimate time on treatment for mFOLFOX for up to 12 cycles of treatment. The EAG preferred to use an exponential distribution informed by the median number of FOLFOX treatment cycles observed in the ABC-06 trial. The EAG noted that the company's approach failed to account for discontinuation because of other reasons. It noted that the company's approach also overestimated the number of cycles that people have in the model compared with what was observed in the ABC-06 trial. The company commented that people are more likely to complete a course of treatment with a fixed maximum duration (such as mFOLFOX, which is administered for up to 12 cycles) compared with treatment administered over a longer term. So, to assume that people stop treatment at a constant rate based on the median number of cycles, may underestimate the proportion of people who complete all 12 cycles. The EAG checked the impact in the model of applying the constant rate of discontinuation based on the median number of FOLFOX cycles observed in the ABC-06 trial. The exact proportion of people who complete all 12 cycles using this method is confidential and cannot be reported here. But the EAG noted that it appeared to provide a reasonable fit to the observed treatment data from the ABC-06 trial. The committee agreed that the company's approach may have overestimated the number of cycles that people have in the model compared with the ABC-06 trial. It concluded that the most appropriate method for modelling mFOLFOX time on treatment was to use an exponential distribution informed by the median number of FOLFOX treatment cycles observed in the ABC-06 trial.

Inclusion of subsequent treatment costs

3.10 A proportion of people in the ClarIDHy trial (38.9%) went on to have further systemic anticancer treatment after disease progression on ivosidenib. The

company noted that chemotherapy was the most common subsequent treatment. The company excluded the costs of further treatment upon disease progression from its base-case cost-effectiveness analysis. It noted that the exclusion of subsequent treatment costs is consistent with the approach taken in NICE's technology appraisal guidance on pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Also, the company commented that many of the subsequent treatments used in the ClarIDHy trial were investigational treatments that are not routinely used in clinical practice. The company provided scenarios that included subsequent mFOLFOX treatment costs across both the ivosidenib and placebo treatment arms. The company estimated the costs by multiplying treatment cycle cost by a median number of treatment cycles. The EAG considered it more appropriate to include the costs of subsequent treatment with chemotherapy for the ivosidenib arm only. It noted that this was consistent with the efficacy data informing the model and expected clinical practice. The EAG also modelled subsequent treatment costs by recycling the expected discounted cost of mFOLFOX and applying it to the observed proportion of people who had further treatment in the ivosidenib arm. At technical engagement, 2 clinical experts confirmed that subsequent treatment would likely be offered to people after progression on ivosidenib if they were fit enough to have it. One expert also noted that it was unlikely that people having BSC for symptom control would have a subsequent treatment. The committee concluded that subsequent treatment costs should be included for the ivosidenib arm only.

Inclusion of IDH1 testing costs

3.11 The company claimed that costs incurred by IDH1 testing should not be included in the economic model because it is now part of NHS England's national genomic test directory. The EAG noted that IDH1 testing is not necessarily requested or reported in practice, despite being in the national test directory. Because ivosidenib is an IDH1-targeted treatment, the EAG believed that the cost of IDH1 testing should be applied in the economic model. The committee agreed with the EAG's approach and concluded that IDH1 testing should be included in the cost-effectiveness analysis.

Application of health state utility

3.12 The company preferred to incorporate health state utility values based on treatment status only. Health state utility in the progression-free and progressive disease states differed only according to the proportion on treatment in each state for each comparator. The company noted that this approach provided the best fit to the data. The EAG commented that this approach was unsuitable. It noted that this approach does not account for any benefit from remaining progression free in the BSC arm of the model. It also noted that it limits the benefit for remaining progression free in the mFOLFOX arm for the fixed-duration treatment period. The EAG preferred to use utility values linked to progression status and treatment status. It noted that this approach fits better with the model structure, is more clinically credible, and is more consistent with the approach taken in previous relevant NICE technology appraisals. The committee agreed that the company's approach likely underestimated the benefits of remaining progression free in both the BSC and mFOLFOX arms of the model. It concluded that it preferred the EAG's approach to incorporating health state utility values linked to progression status and treatment status into the economic model.

Severity

3.13 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a severity modifier (a greater weight to quality-adjusted life years [QALYs]) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. In both the company and EAG analyses the proportional QALY shortfall was above 0.95, so a severity weight of 1.7 was applied. The committee concluded that the severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.14 NICE's health technology evaluations manual notes that, above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of uncertainty around the ICER and any benefits of the technology that were not captured in the QALY calculations. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented. The committee noted that there are no treatments recommend by NICE for people with cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments. So, it concluded that there is a substantial unmet need in this population (see section 3.1). The committee also noted that the maximum severity weighting was applied to the QALYs (see section 3.13) and took this into account. The committee noted uncertainty in the appropriateness of the indirect treatment comparison and the selection of the subgroup (see section 3.4). It also noted uncertainty in the parametric curves used to extrapolate OS for ivosidenib (see section 3.6) and for BSC (see section 3.7). It then agreed that the maximum acceptable ICER would be at the upper end of the £20,000 to £30,000 per QALY gained range that NICE considers a cost-effective use of NHS resources.

Committee-preferred cost-effectiveness estimates

3.15 The committee considered the results of its preferred scenarios. These included:

- using both the log-normal and generalised gamma curves to extrapolate OS for ivosidenib (see section 3.6)
- extrapolating time on treatment for ivosidenib using a generalised gamma curve (see section 3.8)
- modelling time on treatment for mFOLFOX using an exponential distribution that aligns with the median number of treatment cycles (see section 3.9)
- including subsequent treatment costs in the ivosidenib arm only (see section 3.10)

- including IDH1 testing costs (see section 3.11)
- linking utility values to progression status and treatment status (see section 3.12)
- applying a 1.7 severity weighting to the QALYs (see section 3.13).

In a fully incremental analysis, ivosidenib was the most cost-effective treatment compared with BSC and mFOLFOX. The exact results include the confidential price for ivosidenib, which means they cannot be reported here. When the generalised gamma curve was used to extrapolate OS for ivosidenib, the ICER for ivosidenib compared with best supportive care was slightly above the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). When the log-normal curve was used to extrapolate OS for ivosidenib, the ICER for ivosidenib compared with best supportive care was within the range. The committee was satisfied that the most plausible ICER for ivosidenib compared with best supportive care was likely to be between these 2 estimates, so within the range that NICE considers a cost-effective use of NHS resources. The ICER for mFOLFOX compared with best supportive care was higher than the ICER for ivosidenib compared with best supportive care (that is, mFOLFOX was extendedly dominated in both scenarios).

Other factors

Equality

3.16 The committee did not identify any equality issues.

Innovation

3.17 The committee considered if ivosidenib was innovative because it is an oral treatment. It noted that the benefit of ivosidenib being an oral treatment was likely accounted for in the disutility attributed to mFOLFOX. So, the committee

concluded that all additional benefits of ivosidenib had already been taken into account.

Conclusion

Ivosidenib is recommended

3.18 The committee noted that the most plausible ICER was within the range that NICE considers to be a cost-effective use of NHS resources. This included a severity weight of 1.7 applied to the QALYs. The committee concluded that ivosidenib is recommended for treating locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation in adults after 1 or more systemic treatments.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 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 draft guidance.

4.4 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 locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation and the doctor responsible for their care thinks that ivosidenib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien
Chair, technology appraisal committee C

NICE project team

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

Giacomo De Guisa and Madiha Adam
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