

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

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	4
2 Information about nivolumab with ipilimumab.....	5
Marketing authorisation indication	5
Dosage in the marketing authorisation	5
Price.....	5
3 Committee discussion	7
The condition.....	7
The treatment pathway	8
Clinical evidence	10
Economic model	12
Survival extrapolations	13
Utility values	14
Subsequent treatments	16
Cost-effectiveness estimates	17
Other factors	18
4 Implementation.....	19
5 Appraisal committee members and NICE project team	21
Appraisal committee members	21
NICE project team	21

1 Recommendations

- 1.1 Nivolumab plus ipilimumab is recommended, within its marketing authorisation, as an option for treating metastatic colorectal cancer with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency after fluoropyrimidine-based combination chemotherapy. It is recommended only if the company provides nivolumab and ipilimumab according to the [commercial arrangement](#).

Why the committee made these recommendations

People with previously treated metastatic colorectal cancer that has high MSI or MMR deficiency are usually offered combination chemotherapy including FOLFOX, FOLFIRI or trifluridine–tipiracil, and best supportive care. This is the same as what is offered for most other types of metastatic colorectal cancer.

Clinical trial evidence suggests that nivolumab plus ipilimumab may extend how long people live. The most relevant trial did not directly compare nivolumab plus ipilimumab with usual treatments, but indirect comparisons suggest that it substantially increases how long it takes for the cancer to get worse and how long people live.

The cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So, nivolumab plus ipilimumab is recommended.

2 Information about nivolumab with ipilimumab

Marketing authorisation indication

- 2.1 On 21 May 2021 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the extension of indication for nivolumab with ipilimumab (Opdivo and Yervoy, Bristol–Myers Squibb). The CHMP adopted a new indication as follows: adults with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.
- 2.2 The exact wording of this indication will be available in the summary of product characteristics when nivolumab and ipilimumab receives its marketing authorisation.

Dosage in the marketing authorisation

- 2.3 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.4 The list price of nivolumab is £2,633 per 240 mg per 24-ml vial (excluding VAT; BNF online, assessed March 2021). The company has a [commercial arrangement](#). This makes nivolumab 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.
- 2.5 The list price of ipilimumab is £15,000 per 200-mg vial (excluding VAT; BNF online, assessed March 2021). The company has a [commercial arrangement](#). This makes ipilimumab 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 [appraisal committee](#) considered evidence submitted by Bristol–Myers Squibb, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee recognised that there were areas of uncertainty associated with the analyses presented (see ERG report, table 1, page 18), and took these into account in its decision making. It discussed the following issues (issues 1 to 6), which were outstanding after the technical engagement stage.

The condition

There is an unmet need for treatments for metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

- 3.1 Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Mutations can cause microsatellite instability (MSI) or DNA mismatch repair (MMR) deficiency in some metastatic colorectal cancer cells. DNA MMR corrects errors that occur during DNA replication, so problems with DNA MMR can lead to mutations in the microsatellites (repetitive DNA sequences). This causes them to become unstable, resulting in cancerous tumours with high MSI. High MSI or DNA MMR deficiency occurs in around 4% of metastatic colorectal cancer. It is associated with a poorer prognosis and a greater risk of death than metastatic colorectal cancer without microsatellite instability. There are currently no specific treatments routinely commissioned for this type of colorectal cancer, so people are offered the same treatment whether or not their colorectal cancer has high MSI or DNA MMR deficiency. The committee concluded that there is an unmet need for treatments for this condition.

People with the condition and clinicians would welcome new

treatment options

- 3.2 The patient experts explained that a diagnosis of metastatic colorectal cancer with high MSI or DNA MMR deficiency affects the quality of life both physically and psychologically. They highlighted that current treatment options approved for use in the NHS for metastatic bowel cancer are extremely limited. They explained that nivolumab with ipilimumab offers them greater hope, additional treatment choice and extended survival. It also may have less debilitating side effects compared with current treatments that may not work as well for this type of colorectal cancer. In contrast to chemotherapy, the absence of side effects like nausea, stomach pain and fatigue means people have a better quality of life. The committee noted that nivolumab and ipilimumab are immunotherapies and work in a different way to chemotherapy and have a different safety profile. The patient experts noted that people appreciated the faster and less frequent administration of nivolumab with ipilimumab, and having potential fewer adverse effects compared with standard care. A clinical expert explained that, with a more effective treatment, there was potential that a person's cancer would respond well enough to have both longer survival and a better quality of life. The committee concluded that people with the condition and clinicians would welcome new treatment options.

The treatment pathway

Current standard care for people who have had previous treatment usually includes another fluoropyrimidine-based chemotherapy

- 3.3 Clinical experts explained that treatment options for previously treated metastatic colorectal cancer depend on previous treatments, fitness level and patient and clinician preference. Clinical experts explained there are currently no specific treatments available for colorectal cancer with high MSI or MMR deficiency, so the treatment pathway is normally the same as for colorectal cancer without these mutations. First-line treatments would normally use fluoropyrimidine-based combination chemotherapies such as folinic acid, fluorouracil (5-FU) and oxaliplatin (FOLFOX) or folinic

acid, 5-FU and irinotecan (FOLFIRI) or capecitabine and oxaliplatin (CAPOX). The clinical experts also noted that a proportion of people have 'triple therapy' that consists of folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFOXIRI or FOLFIRINOX), but this has a higher toxicity than other combinations. Clinical experts explained that there are limited second-line treatment options, so the treatment options are very similar and would normally involve trying an alternative combination (for example, FOLFOX if previously treated with FOLFIRI). Trifluridine–tipiracil is used as a third-line treatment and beyond, and once other options are exhausted. Best supportive care is used for people who cannot tolerate active treatment. The NICE scope also included single-agent irinotecan and raltitrexed as comparators, but the company did not include these as comparator treatments. Clinical experts explained that single-agent irinotecan is rarely used because of the toxicities compared with other options and similar efficacy. They also explained that raltitrexed is rarely used in clinical practice for specific indications only, such as for people with a history of heart disease or who develop angina on 5-FU-based chemotherapy. The committee concluded that the most appropriate comparators are FOLFOX, FOLFIRI and best supportive care for second-line treatments, and trifluridine–tipiracil and best supportive care for further lines of treatment.

Testing is routinely funded at diagnosis of metastatic colorectal cancer, and nivolumab with ipilimumab will be used as a second-line treatment

- 3.4 The committee was aware that molecular testing is needed to confirm high MSI or MMR deficiency. [NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer](#) recommends testing all people with colorectal cancer, when first diagnosed. The clinical experts explained that nivolumab with ipilimumab would likely be used as a second-line treatment for people with high MSI or MMR deficiency because it has a higher expected benefit and lower treatment burden. The clinical lead for the Cancer Drugs Fund explained that testing for high MSI and MMR deficiency is routinely commissioned for all people newly diagnosed with metastatic colorectal cancer. Therefore, people who are eligible would already be identified at an earlier treatment stage. The committee was satisfied with the place in

therapy and that people who are eligible would be identified at diagnosis of metastatic disease.

Clinical evidence

The population in CheckMate 142 is generalisable to people seen in NHS clinical practice

- 3.5 The clinical evidence for nivolumab with ipilimumab came from the single-arm phase 2, open-label, CheckMate 142 study. This study included 119 people with metastatic colorectal cancer with high MSI or MMR deficiency, previously treated with combination therapies. The clinical experts considered that people in the trial had a lot of previous treatments, with 40% having 3 or more previous systemic treatments. Some treatments did not reflect the UK treatment pathway, including vascular endothelial growth factor inhibitors and regorafenib. However, the clinical experts considered that these treatments would have minimal effect on treatment outcomes. The clinical experts considered the population included in CheckMate 142 would be generalisable to the people who would have nivolumab with ipilimumab in clinical practice. However, the population in CheckMate 142 may have had more extensive previous treatments than in NHS clinical practice because clinicians would prefer to use nivolumab with ipilimumab as a second-line treatment (see [section 3.4](#)). The committee concluded that CheckMate 142 is broadly generalisable to NHS clinical practice and appropriate for decision making.

The CheckMate 142 outcomes show high response rates and long overall and progression-free survival

- 3.6 The primary outcome in CheckMate 142 was objective response rate, which was a composite end point of complete and partial response measured by RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours). The objective response rate was 65% after a follow up of 51 months. The clinical experts considered that these response rates for nivolumab with ipilimumab were considerably greater than those they were used to seeing with current treatment. Clinical and patient experts

explained that response rates in colorectal cancer are not always accurate because inflammatory tissue or scarring can be seen with conventional imaging techniques. Therefore, the committee noted that response rates may not fully represent clinical benefit and other outcomes should also be considered. Secondary outcomes in the trial were progression-free survival and overall survival. The clinical experts considered that the observed survival results suggested highly promising efficacy of nivolumab with ipilimumab with long progression-free and overall survival, which suggested that the treatment could be curative. Median progression-free and median overall survival are academic-in-confidence and cannot be reported here. The committee concluded that nivolumab with ipilimumab is likely to be a clinically effective treatment for metastatic colorectal cancer.

The indirect comparison is highly uncertain, but nivolumab with ipilimumab is likely to substantially improve overall survival

- 3.7 CheckMate 142 is a single-arm trial and there is no evidence directly comparing the efficacy of nivolumab plus ipilimumab with other treatments. So, the company presented an indirect treatment comparison using unanchored matching-adjusted indirect comparisons (MAICs) with each relevant comparator. Mean progression-free survival and overall survival results from different studies were estimated by extrapolating from single arms of randomised controlled trials that used each comparator. The MAIC uses individual patient data from trials of 1 treatment to match baseline characteristics with trials of another treatment. After matching, outcomes may be easier to compare because the populations are likely to be more balanced. The company considered that this analysis compensated for some of the differences in study populations and was most appropriate in the absence of head-to-head clinical trial evidence or anchored indirect comparisons. The ERG considered that the adjustment provided in the MAIC analysis may have provided less biased estimates but there was no way of assessing residual bias or evaluate which adjustments reduced bias. Therefore, the ERG preferred a naive comparison because it was transparent in terms of the likely biases that existed within the comparison and to ensure the analysis did not introduce additional bias. The ERG also noted that both the naive comparison and the MAIC gave similar results. The committee

understood that for an unanchored MAIC, population adjustment methods should adjust for all effect modifiers and prognostic variables. It considered this was unlikely for each analysis in the MAIC and this would allow for residual bias. The committee considered whether the use of mean survival was appropriate because it is very sensitive to the extrapolation used (see [section 3.10](#)), and whether a restricted mean may have been more appropriate to provide the lower bound for the matching adjustment. The committee considered that both the unanchored MAIC and naive comparisons may not reduce the uncertainty or bias in any meaningful way. It concluded that, despite methodological concerns and substantial uncertainty, the size of benefit of nivolumab plus ipilimumab as measured by overall survival and progression-free survival was likely to be greater than current standard care.

Economic model

The company's economic model is suitable for decision making

- 3.8 The company used a partitioned survival model to estimate the cost effectiveness of nivolumab plus ipilimumab compared with FOLFOX, FOLFIRI, trifluridine–tipiracil and best supportive care. The model included 3 health states: pre-progression, post-progression, and death. Transitions between each health state were informed by progression-free survival and overall survival from CheckMate 142 and the MAIC comparison (see [section 3.7](#)). Each progression health state was also divided into people having treatment and not having treatment, with proportions determined by time on treatment in each trial. The ERG agreed that the company's model captured all relevant health states and partitioned survival models are used widely used in cancer modelling. The committee concluded that the company's model structure was acceptable for decision making.

Nivolumab with ipilimumab should be stopped as seen in CheckMate 142

- 3.9 In CheckMate 142, nivolumab with ipilimumab could be used until

disease progression or stopping treatment because of toxicity or death. The company also introduced a change in study protocol that meant people could stop treatment when clinicians considered maximum clinical benefit had been achieved after a minimum of 2 years. The company originally included a 2-year stopping rule in its model but removed this at technical engagement. The ERG considers that using the time on treatment seen in CheckMate 142 was appropriate and reflected how nivolumab with ipilimumab will be used in NHS clinical practice. Clinical experts explained that in NHS clinical practice, some people may benefit after 2 years of treatment and treatment would be stopped at the clinician's discretion. The patient experts also agreed that continuing treatment is circumstantial, and some people would benefit from continued treatment. The committee considered that the maximum clinical benefit had not been explicitly defined, but that the trial was likely to reflect clinical practice. The committee also considered a scenario where people did not stop treatment based on maximum clinical benefit and continued treatment until progression, but did not consider this would reflect its expected use. Therefore, it concluded that implementing a formal stopping rule was not necessary and the observed treatment stopping in CheckMate 142 was likely to be appropriate.

Survival extrapolations

A log-logistic parametric distribution is appropriate for extrapolating overall survival

- 3.10 For overall survival, progression-free survival and time on treatment, the company used semi-parametric models to extrapolate the outcomes of nivolumab plus ipilimumab across the full time horizon. These extrapolations used 6.44 months of Kaplan–Meier data and different parametric distributions for each outcome. The ERG considered that at the latest data-cut, using Kaplan–Meier data until 6.44 months was appropriate. The company used the log-logistic distribution to extrapolate progression-free survival, which the ERG considered had an excellent visual and statistical fit and appropriately represented the decreasing hazard. The company used the log-normal distribution to

extrapolate overall survival. The ERG considered the log-logistic distribution to be more appropriate to extrapolate overall survival because this was also chosen for progression-free survival and both distributions have excellent visual and statistical fit. The committee noted that the choice of either log-normal or log-logistic extrapolation had minimal effect on the cost-effectiveness results. It noted concerns that using the partitioned survival model (see [section 3.8](#)) and the chosen extrapolations resulted in a modelled output that suggested people would stay in the post-progression health state for extended periods of time. The clinical experts considered it more likely that people would survive in a progression-free state and that the modelled output would not reflect what would be seen in clinical practice. The committee was aware that the company had incorporated background mortality into survival projections, which it considered appropriate. Also, the semi-parametric modelling approach was used to account for the complex shape of hazard and survival functions. The committee considered that there are limitations associated with combining the Kaplan–Meier data and parametric models in this way. Instead, a more flexible parametric model could have been used. It concluded that the log-logistic extrapolation was appropriate for decision making but that long-term survival extrapolations are highly uncertain.

Utility values

It is more appropriate to use post-progression utility values from the CORRECT study than the company approach

- 3.11 The company used progression-based health state utility values in the economic model from [NICE'S technology appraisal guidance on cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy](#) (from now, TA242). It considered these utility values most represented the population in CheckMate 142 because TA242 is for people with metastatic colorectal cancer after 1 line of therapy. The ERG noted some concerns with the source of data and considered the post-progression utility value of 0.69 as being too high. The ERG explained that the utility source used in TA242 was derived from health utility index rather than

EuroQol 5D (EQ-5D), so it does not follow the NICE reference case. In addition, it considered there were issues with reporting because people were alive for many months after their final health-related quality-of-life measurement. The ERG proposed using data from the CORRECT study with a utility value of 0.59 for the post-progressed state. These people had more previous treatments but the data were derived from a more recent study and used EQ-5D. The clinical experts considered that because nivolumab and ipilimumab are expected to be used second line (see [section 3.4](#)), the utility values may be higher than those derived at later lines. But they also considered it appropriate to make conservative assumptions about post-progression utility values. The committee noted that the source of the progression-based utility values had minimal effect on the cost-effectiveness results. It concluded that the scenario using the CORRECT utility values was more appropriate but could be conservative.

It is not appropriate to use treatment-specific utility values for nivolumab with ipilimumab

- 3.12 The company measured health-related quality of life using EQ-5D-3L in the single arm of CheckMate 142 and mapped this to UK preference scores to derive treatment-specific utility values for nivolumab with ipilimumab. The utility values derived for treatment with nivolumab were higher than in the general population and so, for face validity, the company capped utility values to that of the general population. The company explained that the novel mechanism of action for nivolumab with ipilimumab drives several key benefits, including improved toxicity and survival, that improve quality of life. The ERG considered that it would expect people having second-line treatment for metastatic colorectal cancer to have a lower quality of life than the general population. Without utility values from a randomised controlled trial with an appropriate comparator arm, the ERG did not consider there was enough justification to use utility values according to treatment status. Therefore, it considered using utility values according to progression status only from 1 source to be appropriate and used the CORRECT study in their base case. Removing treatment-specific utility values resulted in minimal effect on cost-effectiveness results. The committee concluded that it is more appropriate to use conservative utility values

according to progression status from the CORRECT study.

Subsequent treatments

The costs of subsequent treatments in CheckMate 142 do not reflect NHS clinical practice

3.13 For simplicity, the company considered that the cost of treatments after any current line would be the same for all treatment arms and applied this as a one-off cost in the economic model. The ERG considered that the composition and duration of subsequent treatments are likely to differ according to treatment arm and requested further scenarios to explore these differences. To address the ERG's concerns, the company provided 3 scenarios:

- A scenario based on clinical expert opinion that patients having nivolumab with ipilimumab would try further combination chemotherapy after progression.
- A scenario as above but including encorafenib and cetuximab for about one-third of patients that also have BRAF mutations to align with [NICE technology appraisal guidance on encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer](#).

- A scenario based on the subsequent treatment data collected in CheckMate 142.

The ERG highlighted that both scenarios based on clinical expert opinion used a median of 3 to 4 cycles of FOLFOX. But clinical experts noted that up to 12 cycles could be given if people are very fit and therefore increased the number of cycles to account for this. The ERG also considered that scenarios based on subsequent treatment data from CheckMate 142 were less appropriate because they included treatments that are not available in NHS clinical practice and the subsequent treatment data from CheckMate 142 are very immature. The ERG considered that analysis based on clinical expert opinion, including encorafenib with cetuximab for BRAF mutated, is one step closer to reflecting the subsequent treatments that will be used in clinical practice. The committee preferences were more aligned with the ERG but noted that all scenarios had minimal effect on the cost-effectiveness results.

Cost-effectiveness estimates

Nivolumab with ipilimumab is cost effective compared with all comparators

3.14 The company's cost-effectiveness estimate included a patient access scheme discount, the results of which cannot be presented because of confidentiality. The company's base case gave an incremental cost-effectiveness ratio (ICER) range below £20,000 per quality-adjusted life year (QALY) gained for nivolumab plus ipilimumab compared with all other comparators. Some of the comparators and subsequent treatments also had confidential patient access schemes that were included in the ERG analysis. The ERG assumptions included:

- A naive comparison in the MAIC (see [section 3.7](#)).
- Overall survival extrapolation using the log-logistic distribution for extrapolation (see [section 3.10](#)).
- Progression-based utility values from the CORRECT study (see [sections 3.11 and 3.12](#)).

- Subsequent treatment costs using clinical expert opinion and assuming some people have encorafenib and cetuximab (see [section 3.13](#)).

All ERG base-case analyses ICERs were also below £20,000 per QALY gained. The committee considered these results to be robust despite major uncertainties about comparative effectiveness (see section 3.7). It concluded that nivolumab with ipilimumab is a cost-effective use of NHS resources compared with all other comparators.

Nivolumab and ipilimumab is likely to meet the end of life criteria

- 3.15 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](#). Clinical experts explained that life expectancy after progressing in absence of nivolumab with ipilimumab was likely to be less than 24 months in most cases. They also explained that the preliminary overall survival results from CheckMate 142 were promising, with the likely extension to life of at least 3 months. The ERG agreed that, based on the latest data-cut, there is an improvement in overall survival of at least 3 months. The committee agreed that nivolumab with ipilimumab was likely to give an extension to life of at least 3 months. It concluded that nivolumab with ipilimumab meets the end of life criteria.

Other factors

There are no equality issues relevant to the recommendations

- 3.16 No equality or social value judgement issues were identified.

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 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 nivolumab and ipilimumab receiving its marketing authorisation.
- 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement 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 appraisal document.
- 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 people have metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and the doctor responsible for their care thinks that nivolumab with ipilimumab 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 B](#).

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.

Harsimran Sarpal

Technical lead

Adam Brooke

Technical adviser

Joanne Ekeledo

Project manager

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Accreditation

