Role of Relative Dose Intensity in Health Economic Evaluations: A Review of National Institute for Health and Care Excellence Technology Appraisals of Treatments in Solid Tumors

Poster HTA2

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Conclusions

- This review examined the derivation and implications of incorporating relative dose intensity (RDI) and dose modifications into economic evaluations of oncology drugs in solid tumors undergoing health technology assessments (HTAs)
- Most of the HTAs demonstrated that RDI and dose modifications impacted costs in economic evaluations and therefore cost-effectiveness results
- However, there was considerable heterogeneity in how RDI and dose modifications were handled in United Kingdom (UK) HTAs of oncology drugs, resulting in ongoing dialogue between drug manufacturers and HTA review groups to refine these models to better reflect real-world clinical practice and inform appropriate resource allocation within health care systems
- Hence, there is a need for transparent, accurate, and consistent RDI calculations in economic evaluations of cancer therapies incorporating delayed, missed and/or reduced doses

Plain Language Summary

- This review looked at how changes in cancer drug doses can affect costs associated with their use
- Most cost evaluations used dose changes (eg, missed, delayed, or reduced doses), but methods varied. This inconsistency affected cost calculations for new cancer drugs considered by payor bodies, like the United Kingdom National Health Service (NICE), and could impact whether a drug is made available to patients
- This review found several areas for improvement in assessing the cost of new drugs, mainly the need for standard approaches to dose handling while addressing reimbursement challenges for oncology drugs

References: 1. Havrilesky LJ, et al. *Crit Rev Oncol Hematol*. 2015;93(3):203-10. **2.** Chambers P, et al. *ESMO Open*. 2023;8(1):100743. **3.** NICE. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk. Last accessed March 2025.

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Introduction

- RDI and dose delay factor (DDF) are important variables in cost-effectiveness analyses of oncology drugs. They impact drug acquisition, administrative costs, and incremental cost-effectiveness ratios (ICERs)
- **RDI** is usually defined as the ratio (%) of the delivered dose intensity of an intervention to the planned (referenced) dose intensity[1]
- **DDF** usually relates to administrative drug delays (> 7 days)[2]
- However, there is little published evidence on how RDI and DDF affect ICER values, and the extent to which the calculation and application of these measures vary across HTAs

Objective

- To examine the derivation and implications of incorporating RDI and DDF into economic evaluations of oncology drugs across solid tumors including breast, renal, colorectal, urothelial, esophageal squamous cell cancers, and malignant pleural mesothelioma, published in UK NICE HTAs

Methods

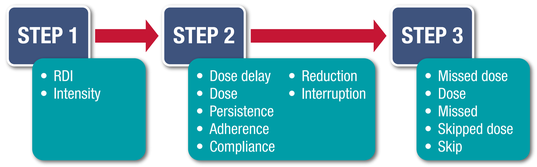
Search Strategy and Inclusion Criteria

- The NICE website was manually searched for HTA submissions, Evidence Review Group (ERG; known as External Assessment Group [EAG] since 2022) appraisals, NICE appraisals, and company responses from date of initial HTA submission to March 31, 2024[3]
- The search strategy was performed using free text terms related to RDI and dose delays (Step 1). After Step 1, the searches were further augmented using concepts such as adherence and persistence reflecting RDI and dose delay, respectively (Step 2). This tiered approach was used to maximize HTAs captured across multiple indications (**Figure 1**)
- Inclusion criteria are shown in **Figure 2**

Data Extraction and Analysis

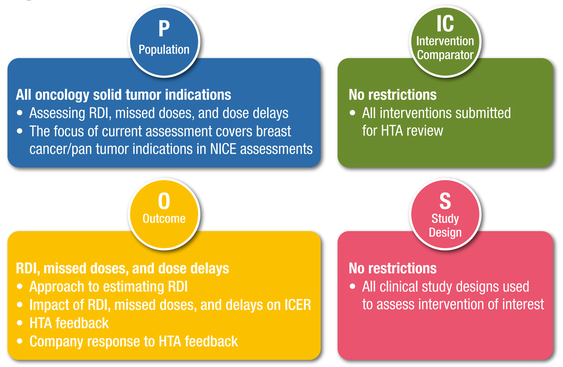
- Data extraction was performed by a single reviewer and quality checks were conducted by another independent reviewer. Data were described descriptively

Figure 1. Search Strategy



RDI, relative dose intensity.

Figure 2. Inclusion Criteria



ICER, incremental cost-effectiveness ratio; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; RDI, relative dose intensity.

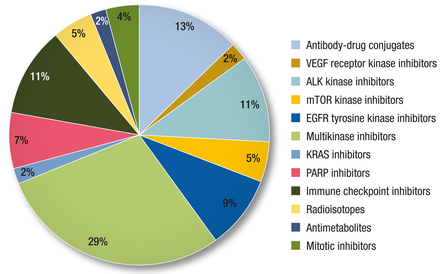
Results

Search Results

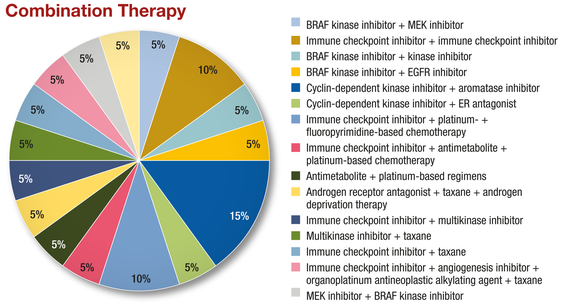
- 265 NICE HTAs were sourced, and 63 were selected for further review
- Overall, 68% of the included HTAs were monotherapy and 32% were combination therapy submissions in solid tumors. The most common monotherapy was multikinase inhibitor therapy (29%), and the most common combination therapy was immune checkpoint inhibitor-based regimens (40%) (**Figure 3**). Most HTAs (63%) were in lung (17%) and breast (12%) cancer (**Figure 4**)
- Nineteen relevant HTAs provided detailed information on handling of RDI and/or DDF and were included (**Table 1**). A total of 44 HTAs were excluded due to RDI not being reported or incorporated into the model (n = 42) or the HTA was terminated (n = 2)

Figure 3. Search Strategy

Monotherapy

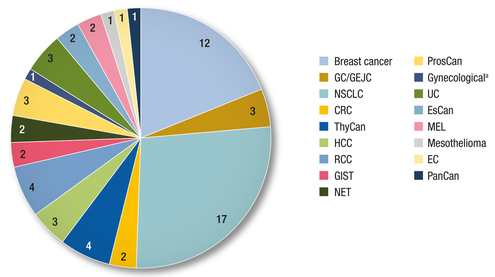


Combination Therapy



ALK, anaplastic lymphoma kinase; BRAF, B-raf proto-oncogene; EGFR, epidermal growth factor receptor; ER, estrogen receptor; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

Figure 4. HTA Therapeutic Area Breakdown



[a]Ovarian, fallopian tube, or peritoneal cancer.
CRC, colorectal cancer; EC, endometrial cancer; GC, gastric cancer; GEJC, gastroesophageal junction cancer; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; HTA, health technology assessment; MEL, melanoma; NET, neuroendocrine tumors; NSCLC, non-small cell lung cancer; EsCan, esophageal cancer; PanCan, pancreatic cancer; ProsCan, prostatic cancer; RCC, renal cell carcinoma; ThyCan, thyroid cancer; UC, urothelial cancer.

Table 1. NICE HTAs that Reported RDI and/or Dose Delays

Line of Therapy	NICE Document Number	Therapeutic Area
Monotherapy (2L+)	TA423 (subgroup 2), TA515, TA704, TA819, TA862, TA952, TA10813	Breast cancer
Combination therapy (1L/2L)	TA495, TA496, TA563, TA639, TA725	Breast cancer
Monotherapy (1L/2L+)	TA530, TA788, TA817	Urothelial cancer
Monotherapy (2L+)	TA866	Colorectal cancer
Monotherapy (2L+)	TA417	Renal cell cancer
Combination therapy (1L)	TA818	Pleural mesothelioma
Combination therapy (1L)	TA865	ESCC

1L, first line; 2L, second line; 2L+, second line plus; ESCC, esophageal squamous cell cancer; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; RDI, relative dose intensity.

RDI/DDF findings

- NICE acknowledged RDI as one of the key drivers of drug cost and ICER values
- RDI estimates (< 100%) were available in 12 HTAs. Nine HTAs provided RDI calculation details, covering missed or delayed dose (HTA788, 818, 865), missed and delayed dose (HTA417, 530), reduced and delayed dose (HTA423, 515), reduced, missed, and delayed dose (HTA10813), and reduced, delayed, or interrupted dose (HTA819)
- RDI was applied to treatment costs in the base-case analysis of 13 HTAs. The ERG/EAG recommended excluding (HTA417, 818, 819, 952) or changing the RDI calculation (HTA530, 865) as the derivation of RDI was unclear. In response to ERG/EAG comments, some manufacturers in their economic evaluation submissions to NICE agreed to use RDI 100% (HTA819, 952), recalculate RDI (HTA417, 865), or apply RDI multipliers uniformly across all treatment arms (TA417, 865)
- Excluding RDI adjustments generally increased ICER values. The magnitude of which varied but increases of 5%-10% were common when moving to 100% RDI (TA819, 952)
- Uncertainty around assumptions on whether patients would eventually receive all missed or delayed doses remained. Suggestions to use time-to-treatment discontinuation data instead of progression-free survival for ongoing treatment duration was offered by the ERG/EAG as an option to reduce reliance on assumptions
- Based on the findings, recommendations for handling RDI/DDF in future HTAs are summarized in **Table 2**

Table 2. Recommendations for Future HTAs

Area	Recommendations
Study design and future research	• Precise estimates of how much drug (RDI/DDF) is used by patients within a primary clinical study setting that provides progression-free survival/overall survival results are vital • Further research is needed to assess how study-based RDI data compare to real-world dose intensity to inform appropriate modeling approaches
Guidance	• Standardized RDI calculation methods: development of consensus guidelines on preferred approaches to calculate and apply RDI adjustments in economic models • Clear guidance from HTA bodies on preferred methods would be beneficial. As methods evolve, HTA bodies should provide updated guidance on best practices for incorporating dose modification data into economic models • HTA bodies are cautious as international, protocol-driven randomized controlled studies are often not typical of their reimbursement population in routine clinical practice and to ensure that drug costs are not down-weighted to artificially improve the ICER • Sensitivity and scenario analysis is often used to characterize uncertainty about this parameter in the cost-effectiveness model
Nuanced approaches	• Use advanced modeling techniques and software tools
Training	• Educational initiatives for manufacturers and reviewers based on best practices

DDF, dose delay factor; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity.