Assessing the Use of Time-to-Death Utilities for Advanced NSCLC Treatments: An HTA-Targeted Literature Review

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Background

- In economic evaluations, utility values are crucial, as they reflect people's preferences for different health states.
- In oncology, health state utilities traditionally anchor on disease progression. However, progression-based utilities may not adequately capture the decline in the quality of life as patient's health deteriorates near the end of life.[1]
- In non-small cell lung cancer (NSCLC), increasing evidence suggests that disease progression may not be a reliable proxy for a deterioration in health-related quality of life (HRQoL), especially for patients treated with immuno-oncology therapy. To address this limitation, a time-to-death (TTD)-based utility approach has been employed.[2]
- The choice of a utility-measurement approach can influence incremental cost-effectiveness ratios (ICERs), which are critical for health technology assessment (HTA) decision-making, yet there is limited knowledge about the acceptance and criticisms of TTD approaches by HTA bodies.

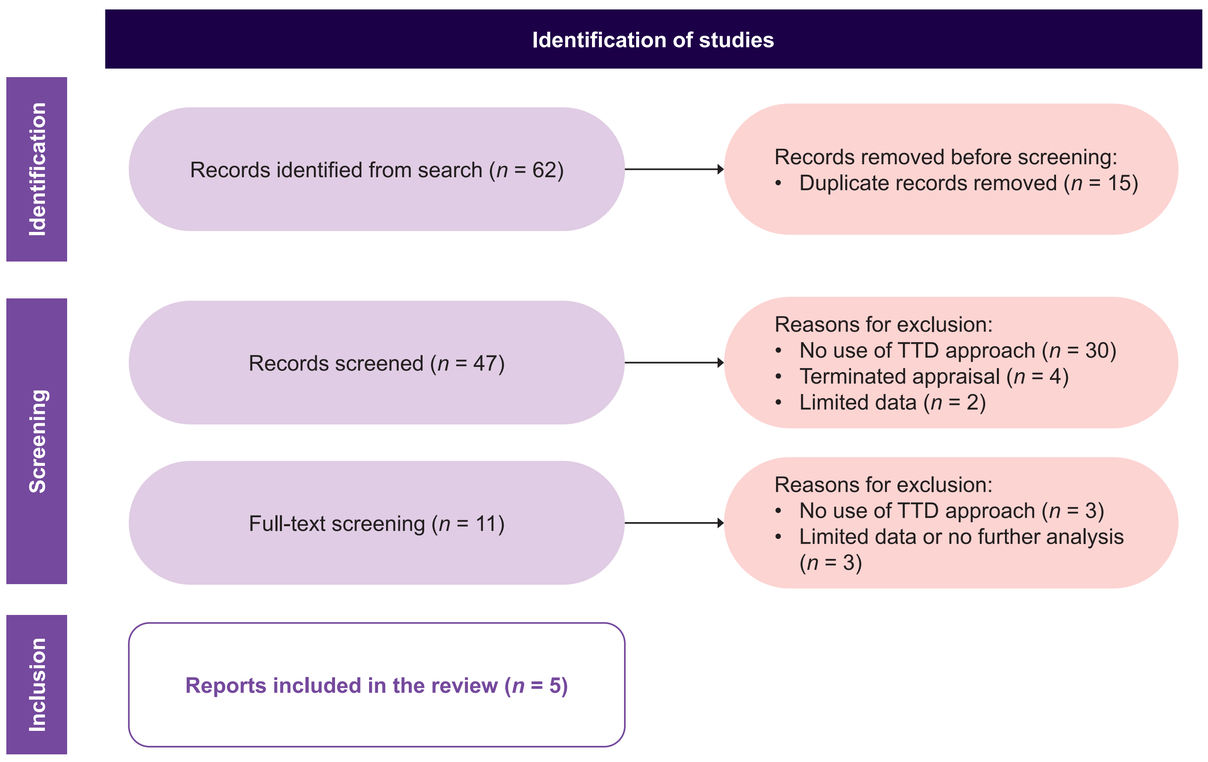
Objectives

- To address the gap in understanding HTA reactions to the TTD utilities compared with alternative approaches:
  - Describe the utility approaches used by manufacturers in their HTA submissions and explore the relationship between the utility approach (TTD, progression-based, or a combination) and quality-adjusted life year (QALY) gain.
  - Analyse the responses and levels of acceptance by HTA bodies.

Methodology

- A targeted literature review (TLR) was conducted using methodologies adapted from the Cochrane Handbook for Systematic Reviews of Interventions.
- The National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH) appraisals in advanced NSCLC were searched, focusing on first-line and second-line treatments, limited to submissions after January 2015. Because of limited data availability in the CADTH, only the NICE technology appraisal (TAs) were included in the analysis.
- The selection criteria were defined using the PICOS framework. The population included adults (age ≥18 years) with advanced (American Joint Committee on Cancer [AJCC] stage III or IV) NSCLC, either receiving first-line treatment or having progressed following first-line treatment.
- The study included any systemic intervention where the TTD utility approach was used in the economic evaluation submission.
- Studies were grouped by utility approach employed in the base case. The level of acceptance by HTA bodies and criticisms of the two methods used were collated and analysed. Additionally, the relationship between the utility approach used, the QALY gains estimated, and ICERs derived from the different utility approaches was assessed.
- The acceptance and impact of TTD utilities in HTA submissions, and identifying trends, patterns, and gaps were reported.

Figure 1: PRISMA flowchart



n, number of records; TTD, time-to-death
Note: Data include first- and second-line research in NICE website.

Results

- From the search, 62 TAs were identified, and 5 TAs met the inclusion criteria and were included in the analysis (**Figure 1**).
- Of the 5 base case submissions, 3 TAs utilised the TTD approach (TA781, TA683, and TA724), 1 used a progression-based approach in the original base case and the TTD approach in the updated case (TA531), and 1 combined both approaches with a state-transition model (TA428). The approaches are described in **Table 1**.

Table 1: Summary of the utility approaches in the NICE TAs for NSCLC

Intervention, TA, date	Population	Comparator	Utility approach in the base case
Second-line treatment			
Sotorasib **TA781**, June 2021	Adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC	Docetaxel	TTD utilities obtained from **EQ-5D-5L** data collected in CodebreaK100: • ≥6 months to death • 3–6 months to death • 1–3 months to death • in the last month of life

Pembrolizumab **TA428**, March 2016	People with locally advanced or metastatic NSCLC whose tumors express PD-L1	Docetaxel	State-transition model (combination of time to death and progression-based utilities) from **EQ-5D** collected in KEYNOTE-010:
			• Progression-free
			  ○ ≥30 days to death
			  ○ <30 days (*n* = 27 patients with EQ-5D score) to death
			• Progressed
			  ○ ≥30 days to death
			  ○ <30 days (*n* = 12 patients with EQ-5D score) to death

First-line treatment			
Nivolumab+ Ipilimumab **TA724**, November 2020	Adults with untreated metastatic NSCLC without sensitising EGFR mutations or ALK fusions	Platinum Doublet Chemotherapy (PDC)	TTD utilities obtained from **EQ-5D-3L** collected in CheckMate-9LA: • ≥52 weeks to death • 27–52 weeks to death • 5–26 weeks to death • 4 weeks or less to death
Pembrolizumab + premetrexed and chemotherapy **TA683**, October 2020	Adults with untreated, metastatic, non-squamous, NSCLC lacking EGFR and/or ALK mutation	Pemetrexed and chemotherapy	TTD utilities with a decrement applied to account for progression obtained from published utilities values by Huang *et al*.[3] for metastatic NSCLC: • ≥360 days to death • 180–360 days to death • 30–180 days to death • <30 days to death
Pembrolizumab **TA531**, November 2017	Patients with PD-L1 positive metastatic NSCLC not treated with chemotherapy in the metastatic setting	Chemotherapy in combination with a platinum drug	TTD utilities obtained from **EQ-5D-3L** collected in KEYNOTE-024: • ≥360 days to death • 180–360 days to death • 30–180 days to death • <30 days to death

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EQ-5D-5L, EuroQoL-5 dimensions-5-levels; KRAS; Kirsten Rat Sarcoma; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TAs, technology appraisals; TTD, time-to-death.
Note: TA531 initially used a progression-based approach in the original base case submission and updated to TTD utilities in the revised base case.

- The ICER was 10 to 15% lower with TTD utilities (range: £28,517–£43,660) than with progression-based utilities (range: £32,150–£47,208) (**Table 2**).
- The TTD utility approach yielded higher QALY gains where there was a greater difference in mean overall survival (OS) and mean progression-free survival (PFS) between treatment arms.
- For example, PFS gains for pembrolizumab versus docetaxel arm in TA428 were negligible relative to OS gains (**Table 2**). Applying TTD utilities instead of progression-based utilities generated higher QALYs.
- The main rationales for using the TTD approach across the TAs include its enhanced accuracy in capturing quality-of-life decline, precedence in former submissions, and strong support from clinical experts, particularly oncologists, for its improved fit for HRQoL data (**Table 3**).

Table 2: Comparative effectiveness and cost-effectiveness of treatments for advanced NSCLC in the NICE TAs

	Sotorasib TA781	Pembrolizumab TA428	Pembrolizumab TA683	Pembrolizumab TA531	Nivolumab + Ipilimumab TA724
Survival data					
Gain in mean OS vs control arm (months)	6.5 (23.5 vs 17.0)	12.36 (22.8 vs 10.44)	13.92 (30 vs 16.08)	12.8 (35.1 vs 22.3)	*Redacted*
Gain in mean PFS vs control arm (months)	4.2 (9.2 vs 5.0)	At 6 months: −0.05 (3.71 vs 3.76) At 15 months: 0.57 (5.60 vs 5.03)	At 15 months: 0.57 (5.60 vs 5.03)	*Redacted*	*Redacted*
Incremental QALY by utility approach					
Progression-based	*Redacted*	0.6858	*Redacted*	0.90	*Redacted*
TTD	*Redacted*	0.7552	*Redacted*	1.02	*Redacted*
State-transition		0.6976			
ICER (£ per QALY)					
Progression-based	£47,208	£44,096	*Redacted*	£32,254	£32,150
TTD	£43,660	£40,045	>£30,000	£28,517	£29,133
Combined method		£43,351			

ICER, incremental cost-effectiveness ratios; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TAs, technology appraisals; TTD, time-to-death.
Note: Redaction is the process of editing or blacking out portions of a document or dataset to protect confidential or sensitive information before publication or dissemination.

- The evidence review groups (ERGs) and NICE have not raised concerns about the rationale for using the TTD approach; instead, their concerns focus on the limitations of the underlying data used to generate utilities. Specifically, the scarcity of EQ-5D data for states closer to death raises questions about the reliability of TTD utility estimates **(Table 3)**.

Table 3: Rationale and concerns for the use of TTD utilities across NICE TAs for advanced NSCLC

	TA781	TA428	TA683	TA531	TA724
Company's rationale					
TTD utilities better reflect quality-of-life deterioration towards the end of life than state-based utilities	✕	✕	✕	✕	✕
Precedence in previous TAs				✕	✕
Support from clinical experts	✕	✕	✕		
HTA concerns					
HRQoL data is based on immature earlier events, with more observations in progression-based states than TTD, especially near death	✕		✕		✕
Arbitrary nature of TTD categories					✕
Double counting and overestimation when using TTD and state progression utilities[1]		✕	✕		
Utility values' appropriateness is questioned because of the discrepancies in patient characteristics and values across different studies		✕		✕	

HTA, health technology assessment; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; TAs, technology appraisals; TTD, time-to-death.
Note: (1) TA683 used the combined method as a sensitivity analysis.

- For the combined method, ERG noted that this approach might double the count of the effects of progression and proximity to death.

Conclusions

The NICE has acknowledged the potential validity of both TTD and progression-based utilities despite existing challenges. By improving data collection beyond disease progression and robustly justifying the chosen utility approach, manufacturers can develop stronger and more transparent HTA submissions, leading to informed and effective healthcare decisions.

REFERENCES
1. Hatswell AJ, *et al. Appl Health Econ Health Policy*. 2021;19:389–401. **2.** Hatswell AJ, *et al. Health Qual Life Outcomes*. 2014;12:140. **3.** Huang M, *et al. Value Health*. 2018;21:S72–S73.

CONFLICTS OF INTEREST
EC, **IB**, **KA,** and **YZ**: Employees of Sanofi; may hold stocks and/or stock options in the company.

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