NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tucatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: October 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using tucatinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 16 November 2021

Second appraisal committee meeting: 07 December 2021

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Tucatinib with trastuzumab and capecitabine is not recommended, within its marketing authorisation, for treating HER2-positive locally advanced or metastatic breast cancer in adults after at least 2 prior anti-HER2 treatment regimens.

1.2 This recommendation is not intended to affect treatment with tucatinib with trastuzumab and capecitabine 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

Current treatment for HER2-positive locally advanced or metastatic breast cancer after 2 or more anti-HER2 regimens includes chemotherapy, such as capecitabine, vinorelbine or eribulin. Tucatinib with trastuzumab and capecitabine (from now, tucatinib combination) is another anti-HER2 therapy that could be used after 2 or more anti-HER2 regimens.

Clinical trial evidence shows that tucatinib combination increases the time people have before their cancer gets worse and how long they live compared with trastuzumab with capecitabine. However, trastuzumab with capecitabine is not standard care in the NHS. Comparing tucatinib combination indirectly with chemotherapy suggests it may increase the time people have before their cancer gets worse and how long they live. But the extent of benefit is uncertain because of differences between the trials.

The cost-effectiveness estimates for tucatinib combination are higher than what NICE normally considers an acceptable use of NHS resources. Therefore, it is not recommended.

2 Information about tucatinib

Marketing authorisation indication

2.1 Tucatinib (TUKYSA, Seagen Inc.) has a marketing authorisation for use 'in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens'.

Dosage in the marketing authorisation

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

Price

2.3 The company's list price is £5,636.84 per pack of 84, 150 mg film-coated tablets (company's submission). The average cost of a course of combination treatment at list prices is £7,016.91 for the loading dose and £6,677.14 for the following cycles.

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Seagen Inc., 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 committee discussed the following issues.

Clinical need and treatment pathway

HER2-positive breast cancer has a high disease burden

3.1 Some breast cancer cells have higher levels of a protein called HER2 on their surface, which stimulates them to grow. This is known as HER2-positive breast cancer and around 1 in 5 breast cancers are HER2-positive. Patient experts explained that being diagnosed with locally advanced or metastatic breast cancer is extremely difficult for people and their family and friends. It can cause considerable anxiety and fear, with the uncertainty being the hardest part for many people. These feelings can negatively affect mental health. People with metastatic breast cancer must organise their lives around hospital appointments, which constrain their everyday activities. Brain metastases may develop in up to half of people with HER2-positive cancer, which negatively affects people's prognosis and quality of life. Patient experts explained they were not able to drive or work, and lost their independence. There is no cure for metastatic breast cancer. Treatment aims to stop progression of the disease, extend life, and maintain or improve quality of life for as long as possible. Treatment is continued for as long as it works. The committee concluded that there is a high disease burden for people with HER2-positive metastatic breast cancer, especially for those with brain metastases.

There is a need for anti-HER2 therapies after second-line treatment, especially for people with brain metastases

3.2 Clinical experts explained that people with HER2-positive metastatic breast cancer that has progressed after 2 or more anti-HER2 regimens have a high symptom burden, and their disease is resistant to the previous lines of therapy. First-line treatment of HER2-positive metastatic breast cancer includes the anti-HER2 therapies pertuzumab with trastuzumab and docetaxel, or trastuzumab with paclitaxel (see NICE's technology appraisal guidance on pertuzumab with trastuzumab and

docetaxel for treating HER2-positive breast cancer and NICE's guidance on trastuzumab for the treatment of advanced breast cancer). Trastuzumab emtansine is an anti-HER2 therapy used at second line (see NICE's technology appraisal guidance on trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane, TA458). The committee noted that, although some trusts may offer third-line anti-HER2 therapy, it is not available across the NHS and cannot be considered standard care. Trastuzumab deruxtecan is available through the Cancer Drugs Fund only so is not considered standard care (see NICE's technology appraisal guidance on trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies, TA704). Instead, standard care for people whose disease has progressed on or after 2 anti-HER2 therapies is non-targeted chemotherapy, including capecitabine, vinorelbine or eribulin (see NICE's clinical guideline on breast cancer: diagnosis and management [CG81] and NICE's technology appraisal guidance on eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens, TA423). Treatment options for people with brain metastases are stereotactic radiosurgery or radiotherapy (see NICE's clinical guideline on brain tumours and metastases). The clinical experts explained that these treatments usually stop working after some time and most patients cannot have more than 2 courses of radiotherapy because of its neurological toxicity. Currently there are no further treatment options for these patients. The committee concluded that there is an unmet need for anti-HER2 treatment after second-line HER2 treatment. This is particularly important for the significant proportion of people who have brain metastases because all the existing HER2 and chemotherapy treatments have limited penetration through the blood-brain barrier and are not of proven benefit for brain metastases.

The relevant comparators are capecitabine, vinorelbine and eribulin

3.3 The company used eribulin as its base-case comparator and stated that eribulin is the only treatment approved by NICE in the third-line setting for HER2-positive locally advanced or metastatic breast cancer and has clinical equivalence to capecitabine and vinorelbine. The ERG noted that CG81 recommends that patients may also receive treatment with other non-HER2-targeted chemotherapies such as capecitabine or vinorelbine. The clinical experts confirmed that current standard care in the third-line setting in the NHS is non-targeted chemotherapy, including capecitabine, vinorelbine or eribulin. The clinical experts explained that although some patients receive trastuzumab with capecitabine, there was wide regional variation in its availability. As it is not available to all patients on the NHS, the committee agreed that trastuzumab with capecitabine is not a relevant comparator. The committee concluded that the relevant comparators for tucatinib with trastuzumab and capecitabine (from now, tucatinib combination) are capecitabine, vinorelbine and eribulin.

Clinical evidence

HER2CLIMB is generalisable to UK clinical practice

3.4 The clinical evidence was based on HER2CLIMB, a randomised, double-blind, placebo controlled, active comparator trial for people with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab, pertuzumab and trastuzumab emtansine. Approximately 50% of people in HER2CLIMB had brain metastases. The clinical experts explained that HER2CLIMB represents patients in the NHS in terms of characteristics and previous treatment, including the proportion of people with brain metastases. The committee concluded that HER2CLIMB is generalisable to the eligible population in clinical practice in the UK.

Tucatinib combination is more effective than trastuzumab with capecitabine, but this comparison does not reflect NHS practice

3.5 HER2CLIMB assessed tucatinib combination versus placebo with trastuzumab and capecitabine (from now, placebo combination). However, trastuzumab with capecitabine is not used in NHS practice (see section 3.3). Patients receiving tucatinib combination had a median progression-free survival of 7.8 months versus 5.6 months for patients receiving placebo combination. The hazard ratio for progression-free survival was 0.54 (95% confidence interval [CI], 0.42 to 0.71; p<0.001). Patients receiving tucatinib combination had a median overall survival of 21.9 months versus 17.4 months for patients receiving placebo combination. The hazard ratio for overall survival was 0.66 (95% CI, 0.50 to 0.88; p=0.005). An improvement in progression-free and overall survival was observed in people with and without brain metastases. The clinical experts explained that this is because, unlike existing treatments, tucatinib is a small molecule that can readily pass through the blood-brain barrier. The clinical experts also explained that the clinical data in the company submission is supported by some longer follow-up data from the trial presented at the American Society of Clinical Oncology annual meeting. The committee concluded that tucatinib combination is more effective than trastuzumab with capecitabine, but that this comparison does not reflect NHS practice.

Indirect treatment comparison

Results of the network meta-analysis are uncertain because of heterogeneity across trials

3.6 There is no head-to-head evidence comparing tucatinib combination against the relevant comparators, capecitabine, vinorelbine or eribulin (see section 3.3). Therefore, the company did a network meta-analysis to allow for an indirect treatment comparison. The results showed increased progression-free and overall survival for tucatinib combination compared

with other treatments (the exact numbers are academic in confidence and cannot be reported here). However, the ERG explained that these results are uncertain because there were differences between patient populations in the trials included. The HER2CLIMB trial included patients with and without brain metastases; approximately 28% had active brain metastases (that is, either treated and progressing, or untreated) and 19% had stable brain metastases. None of the comparator trials included people with active brain metastases. All but one included people with stable or inactive brain metastases, but the proportion was usually not reported. Other differences between patient populations were the number of prior lines of therapy, prior anti-HER2 treatment, HER2 positivity status, performance status and family background. The clinical experts explained that people with brain metastases have a poorer prognosis than those without. The committee noted that an anchored indirect treatment comparison can account for differences in prognostic factors between trials. However, if tucatinib or its comparators had different effectiveness in people with and without brain metastases, this uncertainty would be much more difficult to resolve. The clinical experts explained that tucatinib is the only treatment shown to cross the blood-brain barrier with demonstrated activity in people with brain metastases. But they highlighted that the impact of other treatment options on brain metastases is complex. Although comparator drugs generally cannot cross an intact blood-brain barrier, small amounts can cross when the barrier is compromised, for example after whole-brain radiation therapy. The clinical experts also noted that good control of disease and metastases in other parts of the body may delay brain metastases development and progression, so treatments that are more effective in controlling other metastases are also believed to be more effective for people with brain metastases. They also noted that lapatinib with capecitabine (not a relevant comparator, but was included in the network) was shown to have at least some activity for brain metastases. The committee understood that differences in the proportions of people with brain metastases across

trials may bias the results of the network meta-analysis if these patients had a worse prognosis than those in comparator trials, and also an enhanced benefit of treatment because of the ability of tucatinib to cross the blood-brain barrier. The committee agreed that the network may be biased against tucatinib because if more patients with brain metastases, particularly active metastases, had been included in the comparator trials, the outcomes in those trials may have been worse. The committee would like the company to explore this further (see section 3.8). It concluded that tucatinib is likely to improve clinical outcomes relative to eribulin, capecitabine and vinorelbine, but the size of effect is uncertain because of clinical heterogeneity in several areas, particularly the inclusion of people with brain metastases in the HER2CLIMB trial.

A random effects model is appropriate because of heterogeneity in the network, but does not account for systematic differences between trials

3.7 The company used a fixed-effects model for the network meta-analysis. This was because random effects modelling had limitations such as convergence issues and a higher degree of uncertainty. The ERG used a random effects model, explaining that it better accounted for heterogeneity in the network meta-analysis and is preferred to fixed-effects modelling despite its limitations. The committee noted that the results from using the 2 methods were similar, although the random effects model gave wider confidence intervals. The committee concluded that the random effects methodology was more appropriate because of heterogeneity in the network, but it noted that using a random effects model did not account for any systematic bias in the network related to differences in the proportions of people with brain metastases.

The company should further explore the relative efficacy of tucatinib combination in people with and without brain metastases

3.8 The committee noted that the subgroup of people without brain metastases from HER2CLIMB better corresponds to the patient

populations in other trials included in the network. Therefore, the meta-analysis results better reflect the relative efficacy of tucatinib in this subgroup than they do in the overall population. The committee further noted that an effect modifier, reflecting how much less effective the comparator treatments would be in people with brain metastases, could be estimated either from HER2CLIMB data or from literature. Such a modifier could then be applied to the network meta-analysis results to estimate the relative efficacy of tucatinib combination in people with brain metastases. The committee recalled the complexities of estimating treatment effects in people with brain metastases (see section 3.6) and acknowledged that such analyses would be highly exploratory, but nevertheless useful to its decision-making. The committee concluded that the company should further explore the relative efficacy of tucatinib combination in people with brain metastases. A subgroup analysis of people in HER2CLIMB without brain metastases would also be useful for decision making, as this subgroup is more comparable to the populations in the other trials in the network, making the indirect comparison more valid.

Cost-effectiveness evidence

The company's economic model is suitable for decision making

3.9 The company submitted a partitioned survival model to estimate the cost effectiveness of tucatinib combination compared with eribulin, capecitabine and vinorelbine. It had 3 health states: progression-free, progressed, and death. The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making.

Directly extrapolating HER2CLIMB data is most appropriate to estimate progression-free and overall survival for tucatinib

3.10 The company chose lapatinib with capecitabine as a reference treatment to model progression-free and overall survival because this was the most commonly used treatment in the network meta-analysis. It explained that lapatinib with capecitabine data was generated using an average of the evidence in the network. It used fractional polynomial curves to extrapolate survival data for the reference arm. It then used hazard ratios from its network meta-analysis to estimate survival for other treatments. The ERG explained that the company approach resulted in estimated survival data for tucatinib combination that had a poor visual fit to data from the HER2CLIMB trial, particularly for overall survival. Instead, it preferred to fit survival curves directly to the HER2CLIMB data using trastuzumab with capecitabine as the reference treatment. It chose the Weibull curve because it provided better visual fit and the best statistical fit. The company explained the ERG's approach created bias against tucatinib because HER2CLIMB included people with brain metastases who have poorer outcomes than people without brain metastases. The committee noted that because HER2CLIMB was representative of clinical practice, while other trials were not (see section 3.4 and section 3.6), it should be used to model survival expected in NHS practice. It also noted that lapatinib with capecitabine is not a relevant comparator in this appraisal (see section 3.3). The committee agreed that the curves fitted to the HER2CLIMB data better fitted outcomes observed in the trial and more closely matched the clinical expert estimates of progression-free survival and overall survival. The committee concluded that fitting survival curves to HER2CLIMB data is most appropriate but acknowledged that this did not address the underlying issues with network meta-analysis (see section 3.6 and section 3.8).

Subgroup and threshold analyses could help better understand uncertainty around the effectiveness of tucatinib in people with and without brain metastases

3.11 The company did not model the cost-effectiveness of tucatinib combination relative to its comparators separately for people with and without brain metastases because there is limited evidence on the efficacy of comparators in people with brain metastases. The ERG agreed that there is a lack of evidence for the comparators in people with brain metastases. The committee noted that despite these limitations, the company should have explored this further. It considered that modelling survival for tucatinib combination and its comparators separately for people with and without brain metastases could help better understand the uncertainty in the cost effectiveness of tucatinib. This is because presence of brain metastases is a prognostic factor, and therefore the shape and extrapolation of survival curves are likely to differ for people with and without brain metastases. The committee also recalled that the relative benefit of tucatinib compared with existing treatments might well be different for the 2 groups (see sections 3.6 and 3.8). It agreed that a threshold analysis, showing how much worse the outcomes for the comparators would have to be for tucatinib combination to be considered cost effective, would be helpful. The committee concluded that subgroup and threshold analyses could help better understand the uncertainty around the effectiveness of tucatinib combination in people with and without brain metastases.

Some differences in pre-progression health state utilities are plausible, but post-progression utility differences are not justified

3.12 For tucatinib combination, the company used EQ-5D-5L health-related quality of life data collected in HER2CLIMB, mapped to the EQ-5D-3L with UK preference weighting. Utilities for the comparator therapies were from TA423. This resulted in higher utility values for tucatinib combination compared with comparators in both pre- and post-progression health

states. The company explained tucatinib has better efficacy and safety profiles. It noted that in TA423, eribulin had higher pre-progression utilities than other single agent chemotherapies. The ERG explained the company approach is inappropriate because differences in utilities between tucatinib and comparators are not based on comparative evidence. It preferred to use the same utility values for all treatments for each health state, and to derive them all from HER2CLIMB data. The ERG noted that in the HER2CLIMB trial, there was no difference in utility values between the 2 trial arms. It also explained that TA423 used different post-progression utility values than those used by the company, making the company approach inconsistent. In that appraisal, the committee did not agree with the company value because it was too low. The clinical experts explained that the safety profile of tucatinib is good, but it is difficult to separate out the effects of disease progression and toxicity on quality of life. The clinical experts also noted that disease control could support different pre-progression utility values because treatments offer different levels of overall response rate. The committee agreed that different pre-progression utility values are plausible, but noted the values used by the company were not evidence based, so were uncertain. The committee agreed with the ERG's concerns that the company did not justify a large difference in post-progression utilities once people had stopped treatment. The clinical experts explained that some toxic effects of chemotherapy can be long lasting and affect a person's quality of life after progression. Also, they noted that duration of disease control could affect people's quality of life. However, the committee noted that the toxicity of capecitabine on its own is expected to be similar or lower than the toxicity of tucatinib combination. Therefore, it noted that differences in toxicity cannot explain the large difference in utilities after disease progression between capecitabine and tucatinib combination. It also noted that disease being controlled for longer results in a longer time with better quality of life before progression, which would be accounted for in the model. This is because the model considers both duration of time in each

health state (before and after progression), and quality of life in each health state. The committee also noted that health state utilities should be adjusted for age, to reflect a natural decline in utility values as people age. This was done by the ERG but not by the company. The committee concluded that different pre-progression health state utilities are plausible, although the exact values are not evidence based and therefore uncertain. It also concluded that large differences in post-progression utility values are not plausible, and that more evidence is needed to justify differences in post-progression utilities.

Trastuzumab can be given subcutaneously or intravenously and both administration routes need to be considered

3.13 HER2CLIMB assessed tucatinib combination compared with placebo combination. In the trial, trastuzumab (as part of tucatinib combination) was administered either intravenously or subcutaneously, and this is allowed in tucatinib's summary of product characteristics. But the company model assumed only intravenous administration of trastuzumab. The clinical experts explained that intravenous trastuzumab is no longer standard NHS practice. The clinical and patient experts explained that subcutaneous administration is preferred because patients are able to self-administer, avoiding unnecessary hospital visits. Although biosimilar intravenous trastuzumab products exist, subcutaneous trastuzumab is only available as a branded product, and therefore is more expensive. Therefore, the choice of administration method for trastuzumab as part of tucatinib combination has considerable cost implications. Both the clinical and patient experts explained that if subcutaneous administration was not possible, they would accept intravenous administration if it allowed people to receive tucatinib combination. The committee concluded that because trastuzumab can be administered intravenously and subcutaneously in NHS practice, it would like to see analyses for both routes of administration.

Drug wastage should be included in the analysis

3.14 The company did not include drug wastage for intravenous trastuzumab in its base case because it is packaged in multi-use vials. The ERG preferred including the cost of drug wastage for trastuzumab in the model because some wastage is expected in clinical practice. It noted this has a very small effect on overall costs and the cost-effectiveness estimates. It also noted this applied to intravenous administration only and was not relevant for analyses assuming subcutaneous administration of trastuzumab. The committee concluded that drug wastage should be included in the analysis but noted that this did not have a significant effect on the cost-effectiveness results.

End of life

Tucatinib combination meets 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. The clinical experts and the ERG agreed that the life expectancy for people with HER2-positive locally advanced or metastatic breast cancer receiving third-line treatment is less than 24 months. They also agreed that the gain in life extension with tucatinib combination is expected to be greater than 3 months. The committee also noted that the end of life criteria were accepted in TA423 and TA704 in the third-line setting, and in TA485 in the second-line setting. The committee concluded that tucatinib meets the end of life criteria.

Cost-effectiveness results

The cost-effectiveness estimates are higher than what NICE considers a cost-effective use of NHS resources

3.16 Because of confidential commercial arrangements for tucatinib, trastuzumab, eribulin and post-progression therapies, the incremental

cost-effectiveness ratios (ICERs) cannot be reported here. The committee noted that neither the company nor ERG base cases fully met the committee preferences of:

- using random effects network meta-analysis (see section 3.7)
- extrapolating progression-free and overall survival directly from HER2CLIMB data ('within-trial' approach) (see section 3.10)
- assuming different pre-progression utility values for tucatinib and its comparators (see section 3.12)
- assuming the same post-progression utility values for tucatinib and its comparators, or providing evidence to justify differences in post-progression values (see section 3.12)
- adjusting utility values for ageing (see section 3.12)
- including drug wastage for trastuzumab and capecitabine (see section 3.14).

The committee would also like to see:

- exploration of a treatment effect modifier for brain metastases (see section 3.8)
- subgroup and threshold analyses for people with and without brain metastases (see section 3.11)
- justification for any differences in post-progression utility values for tucatinib combination and its comparators (see section 3.12)
- additional analyses using subcutaneous trastuzumab (see section 3.13).

Taking into account all confidential discounts, the committee noted the company's base-case ICER was above £50,000 per quality-adjusted life year (QALY) gained. When applying all of the committee's preferences, the ICERs would be even higher. The committee concluded that the cost-effectiveness estimates for tucatinib compared with chemotherapy were higher than what NICE considers a cost-effective use of NHS resources,

even when applying the end of life criteria. Therefore, the committee could not recommend tucatinib combination for use in the NHS.

Innovation

Tucatinib has a novel mechanism of action, and all of the benefits may not have been fully captured in the model

3.17 The company and the clinical and patient experts considered tucatinib combination to be innovative. They explained this is because of its improved efficacy and tolerability in patients with HER2-positive metastatic breast cancer, including those with brain metastases. The committee agreed that tucatinib combination had significant potential benefits for patients, and considered that it could not be confident that all the potential benefits in relation to the effect on brain metastases had been explored or captured in the analyses.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comments on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee A
October 2021

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 A.

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.

Sarah Wilkes
Technical lead

Ewa Rupniewska
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Project manager

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