A RETROSPECTIVE REVIEW OF RECENT NICE TECHNOLOGY APPRAISALS FROM 2021 to 2023 TO INVESTIGATE THE CONSIDERATION AND ACCEPTABILITY OF CURE MODELLING ASSUMPTIONS

HTA21

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CONCLUSIONS

- **All NICE appraisals in the last two years where cure assumptions have been applied (n=11) were evaluating oncology treatments. All 11 treatments were recommended by NICE.**
- **NICE and the ERG/EAG typically considered the cure assumption to be uncertain, due to trial data immaturity, small patient populations, cure timepoint variability and uncertainty around extrapolations**
- **Ultimately cost-effectiveness was the key deciding factor. Uncertainty around the cure assumption was deemed acceptable in most cases if the medicine was cost-effective.**

OBJECTIVES

- Curative therapies have the potential to restore patient health and significantly improve survival
- However, cure assumptions in HTA appraisals can be complex to represent in an economic model and support with robust evidence.
- The aim of this research was to investigate how cure assumptions have been clinically justified, modelled and considered by Evidence Review Groups (ERG)/External Assessment Groups (EAG) and NICE Committees in recent NICE technology appraisals across all therapy areas.

METHODS

- A targeted review of all NICE single technology appraisals (STAs) published on the NICE website in the last two years (March 2021 to March 2023) was conducted.
- The term 'cure' was searched on the NICE website and the resulting list of appraisals were reviewed to ensure only those STAs where a cure assumption was applied were included in the review.
- Data extracted included details of the cure assumption, clinical trial and/or other data supporting the cure assumption, cure modelling approach and HTA feedback on the cure assumptions (including conclusions from the ERG/EAG and NICE Committee)

RESULTS

Table 1: Overview of identified NICE appraisals incorporating a cure assumption

Appraisal	Cure timepoint	Cure model approach	Supporting data and validation	Feedback from ERG/EAG and NICE	NICE Decision
TA876: Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer	5 years	• 95% of patients event-free at 5 years were 'cured' and GPM applied thereafter	• Pivotal trial data showed reduction in hazard of progression at 5 years • Clinical validation/precedent supported assumption	• EAG removed cure assumption in scenario given uncertain clinical evidence • NICE satisfied that even with removal of cure assumption ICERs were below threshold	Recommended within MA
TA874: Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma	2 years	• MCM with 'cured' population assumed to have GPM after 2 years	• Immature OS data from pivotal trial so cure fraction informed by PFS and validated by clinical experts	• ERG and NICE accepted MCM but ERG considered survival extrapolations too uncertain so assumed no survival benefit, which NICE considered not plausible • NICE accounted for uncertainty around survival in decision-making	Restricted recommendation
TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	5 years	• MCM with 'cured' population assumed to have GPM after 5 years	• Cure fraction informed by survival data from pivotal trial • Clinical experts validated the cure assumption	• ERG accepted MCM but extrapolations were higher than trial so there was concern of overestimating survival • NICE acknowledged uncertainty but accepted approach	Recommended within MA
TA857: Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma	30 months	• All patients who did not progress at 30 months were 'cured' and GPM applied thereafter	• Pivotal trial data showed hazard of progression/death plateau at 30 months • Other published long-term trial data used to support assumption.	• ERG not supportive of cure assumption due to small numbers of patients from trial at 30 months • NICE acknowledged potential of long-term remission but disagreed with applying GPM in this condition when disease did not recur	Recommended within MA
TA823: Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer	5 years	• 91.5% of patients disease-free at 5 years 'cured' and GPM applied thereafter	• Data from Japanese retrospective chart review from one hospital informed cure assumption • Validated with UK clinical oncologists	• Generalisability of Japanese study to UK was questioned by ERG and NICE • NICE considered proportion of 'cured' and timepoint of cure highly uncertain • ERG explored different cure timepoints and NICE considered all scenarios	Recommended in CDF
TA817: Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence	5 years	• All patients event-free at 5 years were 'cured' and GPM applied thereafter	• Pivotal trial data showed risk of death approaches GPM at 5 years	• ERG explored 10-year cure timepoint and NICE stated cure timepoint is uncertain but all timepoint scenarios had minimal impact on cost-effectiveness • NICE considered all scenarios in decision-making	Restricted recommendation
TA787: Venetoclax with low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable	2 years	• All patients alive after 2 years were 'cured' and GPM applied thereafter	• Separate trial data showed KM plateau at 2 years • Clinical expert opinion supported assumption that relapse after 2 years in remission is low	• ERG commented on lack of long-term data and low patient numbers at 2 years • NICE considered data supporting cure assumption uncertain as it was from different trial with different treatment combination, however ICER remained below threshold even without cure assumption	Restricted recommendation
TA765: Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable	2 years	• All patients alive after 2 years were 'cured' and GPM applied thereafter	• Pivotal trial data showed KM plateau at 2 years • Clinical expert opinion supported assumption that relapse after 2 years in remission is low	• ERG presented scenarios with different cure timepoints, but they had minimal impact on cost-effectiveness • NICE acknowledged uncertain cure assumption and preferred a MCM	Recommended within MA
TA761: Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection	5 years	• 95% of patients disease-free at 5 years 'cured' and GPM applied thereafter	• Cure assumption supported by data from pivotal trial, clinical expert opinion and other published trial evidence	• ERG and NICE preferred a MCM and ERG explored different cure timepoints • NICE concluded there was significant uncertainty but would consider all scenarios in decision-making	Recommended in CDF
TA746: Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer	3 years	• All patients disease-free at 3 years were 'cured' and GPM applied thereafter	• Pivotal trial showed KM plateau at 36 months • Clinical experts validated the cure assumption	• ERG and NICE preferred 5-year cure timepoint which was considered more plausible • NICE considered scenario where mortality slightly higher than GPM in 'cured' group	Recommended within MA
TA693: Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer	5 years	• MCM with 'cured' population assumed to have GPM after 2 years	• Immature OS data from pivotal trial so cure fraction informed by PFS	• ERG and NICE disagreed with MCM approach due to immature pivotal trial data, expressed concern with wide range of cure fractions presented and disagreed with making OS equal to PFS which may have resulted in overestimated survival	Recommended in CDF

Figure 1: Cure timepoint assumptions across included appraisals (n=11)

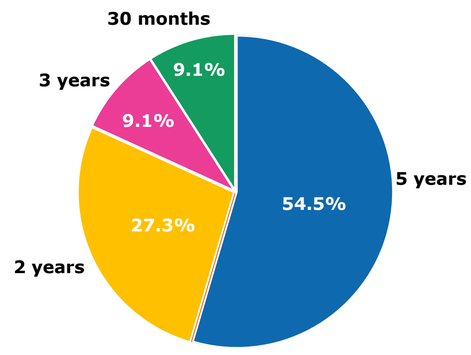
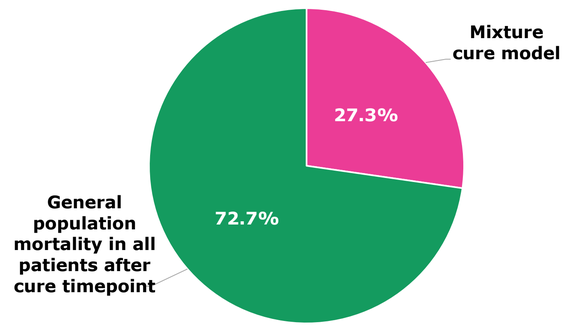


Figure 2: Cure modelling approaches across included appraisals (n=11)



- A total of 11 appraisals were identified in the search (**Table 1**). Although the search was not limited to oncology therapies, all 11 appraisals were in oncology. In all 11 appraisals, NICE issued a positive recommendation (5 recommendations within full label population, 3 restricted recommendations and 3 recommended in the Cancer Drugs Fund)
- Most appraisals (54.5%, n=6) applied a cure assumption after patients were progression-free for 5 years, while 27.3% (n=3) of appraisals used 2 years. The remaining two appraisals applied cure assumptions at 3 years and 30 months (**Figure 1**)
- There were largely two types of approaches to cure modelling noted in the reviewed appraisals. In one approach, general population mortality rate was assumed in all (or nearly all) patients after the cure timepoint. This approach was applied in the majority of appraisals (72.7%, n=8). The other approach was the development of a mixture-cure model which was applied in 27.3% (n=3) of appraisals (**Figure 2**)
- Across the 11 appraisals, MCMs were generally accepted and in some cases ERG/NICE requested this approach. Common challenges with incorporating a cure assumption included immature trial data to support a cure assumption, small trial patient populations at the cure timepoint, exploration of variable cure timepoints, uncertainty around survival extrapolations and in some appraisals assuming GPM after cure timepoint was not considered clinically plausible

Abbreviations: CDF: Cancer Drugs Fund; **EAG**: External Assessment Group; **ERG**: Evidence Review Group; **GPM**: General population mortality; **HTA**: Health technology assessment; **KM**: Kaplan Meier; **MA**: Marketing authorisation; **MCM**: Mixture cure model; **NICE**: National Institute for Health and Care Excellence; **OS**: Overall survival; **PFS**: Progression-free survival

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