# A review of cure assumptions implemented in early-stage oncology NICE appraisals

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## Background

- Clinical research in oncology is progressively moving towards earlier treatment lines and curative settings.
- In early-stage treatment settings (classified as neoadjuvant, peri-operative, and adjuvant), the potential for patients to be 'cured' can create challenges in extrapolating survival outcomes in cost-effectiveness analyses.

## Objective

- To review how the modelling of cure was implemented across National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) for pharmacological treatments in early-stage oncology settings.
- To consider how the external assessment groups (EAGs) and NICE appraisal committees viewed the company's approaches used for modelling cure.
- To determine the evidence required by EAGs and NICE to facilitate the most appropriate approaches for modelling cure in future appraisals.

## Methods

- The NICE website was searched to identify relevant TAs published up to the end of May 2022.
- NICE appraisal documents reviewed included the company submission, EAG report, appraisal consultation(s), and final appraisal determination.
- Appraisal data extracted included:
  - Indication, treatment, and setting of the TA
  - Approach used for incorporating cure into the cost-effectiveness model (by company and by EAG)
  - Model structure
  - Company base case
  - EAG critique of the company's approach
  - Appraisal committee and final appraisal determination discussion on cure assumption and modelling technique

## Results

- The searches yielded 8 adjuvant TAs and 1 neoadjuvant TA in different oncology indications (4 breast, 3 melanoma, 3 gastrointestinal, and 1 lung) (Figure 1).
- Of the 17 TAs identified, 0 were peri-operative, 1 was neoadjuvant, and 16 were adjuvant. After screening, 11 TAs were eligible for inclusion (1 neoadjuvant and 10 adjuvant). Of these, 3 adjuvant TAs were excluded (because they did not incorporate a cure into the model), which resulted in the inclusion of 8 TAs in the analysis (1 neoadjuvant and 7 adjuvant TAs) (Table 1).
- The TAs used either a mixture-cure method that explicitly separate cured and uncured patients ('explicitly modelled' cure; n = 1) or implicitly imposed a cure on patients through the use of assumptions ('implicitly modelled' cure; n = 7).
- Approaches used to model cure included switching from standard parametric survival models to background mortality at a timepoint when patients are clinically considered cured, using both external registry data and background mortality over different time periods, and fitting mixture-cure models that inherently separate cured and uncured patients.
- Different assumptions were made about the timing of cure and proportion of cured patients: 4 TAs modelled a time-varying cured proportion (TA424, TA544, TA569 and TA632), and the remaining 4 used a static approach.
- Model structure did not appear to influence the type or extent of EAG/NICE critical appraisal.
- Approaches used to model cure were generally accepted by the EAGs/NICE. However, additional scenario analyses were often required (e.g., altering cure fraction and timepoint parameters), with more pessimistic parameter values often preferred.

**Figure 1. Study identification**

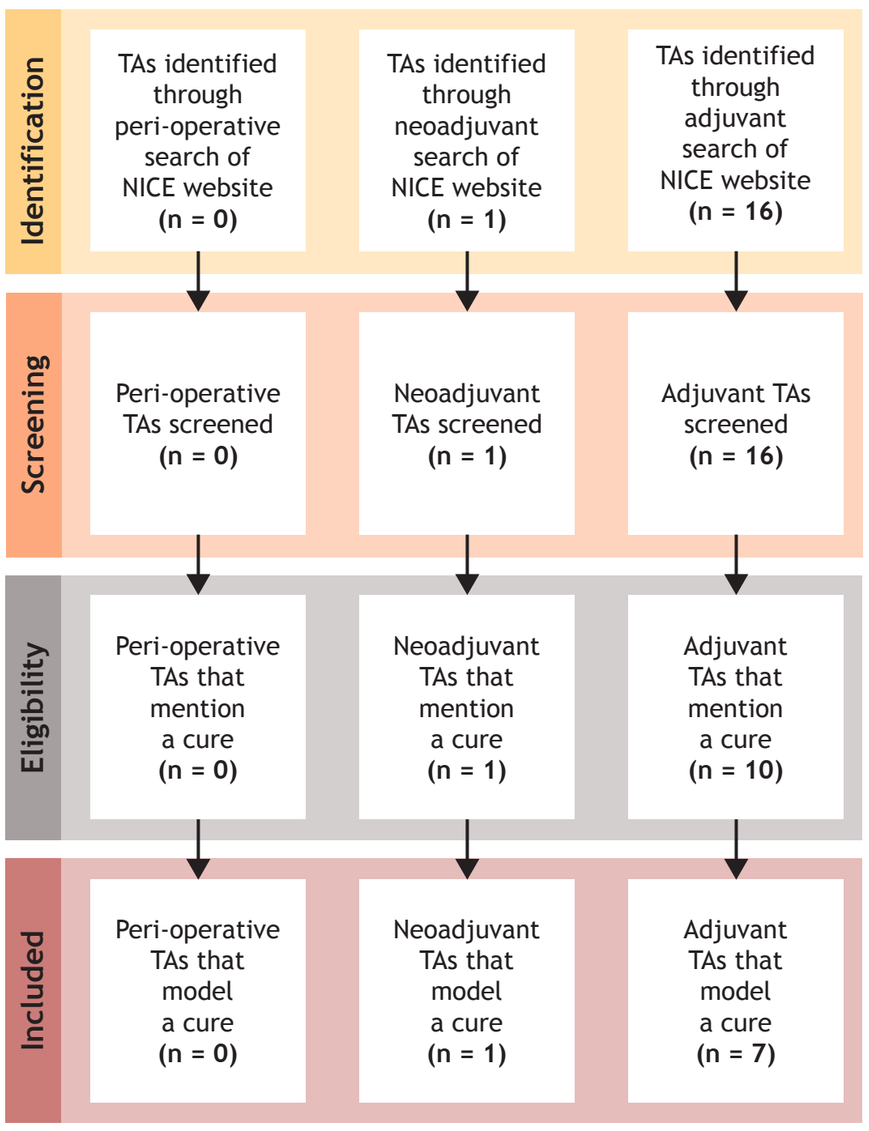


**Table 1. Summary of cure-modelling approach in completed NICE technology appraisals for early-stage oncology**

| Intervention | Model structure | Cure timepoint/ proportion | Cure approach | EAG/NICE appraisal |
|---|---|---|---|---|
| **Dabrafenib + trametinib in adjuvant melanoma (TA544)** | Cohort state-transition model with 4 mutually exclusive health states | The base case included a cure: the mixture-cure model was applied for the first 50 months | *Explicit cure modelled:* Mixture-cure model during trial period, followed by external data and adjusted for general population mortality | • Cure modelling considered appropriate<br>• Disagreed with cure proportion |
| **Nivolumab in the adjuvant gastrointestinal setting (TA746)** | Semi-Markov model structure with 3 health states | The base case included a cure from year 3 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Cure modelling considered appropriate<br>• Disagreed with cure timepoint (wanted a complete plateau of KM data before a cure was assumed)<br>• Would have liked to see an analysis which assessed whether the mortality rate of cured patients is equal to that of the general population |
| **Pertuzumab in the adjuvant breast setting (TA569)** | Markov model structure with 7 health states | The base case included a cure from year 3 for a proportion of patients that increased up to year 10 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Cure modelling considered appropriate<br>• Disagreed with cure timepoint<br>• Disagreed with cure proportion |
| **Trastuzumab emtansine in the adjuvant breast setting (TA632)** | Markov model structure with 7 health states | The base case included a cure from year 3 for a percentage of patients | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Cure modelling considered appropriate<br>• Agreed with cure timepoint<br>• Conducted scenario analyses removing the cure assumption |
| **Osimertinib in the adjuvant lung setting (TA761)** | Markov state-transition model with 5 health states | The base case included a cure from year 5 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Agreed that modelling a cure was appropriate and accepted the timepoint<br>• Disagreed with cure approach and would have preferred a formal statistical modelling of a cure (e.g., a mixture-cure model) |
| **Pertuzumab in the neoadjuvant breast setting (TA424)** | Markov model with 6 health states | The base case included a cure from year 7 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Cure modelling considered appropriate<br>• Agreed with cure timepoint<br>• Conducted scenario analyses using a decreasing risk of recurrence rather than a cure |
| **Nivolumab in the adjuvant melanoma setting (TA684)** | A partitioned survival model and a state-transition model were used | The base case included a cure from year 10 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • Did not explicitly disagree with a cure approach being used but raised concerns about the data used<br>• Requested more appropriate methodology to model a cure |
| **Capecitabine + oxaliplatin in the adjuvant gastrointestinal setting (TA100)** | A partitioned survival model and a state-transition model were used | The base case included a cure at year 5 | *Implicit cure modelled:* Cure assumed at specific timepoint[a] | • No relevant critique provided with regards to a cure approach |

KM = Kaplan Meier.

[a] Those remaining in the disease-free health state beyond the stated timepoint were modelled with the same mortality risk as the general population.

## Conclusions

- Overall, the clinical rationale and implementation of cure in early oncology economic models was seen as reasonable by both the EAG and the NICE committee.
- However, the timepoint for when cure could be assumed to occur and the proportion cured were refuted in most appraisals.
- Timepoint of cure and proportion cured are key areas of uncertainty that additional research may be able to help resolve.
- The results of this review can be used to inform companies on the preferred NICE/EAG cure assumption methodologies and the typical challenges that cure assumptions may generate.

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