MSR7

Incorporating external data to inform overall survival extrapolation: A review of NICE health technology appraisals for oncology drugs

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BACKGROUND

- Extrapolation of overall survival (OS) data from clinical trials is key to estimate lifetime benefits of novel oncology products in the context of health technology assessments, such as those conducted by the National Institute for Health and Care Excellence (NICE)
- OS data from registrational trials are often immature or unsuitable for extrapolation at the time of initial assessment
- Using external evidence to inform OS is one possible solution to reduce uncertainty of long-term OS projections
- However, there is variability in data sources and methods used, with little understanding of which, if any, are accepted by HTA agencies

OBJECTIVES

This study surveyed oncology technology appraisals appraised by NICE and aimed to

- Summarise the data sources and methods used by companies to leverage external evidence to inform OS extrapolation
- Understand Evidence Review Groups' (ERGs) critiques and Appraisal Committees' (ACs) opinions towards such data sources and methods

METHODS

- We reviewed NICE Single Technology Appraisals (STAs) of oncology products completed between November 2019 and December 2022 and in which external data were used to inform OS extrapolation of the assessed intervention
- Information on external data sources and approaches to incorporate data, ERGs' critiques and Committee's decisions were extracted for each STA
- The data were extracted by three reviewers. Where there were discrepancies in opinion, consensus was reached through discussion

Presented at ISPOR Europe 2023; 12-15 November 2023; Copenhagen, Denmark.

FIGURE 1. Single Technology Appraisals using external data to inform OS extrapolation

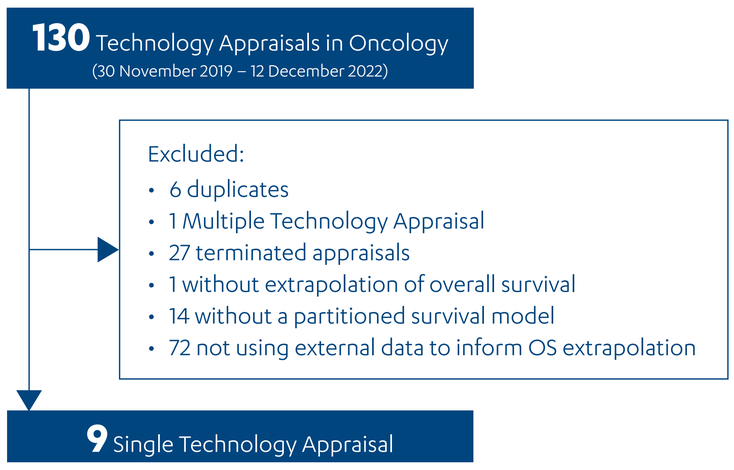


FIGURE 2. STAs by type of external data source used

FIGURE 3. ACs mostly favoured the use of external data

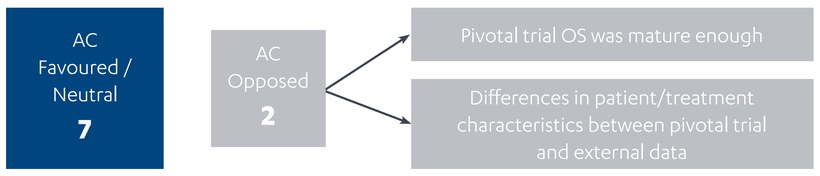
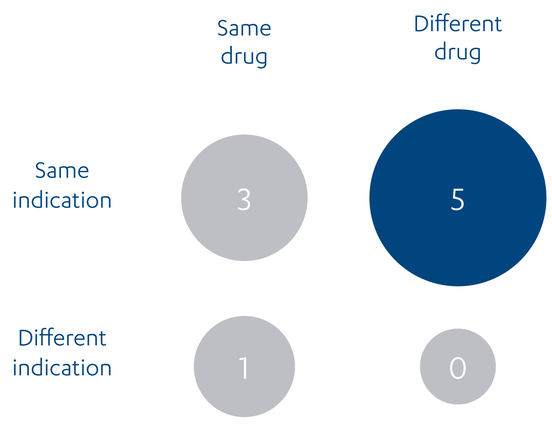


TABLE 2. External data sources by drug and indication



RESULTS

- 9 STAs met the inclusion criteria
- The main argument in favour of external data use was OS immaturity from registrational trial (4/9)
- Data from other clinical trials (7/9) were more frequently used than real-world data (2/9)
  - However, no clear systematic approach was followed in the selection of external data sources
- Data reconstruction from survival curves was used frequently (6/9)
- Methods employed by companies to incorporate external data included:
  - Appending external data after pivotal trial follow-up (3/9)
  - Relative treatment effects from ITC-based methods to reference curve from external data (2/9)
  - Relying on external data source exclusively to generate OS extrapolation (2/9)
- ACs generally favoured or were neutral about the use of external data (7/9) but were more critical of methods used (5/9); a similar trend was found for ERGs
- Main reasons why ACs disagreed:
  - Poor visual fit between extrapolated and observed registrational trial OS
  - The use of the registrational OS data alone already sufficient
  - Applying hazard ratios to extrapolation from external OS data despite violating proportional hazard assumption
  - No/insufficient attempt to match external data

CONCLUSION

- External data to inform OS extrapolation is emerging in NICE technology appraisals of oncology drugs
- Companies employed mostly data from other trials; methods chosen were context-dependent
- ACs and ERGs appear to recognise benefits of the additional evidence when registrational trial follow-up time is limited, and OS extrapolations are clinically plausible and demonstrate reasonable visual fit with pivotal trial OS.

ACKNOWLEDGEMENTS:

Editorial support provided by Lucy Webster

DISCLOSURES:

The study is funded by Janssen Pharmaceutica NV. CYC, DVT, LF, NCB, JH, and FP are employees of Janssen Pharmaceuticals and may hold stock in Johnson & Johnson

TABLE 1. Summary of external data sources, methods, ERG critiques, and AC decisions by STA

Appraisal No.	TA680	TA724	TA772	TA796	TA611	TA712	TA695	TA704	TA786
Intervention	Lenalidomide	Nivolumab + ipilimumab	Pembrolizumab	Venetoclax	Rucaparib	Enzalutamide	Carfilzomib + lenalidomide + dexamethasone (KRd)	Trastuzumab deruxtecan (T-DXd)	Tucatinib with trastuzumab and capecitabine
Registrational/ Pivotal trial	Myeloma Xi (Ph 3 RCT)	CheckMate-9LA (Ph 3 RCT)	KEYNOTE-204 (Ph 3 RCT)	3 single arm trials (Ph 1 & 2)	ARIEL (Ph 3 RCT)	ARCHES (Ph 3 RCT)	ASPIRE (Ph 3 RCT)	DESTINYBreast01 trial (Ph 2 SAT)	HER2CLIMB (Ph 2 RCT)
External data source	CALGB 100104 (Ph 3 RCT)	CheckMate-227 (Ph 3 RCT)	Gopal et al. (Ph 2 SAT)	Cancer Drug Fund (CDF) data (RWE)	Study 19 (Ph 2 RCT)	ENZAMET (Ph 3 RCT)	MyelomaToul (RWE)	TH3RESA trial (Ph 3 RCT)	(Lapatinib + capecitabine) arms of Cameron et al. 2008; Latimer et al 2012; Takano et al 2018 (3 Ph 3 RCTs)
External data drug and indication	Same drug, same indication; slightly different dosing, subsequent treatment and in different countries	Same drug, different indication (but a compatible subgroup); slightly different regimen	Different drug (brentixumib vedotin (BV)), same indication	Same drug, same indication	Different drug (olaparib), same indication	Same drug, same indication	Different drug (lenalidomide alone), same indication	Different drug (trastuzumab emtansine (T-DM1)), same indication	Different drug (Lapatinib + capecitabine), same indication
Company's justification	The company did not consider external data in the initial submission, but the AC requested the use of CALGB 100104 given its longer follow-up	OS data in CheckMate-9LA are immature, and CheckMate-227 provides longer follow-up	OS data are not reported in KEYNOTE-204 trial	CDF data have information regarding mutation and can be better generalisable to UK population compared to original trial data	OS data from ARIEL3 are immature. Study 19 provides more mature data	ARCHES provides immature OS data and is not sufficiently powered to detect statistically significant differences in OS, whereas ENZAMET has a larger sample and longer follow-up time	Given the conservative OS data of the comparator arm (Rd) in ASPIRE, the company considered leveraging lenalidomide (R) data from MyelomaToul to better guide the OS projections	OS data for T-DXd from DESTINYBreast01 trial were immature, and TH3RESA provides longer follow-up for T-DM1, with similarities in mechanism of action, line of therapy, and patient populations	OS data of lapatinib + capecitabine from these trials are used. Lapatinib + capecitabine was selected as anchor as it was most frequent treatment in the network meta-analysis.
Company's method	The company used propensity score to balance patient characteristics of CALGB 100104 population and pivotal trial in the intervention arm. The final OS was based on KM curve of the pivotal trial up to 60 months and the KM from CALGB 100104 (weight-adjusted) thereafter	OS data of CheckMate-9LA were used up to 13 months (where heavy censoring happens), and CheckMate-227 data were appended after 13 months. These hybrid data set was then used for fitting the extrapolation curves, where a 2-knot Spline model was chosen	In base-case model, the company assumed no OS benefit for pembrolizumab over BV. Thus, OS data for BV from Gopal et al. were used to model OS for both treatments	The company did not pool registrational trial data with CDF dataset. Instead, the company reconstructed pseudo-IPD by digitizing the CDF aggregate data. The pseudo-IPD were then used for OS extrapolation	The company used the post-progression survival (derived from OS minus PFS) from another PARP inhibitor (olaparib) to estimate the total OS of the submitted drug	To model overall survival of ADT alone and enzalutamide plus ADT, the company pooled IPD from ARCHES and ENZAMET without adjusting for differences in patient characteristics	Pseudo-IPD were reconstructed from the OS curves from MyelomaToul, fitted to piecewise exponential models. ASPIRE's comparator arm (Rd) was then matched with MyelomaToul to construct a hybrid comparator arm for OS. For ASPIRE's intervention arm (KRd), trial OS data were used for the first 72 months, and hazard ratio between KRd vs. Rd were applied for the OS extrapolation after 72 months	The company applied calculated OS Hazard Ratio of DESTINYBreast01 study (T-DXd) versus TH3RESA trial (T-DM1) OS data to the extrapolated OS curve of T-DM1 from TH3RESA trial	In the base-case model, the company extrapolated OS by applying relative treatment effects from company's network meta-analysis to fractional polynomial OS survival curves for the anchored treatment lapatinib + capecitabine, generated from these three external trials in the NMA.
ERG's comment on company's approach	**ERG did not favour the data source or the approach**	**ERG accepted both the data source and the approach**	**ERG accepted both the data source and the approach**	**ERG accepted the data source and had no comments on the approach**	**ERG accepted the data source but did not favour the approach**	**ERG accepted the data source but did not favour the approach**	**ERG did not favour the data source or the approach**	**ERG did not favour the data source or the approach**	**ERG accepted the data source but did not favour the approach**
AC comments on company's approach	**AC accepted both the data source and the approach**	**AC provided no comments on the data source and accepted the approach**	**AC accepted both the data source and the approach**	**AC accepted the data source and had no comments on the approach**	**AC accepted the data source but did not favour the approach**	**AC accepted the data source but did not favour the approach**	**AC did not favour the data source or the approach**	**AC did not favour the data source or the approach**	**AC accepted the data source but did not favour the approach**

Abbreviations: AC, Appraisal Committee; ADT, androgen deprivation therapy; ERG, Evidence Review Group; IPD, individual patient data; KM, Kaplan-Meier; NMA, network meta-analysis, OS, overall survival; PFS, progression free survival; RCT, Randomized control trial; RWE, real-world evidence; SAT, single arm trial

Favouring both the external data use and the approach | Favouring either the external data use or the approach | Does not favour neither external data use nor the approach