HTA17

Early-Stage (Resectable) Oncology Submissions: Does NICE Accept Early Endpoints?

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Background

- **Overall survival (OS) is considered the gold standard in oncology as it directly measures a treatment's impact on patient survival.** For NICE, OS remains the benchmark outcome and is typically a major driver of quality-adjusted life-year (QALY) gains.
- In appraisals of early-stage cancers, **OS data are often immature** at the time of submission, so company submissions are based entirely on early trial endpoints such as event-/disease-free survival (EFS/DFS), an approach increasingly adopted across tumour types and treatment settings
- NICE recently collaborated with other leading international HTA bodies on a White Paper providing **guidance for the use of surrogate endpoints in economic modelling**[1], and it is tabled as **the subject of an upcoming modular update** on the NICE website
- We sought to understand NICE's view on the use of early endpoints in early-stage oncology appraisals to date

Objective

- To assess **NICE's acceptability of early endpoints** in technology appraisals (TAs) within the **adjuvant, neoadjuvant and periadjuvant oncology settings**, where:

> Adjuvant: a therapy is given after surgical resection, with the aim of reducing the risk of recurrence
> Neoadjuvant: a therapy is given before surgical resection, with the aim of shrinking the tumour and increasing the chance of successful surgery
> Periadjuvant: a therapy is given both before and after surgical resection

- To identify any trends in the acceptability of early endpoints over time, and whether acceptability varies by indication, by NICE Committee, or by the External Assessment Group (EAG) involved in the appraisal.
- **To examine the impact of uncertainties around early endpoints on the final recommendation,** relative to other uncertainties

Methods

- A targeted literature review of NICE technology appraisals was conducted in April 2025, using the inclusion and exclusion criteria listed in Table 1
- A data extraction form was designed to capture all study-relevant information, piloted on four appraisals, and then refined to meet the study objectives
- A classification system was developed to categorise uncertainties in the final draft guidance (FDG) of each appraisal (Table 2)

Table 1. Inclusion and exclusion criteria for the targeted literature review

	Inclusion criteria	Exclusion criteria
Population(s)	Early to locally advanced cancers (stage 1–3)	Metastatic cancers (generally stage 4) Any other disease
Interventions	Adjuvant, neoadjuvant and periadjuvant oncology therapies	Other regimens, non-oncology
Comparisons	Any	None
Outcomes	Early endpoints used in economic model	Early endpoints not used in economic model
Time	Published between Jan 2019 and April 2025 Where a Cancer Drugs Fund (CDF) review TA was published within our time frame, the original TA was also included in the study, for completeness	Appraisals published before 2019
Study Design	Published NICE TA guidance (single/multiple)	Any other study design Any other NICE publications

Table 2. Criteria for grading of uncertainties reported in the FDG

	Definition
Major	Factor, parameter or assumption to which the ICER is very sensitive, or which has major patient impact, a key point of discussion in the FDG. Difficult to test in sensitivity analyses [e.g. in the case of immature data]
Moderate	Factor, parameter or assumption to which the ICER has some sensitivity, or which has moderate patient impact, some discussion in the FDG. Can be addressed to some extent using sensitivity analyses
Minor	Factor, parameter or assumption to which the ICER is less sensitive, or which has minor patient impact, little discussion in the FDG

Results

Appraisal Characteristics

- Our search identified 23 relevant NICE appraisals
- Most (18/23; 78%) were for adjuvant therapies (Figure 1)
- There were two neoadjuvant appraisals (in non-small cell lung cancer [NSCLC] and prostate cancer) and three periadjuvant appraisals (in breast cancer and NSCLC)
- The highest number of appraisals (7) was published in 2022, these involved four different therapies in five different indications (Figure 2)
- The majority of the appraisals were related to melanoma (5, between 2018 and 2022), breast cancer (6, 2019-2023) and NSCLC (8, 2021-2025)

Figure 1. regime of the NICE appraisals identified in the study

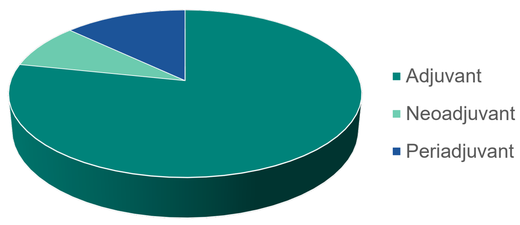
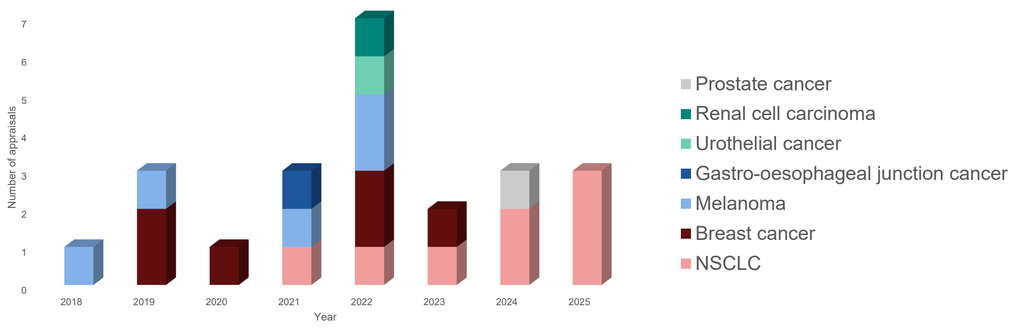
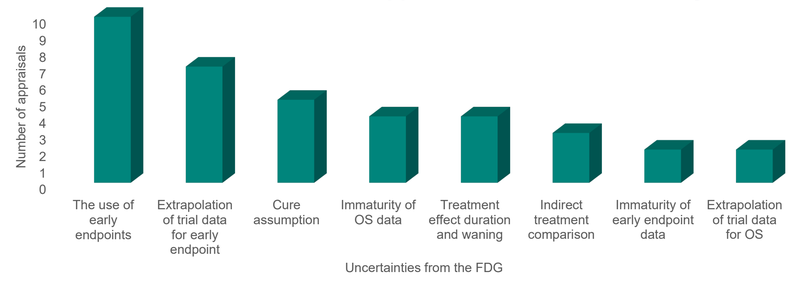


Figure 2. Distribution of identified NICE appraisals by indication over time



- The use of early endpoints as primary outcomes and as a surrogate for OS was the most frequent major uncertainty identified in the FDG of appraisals of (neo/peri)adjuvant oncology therapies (Figure 3)
  - in 10/23 (43%) appraisals, there was major uncertainty around the use of early endpoints
- Other common areas of major uncertainty discussed by the NICE Committee were the extrapolation of trial data over a longer time horizon to inform the modelling, and cure assumptions (Figure 3)
- However, all FDGs discussed uncertainties, and made recommendations, in the context of the NICE cost-effectiveness threshold

Figure 3. Major uncertainties identified in the FDG of appraisals included in our study

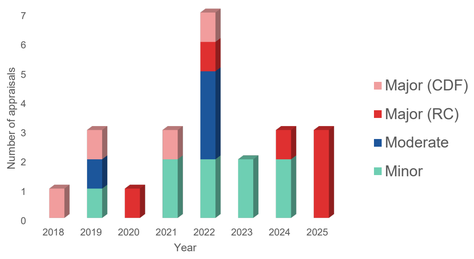


Uncertainty Around Early Endpoints

➢ *Over time*

- Overall, the level of uncertainty around the use of early endpoints showed no clear trend over time (Figure 4)
- Among 10 appraisals with major uncertainty around the use of early endpoints, 4 were routed via the Cancer Drugs Fund (CDF)
  - between 2018 and 2022
  - in melanoma and NSCLC
- No appraisals with minor or moderate uncertainty around the use of early endpoints went into the CDF
- In 2024-2025, 4 (peri/neo)adjuvant appraisals were recommended for routine commissioning (RC) despite major uncertainty

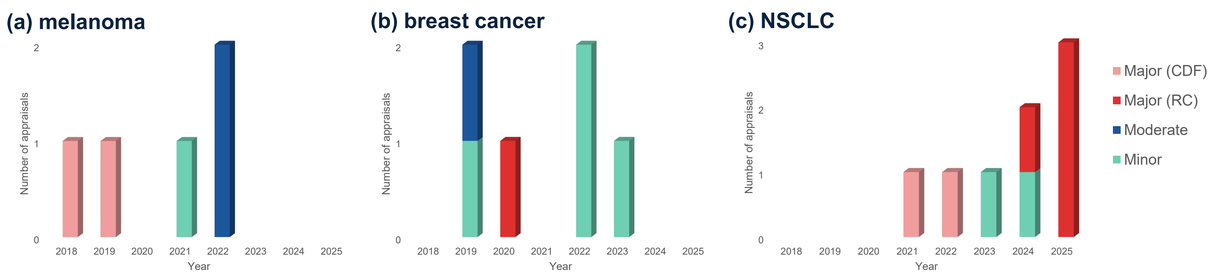
Figure 4. Grading of uncertainty around the use of early endpoints and appraisal outcome over time



➢ *By indication*

- **Melanoma** TAs initially had high uncertainty around early endpoints, which decreased over time (Figure 5a)
  - Two melanoma appraisals in 2021 and 2022 were CDF reviews, so decreased uncertainty was likely due to more mature trial data, supported by data collected during the managed access period
  - The other melanoma TA in 2022 used trial distant metastasis-free survival (DMFS) data as a supplement to RFS, which was a highly relevant endpoint for patients and clinicians and reduced uncertainty in the modelling
- The use of early endpoints in (neo/peri)adjuvant **breast cancer** appraisals was most often (4/6) associated with minor uncertainty (Figure 5b)
- In contrast, 6/8 TAs in **NSCLC** found the use of early endpoints to be associated with major uncertainty (Figure 5c)

Figure 5. Grading of uncertainty around the use of early endpoints over time in (a) melanoma, (b) breast cancer and (c) NSCLC



➢ *By assessors*

- Most appraisals in our study were assessed by NICE Committee A or D. Committee D was more likely to assess early endpoints as a major uncertainty (86% of its appraisals vs 29% for Committee A) (Figure 6)
  - This may reflect differences in therapy area specialty (e.g., lung) rather than Committee caution
- No clear trend was observed between the EAG involved and uncertainty level (Table 3)

Figure 6. Grading of uncertainty around the use of early endpoints by NICE Committee

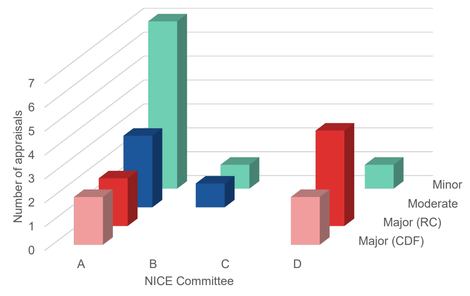


Table 3. Grading of uncertainty around the use of early endpoints by EAG involved

	Grading of uncertainty around the use of early endpoints in FDG			
EAG	**Major (CDF)**	**Major (RC)**	**Moderate**	**Minor**
LRIG	1	1	1	0
BMJ-TAG	1	1	1	2
PenTAG	1	0	1	0
KSR	0	2	1	3
SCHARR	1	2	0	1
Newcastle	0	0	0	1
Bristol	0	0	0	1
SHTAC	0	0	0	1

- In 12/23 appraisals, **clinicians expressed support** for the use of clinically valid early endpoints as surrogates for OS
  - Including 3 of those initially recommended via the CDF
- Clinicians and patient groups also highlighted **the value of early endpoints in and of themselves**:
  - "…clinical experts agreed that disease-free survival is a clinically relevant end point." (TA761, NSCLC)
  - "…for people with melanoma, OS was not their sole focus. Length of time without disease recurrence was also very important." (TA766)

Conclusions

- Early endpoints are routinely used in (neo/peri)adjuvant oncology submissions to NICE, although their use remains **the most common source of major uncertainty** in these submissions
  - Overall, major uncertainty in the use of early endpoints was often (4/10) associated with a recommendation via the CDF
  - However, in recent years, Committees are increasingly making recommendations to routine commissioning
- Despite major uncertainty with early endpoints in many cases, all TAs in our study were recommended, indicating a willingness of Appraisal Committees to recognise the value of these **patient-relevant endpoints**
- The use of early endpoints in NSCLC appears to be a key area in which major uncertainty persists
- Whilst uncertainty around the use of early endpoints may factor into NICE decision making, **recommendations clearly reflect a balance between uncertainty, unmet need, clinical value and cost-effectiveness**

Reference: 1. Canada's Drug Agency, Institute for Clinical and Economic Review, National Institute for Health and Care Excellence and Zorginstituut Nederland. Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment. White paper. 2024.

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Disclosures

AA and VC are employees of MSD (UK) Limited, London, UK, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. AL was an employee of MSD (UK) Limited, London, UK at the time of his involvement with this study. All authors approved the final poster.

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