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Cost-effectiveness modelling challenges and trends in the neoadjuvant and perioperative settings: A review of NICE oncology submissions

Chloi Theriou, Eleni Pavlidou, Alicia N. Pepper | Evidence Synthesis and Decision Modelling, Precision AQ

For further information, contact Chloi.Theriou@precisionaq.com or visit us at https://www.precisionaq.com

INTRODUCTION

- Partitioned survival models (PSM) are well accepted in advanced oncology indications.
- New therapies are increasingly assessed in earlier indications, including neoadjuvant and perioperative settings.
- These earlier indications present modelling challenges, such as immature overall survival (OS) data from the pivotal trial, additional data requirements to capture long-term outcomes and costs for post-recurrence, and consideration of cure assumptions.
- This research aims to evaluate perioperative and neoadjuvant oncology models submitted to the National Institute for Health and Care Excellence (NICE) to assess trends and acceptability of methods.

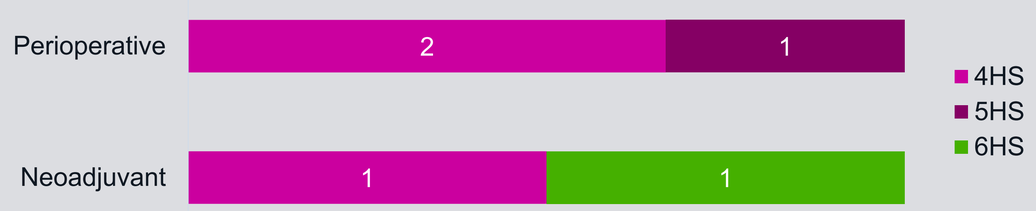
METHODS

- We reviewed all oncology technology appraisals (TAs) in the neoadjuvant and perioperative space submitted to NICE prior to April 2025.
- Data were extracted for model structure, number of health states (HS), methods for estimating transitions, sources informing transitions, implementation of cure assumptions, limitations from the External Assessment Group (EAG), and reimbursement recommendations.

RESULTS

- Five early oncology submissions were identified, two neoadjuvant and three perioperative.
- All submissions evaluated targeted or immunotherapies, two for breast cancer and three for non-small cell lung cancer (NSCLC) (**Table 1**).
- All submissions used a cohort state transition model (STM). Most submissions (3/5) implemented four HS (TA851, TA876, TA1017): event-free (EF), local recurrence (LR), distant metastasis (DM), and death (**Figure 1**).
- Two models further separated DM into pre- and post-progression (TA1030, TA424).
  - TA1030 implemented five HS, splitting the DM into pre- and post-progression with a nested PSM.
  - TA424 implemented six HS, as they also captured cure as a separate HS.

Figure 1: Number of health states in identified NICE submissions



- For transitions out of EF, the relevant pivotal trials were used most often, incorporating indirect treatment comparisons (ITCs) for external comparators if needed.
- Four models assumed cure in the base case with the cure timepoint varying from 5-7 years; the fifth model explored cure as a scenario.
- Most submissions relied on external clinical trials in later disease stages and/or real-world databases to inform transitions out of LR/DM, while one model (TA876) applied a one-off cost and QALY for the DM HS and transitions out of DM were not modelled explicitly.
- EAG noted limitations with assuming constant transitions and uncertainty with extrapolations, cure timepoints, and immunotherapy (IO) retreatment (**Table 2**).

Table 1: Summary of model assumptions and data sources across identified NICE submissions

NICE TA*	Setting	Disease area	Model structure	Cure assumption in EF	ITC	TPs informed by external data
TA1030[1] (2025)	Perioperative	NSCLC	5 HS cohort STM	• At 5 years in EF 95% cured	• Anchored MAIC conducted vs one neoadjuvant treatment. NMA conducted vs one adjuvant treatment and surgery alone • Committee suggested alternative ITC method (i.e., ML-NMR), but company stated unfeasible	• **LR to DM:** due to immature data from pivotal trial, two other RCTs were used; both had slightly more advanced populations (stage IIIA/B and stage III unresectable patients) • **LR to Death:** used data from an RCT and RWE • **DM to Death:** used trials in later line (i.e., metastatic) and RWE
TA1017[2] (2024)	Perioperative	NSCLC, high risk of recurrence	4 HS cohort STM	• Between 5 and 7 years, the cure proportion increased gradually from 0% to 95%	• NMA conducted vs one neoadjuvant treatment • Adjuvant treatments were not considered relevant due to population differences	• **LR-P to DM & Death:** assumed constant over time based on RWE • **DM to Death:** assumed constant over time based on RCTs in later line (i.e., metastatic setting)
TA876[3] (2023)	Neoadjuvant	NSCLC	4 HS cohort STM	• Between 5 and 7 years, the cure proportion increased gradually from 0% to 95%	• NMA conducted vs one neoadjuvant and two adjuvant comparators	• **LR to DM:** assumed constant over time based on RWE and KOLs • **DM to Death:** one-off costs and QALYs assumed based on previous submission in a later line
TA851[4] (2022)	Perioperative	TNBC, high risk of recurrence	4 HS cohort STM	• Explored as scenario analyses (at years 8 and 10) • Not base case due to insufficient data	• No	• **DM to Death:** assumed constant over time based on another RCT for 1L metastatic treatment and RWE for untreated patients
TA424[5] (2016)	Neoadjuvant	HER2+ BC, high risk of recurrence	6 HS cohort STM	• Modelled as a HS; at 7 years in EF 100% cured	• No	• **Remission to 'metastatic not progressed':** based on RWE • **'Metastatic not progressed' to 'metastatic progressed':** based on another RCT in later line (i.e., metastatic setting) • **'Metastatic progressed' to death**: based on RCT in later line

**Recommendation date*

Table 2: Key themes across EAG critiques and recommendations

Item	Key themes from EAG comments across submissions	Recommendations for de novo model development in neoadjuvant/perioperative setting
Structure	• Overall, EAG agreed on STM structure and number of HS with some criticism when 4 HS were used	• STM structure preferred; where possible additional HS to differentiate pre- and post-progression in DM preferred
Cure	• EAG raised uncertainty around cure assumption, specifically around timepoint of cure and proportion of patients being cured	• Allow the cure timepoint and proportion of patients cured to be user modifiable and include scenarios • Provide clinical justification (e.g., based on clinical opinion) or if possible long-term data to support cure assumption
Clinical endpoints	• EAG considered EFS endpoint appropriate • EAG raised uncertainty around the use of pCR as a predictor of EFS	• EFS should be primary efficacy outcome used in model, pCR as a surrogate will likely not be accepted
TPs	• Constant TPs from LR and DM HS often critiqued • TPs from LR/DM should be a function of time in HS not time in model	• Allow time-varying TPs from LR/DM through use of tunnel states or consider use of patient-level simulation • Assumptions of constant TP will require strong justification (e.g., long-term plausibility, clinical justification)
Extrapolation EFS	• EAG raised uncertainty around EFS extrapolations when there was a lack of long-term clinical validation	• Run scenarios using alternative curves • Seek clinical expert validation of long-term outcomes and validate vs available external evidence
External data use	• EAG considered use of external data appropriate to inform transition probabilities for post-recurrence	• Align population of external studies with that of pivotal trial as any heterogeneity could be scrutinized
Comparators	• Important to capture all relevant comparators in NICE scope	• Provide thorough rationale when omitting comparators mentioned in NICE scope
ITC	• Critiques on choice of method and lack of justification when ITC was deemed unfeasible • Critiques over extrapolation of treatment effects from ITC to the full time horizon	• Clearly justify rationale for method (e.g., time-varying vs constant HRs) used in base case and if feasible present alternative ITC method (e.g., ML-NMR) in scenario analyses
Subgroups	• Effectiveness of the intervention across subgroups was often questioned	• Run subgroup analysis if differences in efficacy are observed, or justify why subgroup analyses are not needed
Utilities	• Concerns with utility data from pivotal trials post-recurrence given uncertainty in estimates	• Recommend running sensitivity analyses using both trial and literature sources
IO retreatment	• EAG questioned appropriateness of using a 6-month cutoff for IO retreatment • EAG raised uncertainty around the proportion of eligible patients and effectiveness of IO retreatment	• Include flexibility to assess alternative IO retreatment scenarios

CONCLUSIONS

- There was a consensus in STM structure, with variability in number of HS and approaches to modelling transitions.
- Key critiques from EAG included identifying relevant comparators, implementing a cure assumption, validating long-term extrapolations, justifying use of constant or time-varying TPs, and IO retreatment.
- Limitations and critiques from reviewers did not contribute to any negative recommendations.

ABBREVIATIONS & REFERENCES

ABBREVIATIONS: **BC**, breast cancer; **DM**, distant metastasis; **EAG**, External Assessment Group; **EF**, event free; **EFS**, event-free survival; **HER2**, human epidermal growth factor receptor 2; **HR**, hazard ratio; **HS**, health state; **IO**, immuno-oncology therapy; **ITC**, indirect treatment comparison; **KOL**, key opinion leader; **LR**, local recurrence; **LR-P**, local recurrence and progression; **MAIC**, matching-adjusted indirect comparison; **ML-NMR**, multi-level network meta-regression; **NICE**, National Institute for Health and Care Excellence; **NMA**, network meta-analysis; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **pCR**, pathological complete response; **PSM**, partitioned survival model; **QALY**, quality-adjusted life year; **RCT**, randomized controlled trial; **RWE**, real-word evidence; **STM**, state transition model; **TA**, technology appraisal; **TNBC**, triple-negative breast cancer; **TP**, transition probability.

REFERENCES: **1. NICE 2025** (TA1030, durvalumab plus chemotherapy); **2. NICE 2024** (TA1017, pembrolizumab plus chemotherapy); **3. NICE 2023** (TA876, nivolumab plus chemotherapy); **4. NICE 2022** (TA851, pembrolizumab); **5. NICE 2016** (TA424, pertuzumab).

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