Surrogate measures and the health technology assessment of cancer drugs in Ireland: a retrospective analysis of EMA cancer drug indication approvals between 2017 and 2022 and recommendations made by the NCPE in Ireland

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INTRODUCTION

Surrogate measures are endpoints used in clinical trials as a substitute for patient-centred clinical endpoints, such as overall survival (OS) and health-related quality of life (HRQoL) (1). In oncology, the most commonly used surrogate measures are response rate (RR), progression-free survival (PFS), recurrence-free survival (RFS), disease-free survival (DFS), and tumour response (TR) (2,3). Due to the desire to expediate regulatory approval of new drugs, health technology assessment (HTA) agencies are increasingly faced with reliance on evidence based on surrogate endpoints, leading to decision uncertainty (4).

The correlation between surrogate measures and patient-centred clinical endpoints such as OS is not consistently strong, or even present at all, and the strength of the correlation can vary by histology (2,3,5). In a systematic review of studies that attempted to validate surrogate outcomes, only 23% of the specific surrogate survival pairs correlated highly with OS (2).

The European Medicines Agency (EMA) has yet to produce guidelines specific to the use of surrogate measures and the requirement of demonstrating a strong correlation with patient-centred clinical endpoints. According to the 2020 draft of the EMA guideline for the clinical evaluation of anticancer agents, adequate primary clinical endpoints include OS, PFS, EFS, and DFS, along with specific patient-reported outcomes (PROs) and validated biomarkers (6). The EMA declares greatest support for endpoints with convincing evidence of OS benefit.

The National Centre for Pharmacoeconomics (NCPE) evaluates drugs for the Health Service Executive (HSE) in Ireland based on their efficacy, cost-effectiveness, and impact on the drug budget. The NCPE conducts a rapid review assessment for all medicines wishing to seek reimbursement by the HSE for a particular indication. A full HTA will be indicated if there is uncertainty about effectiveness or the cost of the drug is too high relative to comparators. NCPE recommendations are made following rapid review (RR) and additionally following HTA. The HSE uses NCPE's assessments to decide whether to reimburse new drugs for use in the Irish healthcare system.

OBJECTIVE

To examine the relationship between the use of surrogate measures in pivotal trials underpinning cancer drug approvals by the European Medicines Agency (EMA) between 2017 and 2022 and health technology assessment (HTA) recommendations made the National Centre for Pharmacoeconomics in Ireland (NCPE).

METHODS

The method used for this project was adapted from 'A retrospective analysis of NICE and CADTH reviews of cancer drugs' by Pinto *et al* (7).

1. Search EMA website

- Identified relevant cancer drugs that received initial (conditional) regulatory approval from the EMA between 2017 and 2022 (inclusive). Subsequent indications for these drugs were also identified.
- Using the European Public Assessment Report (EPAR), data relating to the pivotal trial were extracted from the clinical efficacy section.

2. Search NCPE website

- The NCPE website was searched to identify if the cancer drug, for the relevant indication, had undergone assessment by the NCPE (either RR or full HTA).
- Data relating to the NCPE recommendation were extracted (if RR only). If a full HTA had been undertaken, data were extracted from the Technical Summary including the incremental QALY gain reported from cost-effectiveness analyses.

3. Analyse data

- A data extraction form in Microsoft Excel was used to input data from both data sources.
- Primary (and secondary endpoints) from the pivotal trials were categorised into the four following benefit categories for analysis purposes: (1) **OS**; (2) **PFS**; (3) **disease response (DR)** and (4) **single-arm trial (SAT)**, where no comparative benefit can be demonstrated due to lack of a comparative group. Benefit categories are mutually exclusive and categorisation was hierarchical i.e. if both PFS and OS benefit were statistically significant in the pivotal trial evidence, the indication was deemed to have OS benefit.
- For drugs that underwent a full HTA assessment, the NCPE recommendation was categorised for analysis purposes on whether there were conditions (an improvement in cost-effectiveness) attached to the recommendation. As such, four recommendation categories were possible: **positive (conditional/unconditional)** or **negative (conditional/unconditional)**.
- Descriptive analyses were used to analyse the relationship between benefit categories and the NCPE recommendation. If a HTA had been performed, the relationship between benefit category and incremental QALY gain, as reported in the NCPE adjusted base case analysis (if relevant) was analysed.

RESULTS

108
Cancer drug indications identified from the EMA search (2017-2022)

68
Individual cancer drugs included

Figure 1 Proportion of cancer-drug indications receiving (conditional) regulatory approval from the EMA based on each respective benefit category between 2017 and 2022

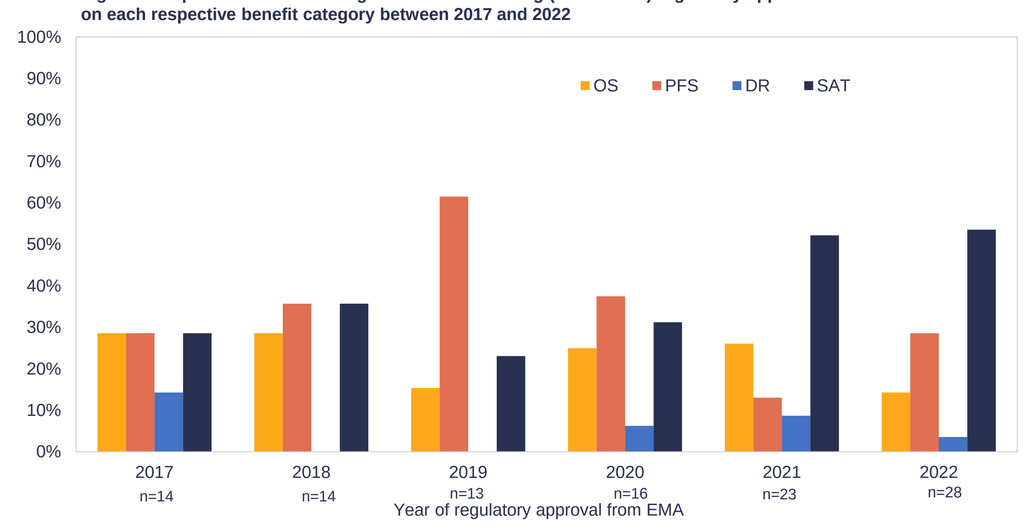
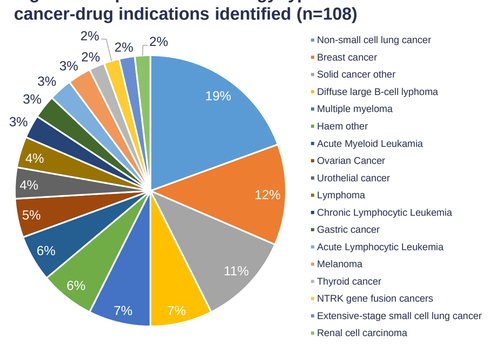
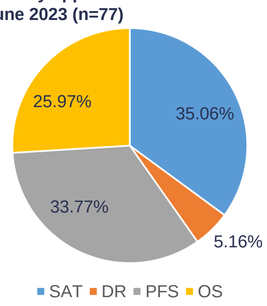


Figure 2 Proportion of histology type included in cancer-drug indications identified (n=108)



77 (71.3%)
Of the 108 cancer-drug indications had submitted an application for reimbursement to the HSE and undergone, at a minimum, a Rapid Review Assessment by the NCPE as of June 2023.

Figure 3 Benefit category for cancer-drug indications that received regulatory approval between 2017-2022 and submitted to NCPE as of June 2023 (n=77)



Of the 15 cancer-drug indications not recommended for HTA:
- 13 cancer-drug indications were not recommended for reimbursement at the submitted price
- PFS was the benefit category with the highest representation (38.46%)
- 11 of these cancer-drugs indications are reimbursed by the HSE (as of June 2023)
- 2 cancer-drug indications were not recommended for reimbursement or HTA as insufficient evidence was available

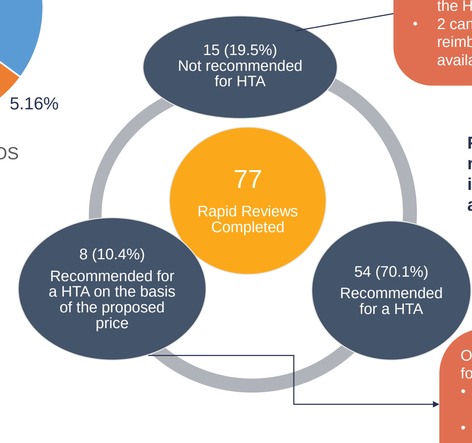


Figure 4 Rapid Review recommendations for cancer-drug indications submitted to NCPE (n=77) as of June 2023.

Of the 8 cancer-drug indications not recommended for HTA on the basis of the proposed price:
- 50% of cancer-drug indications were based on SAT evidence (n=4).
- 37.5% (n=3) indictaions were based on OS benefit with the remaining 12.5% (n=1) based on PFS benefit.
- 6 cancer-drug indications were reimbursed without going through a full HTA (following confidential price negotiations).
- 2 cancer-drug indications with this RR recommendation went forward for full HTA assessment

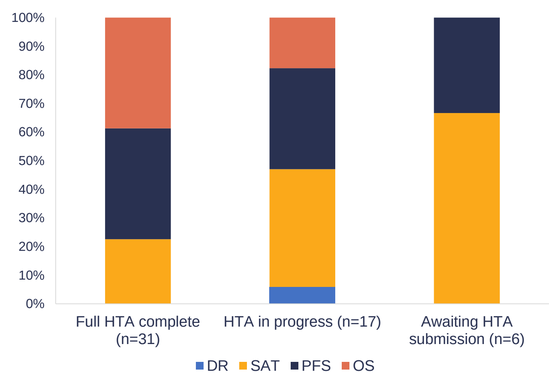
31
Cancer-drug indications with full HTA assessments complete

17
Full HTA assessments in progress

6
Cancer-drug indications awaiting full HTA submission

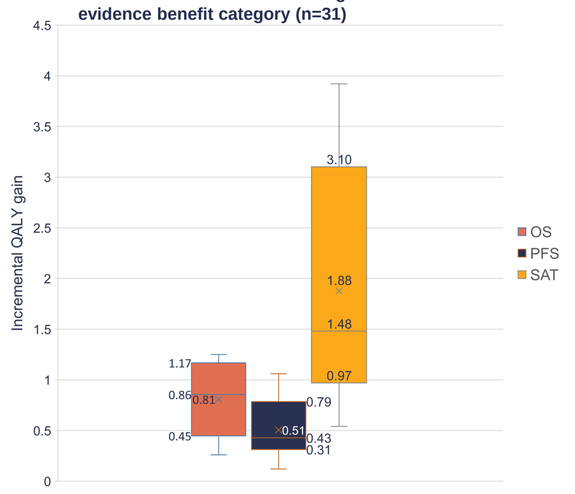
* As of June 2023

Figure 5 Benefit category for cancer-drug indications that were recommended for a full HTA following RR (n=54), dependent on the HTA assessment status



Benefit category as per pivotal trial evidence	NCPE recommendation following HTA assessment N=31			
	Recommended for reimbursement (positive unconditional; n=0)	Not recommended for reimbursement (negative unconditional; n=1)	Recommended for reimbursement if cost-effectiveness improves (positive conditional; n=6)	Not recommended for reimbursement unless cost-effectiveness improves (negative conditional; n=24)
SAT (n=7)	-	-	-	7
PFS (n=12)	-	1	2	9
OS (n=12)	-	-	4	8

Figure 6 Mean incremental QALY gain predicted in the cost-effectiveness modelling* based on evidence benefit category (n=31)



*based on NCPE adjusted base case, where relevant

CONCLUSION

The proportion of cancer-drug indications receiving regulatory approval on the basis of SAT evidence, where no direct comparative evidence, is available is increasing. The proportion of cancer-drug indications that received an initial licence or subsequent licence extension on the basis of SAT evidence increased from 28.6% of indications included in the sample in 2017 to 53.6% of cancer-drug indications approved in 2022. Our analysis indicates that 40.7% of approvals by the EMA were based on SAT evidence between 2017 and 2022. By contrast, the analysis of cancer-drug indications approved between 2012 and 2016 conducted by Pinto *et al.* (7) calculated that 29% of cancer-drug approvals were based on SAT evidence. This leads to inherent challenges when it comes to health technology assessment, as indirect treatment comparison methods are required to inform comparative effectiveness analysis, the results of which are often associated with considerable uncertainty. The proportion of EMA cancer-drug indication approvals based on OS benefit decreased from 28.6% in 2017 to 14.3% in 2022.

In terms of the NCPE HTA, it is interesting to note that cost-effectiveness analyses of cancer-drug indications based on SAT were associated with higher mean incremental QALY gain (1.88) compared with indications based on OS (0.81) or PFS (0.51). As shown in Figure 6, incremental QALY gains for indications based on SAT are associated with increased variation compared with indications based on PFS and OS, respectively. Given the uncertainty associated with relative effectiveness estimates based on naïve or adjusted indirect comparisons, which may also be required for indications with PFS and OS benefit, estimated QALY gains may be unreliable. Of course, there are a number of factors not discussed here that may also influence the estimated QALY gain including assumptions made in the cost-effectiveness analysis, extrapolation distributions chosen etc.

Regarding the NCPE recommendation, it is stark to note that all of the HTA assessments with SAT pivotal trial evidence (n=7; 22.5% of completed HTA assessments) were not recommended for reimbursement by the NCPE unless cost-effectiveness could be improved. However, it was somewhat surprising to observe that, two-thirds of the indications with an OS benefit demonstrated in the trial evidence also had a negative conditional recommendation. This highlights that demonstration of an OS benefit in the trial evidence is not sufficient for a positive NCPE recommendation; many other factors are relevant including the magnitude of the OS benefit relative to the cost of the cancer drug.

Overall, while the sample size of indications contributing to the analysis is too small to make any concrete conclusions, the results suggest that cancer-drug indications approved on the basis of SAT evidence, which are likely based on surrogate endpoints, are more likely to not be recommended for reimbursement by the NCPE. However, the results do not indicate that demonstration of an OS benefit in the pivotal trial, compared with benefit based on surrogate endpoints is sufficient to lead to a positive recommendation. A more in-depth analysis of factors influencing NCPE recommendations for cancer-drugs is required.

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