Overall Survival adjusted for subsequent treatments: a review of health technology assessments

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Objectives:

- Treatment switching, while common in oncology RCTs, can bias overall survival (OS) estimates. Traditional adjustment methods focus on crossover from control to experimental arms. This study explores how Health Technology Assessment bodies (HTABs) view broader adjustment approaches, including those accounting for all subsequent therapies, whether crossover or any another treatment (broadly: "treatment switching").

Methods:

- Methods guides from 17 HTAB were reviewed to identify guidance on adjusting OS data to correct for subsequent treatment confounding.
- HTA appraisals in solid tumours from 13 HTABs were screened and 6 analogues selected (yielding 61 decisions across HTABs). HTAB feedback on adjustment methods for treatment switching was qualitatively analysed in 3 steps:
  1. Acceptance of adjustment usage in a particular trial and SoC context ("use case")
  2. Acceptance of adjustment method
  3. Impact of adjusted results on HTA decision

Results:

- HTAB guidance on OS adjustment is limited and heterogeneous *(Table 1):* Of 5 HTAB that published guidance, 4 (NICE, NoMA, PBAC, AOTMiT) view adjustment as informative; while only IQWiG/G-BA consider adjustment methods too uncertain.
- OS adjustment was submitted in 28/61 HTAs *(Figure 2):* Case studies confirmed IQWiG/G-BA consistently opposed the use of adjusted OS; other HTAB (NICE, PBAC, CDA, NoMA, TLV, HAS-CEESP) accepted it selectively – when switching in the trial did not reflect standard of care and key methodological assumptions were met.
- The most frequently submitted methods were RPSFTM (n=28/28), TSE (n=16/28), and IPCW (n=13/28) *(Table 2).* In 16/28 cases, HTD submitted multiple methods. For 3/6 analogues, HTD tailored submissions per HTAB, offering only RPSFTM to some and additional methods to others. In 2 out of these 3 analogues (pembrolizumab for mUC, crizotinib for NSCLC), some HTAB preferred the additional method (TSE). No analogue had a consistent approach to adjusting OS or not across all HTAB.
- Adjusted OS had a positive impact on 11/28 cases *(Table 2)* mostly by improving the ICER. In one case (*) NICE reversed its decision on accepting TSE-adjusted OS once more mature data resulted in the ICER being more sensitive to the OS adjustment than in the original HTA, leading to a negative recommendation in the reassessment.

Fig. 1 Confounding impact of treatment switching on ITT analyses

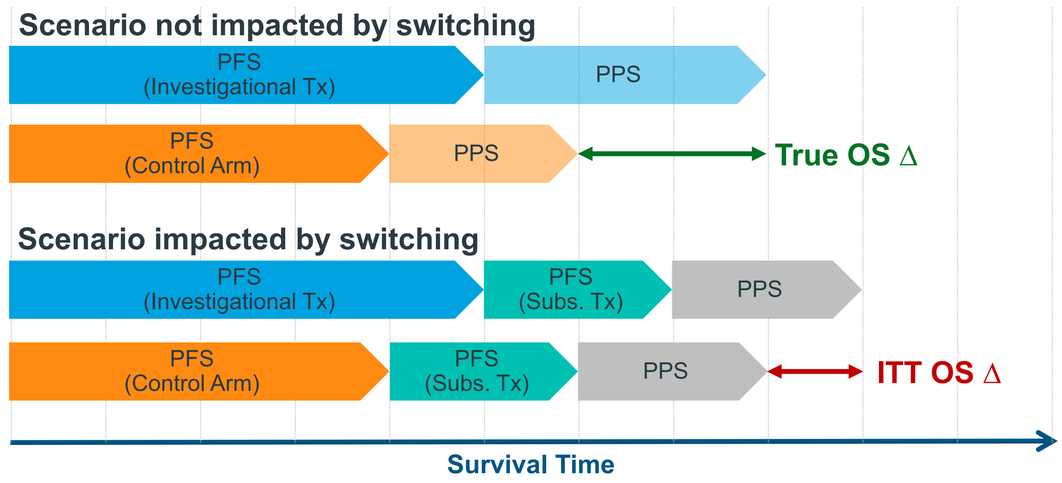

Table 1. HTAB methods guides addressing OS adjustment for treatment switching

☑	☒	☒	☒	☒	☒	☑	☒	☒
☒	☑	☒	☒	☑	☒	☑	☒	☒

Advises to use pre-switch data

Key: ☒ not addressed; ☑ addressed, unfavourable; ☑ addressed, favourable

Fig. 2 Use cases accepted/rejected (from 28/61 HTAs with adjusted OS)

Table 2. OS analysis methods submitted by HTD vs accepted by HTAB & Impact of OS adjustment on HTA outcome

Analogue: Disease	Switching mechanism	G-BA	HAS	INFARMED	NoMA	TLV	NICE	CDA	PBAC
Talazoparib: MBC (2L)	Subsequent therapies	ITT	ITT	ITT	*RPSFTM*	*RPSFTM*	*RPSFTM*	No HTA	ITT
Pembrolizumab: Melanoma (2L)	Crossover to pembrolizumab	*RPSFTM IPCW, TSE Censoring*	RPSFTM IPCW **TSE**	ITT	No HTA	ITT	RPSFTM IPCW **TSE**	ITT	No HTA
Pembrolizumab: mUC (2L)	Subsequent therapies	*RPSFTM IPCW TSE*	**RPSFTM IPCW TSE**	ITT	RPSFTM	RPSFTM	RPSFTM IPCW **TSE***	RPSFTM	RPSFTM IPCW **[TSE]**
Pembrolizumab: mCRC (1L)	Subsequent therapies including crossover to pembrolizumab	*RPSFTM IPCW TSE*	ITT	*RPSFTM IPCW TSE*	*RPSFTM IPCW TSE*	No HTA	RPSFTM IPCW TSE	**RPSFTM IPCW TSE**	**RPSFTM** IPCW TSE
Brigatinib: NSCLC (1L)	Crossover to brigatinib	ITT	ITT	ITT	**RPSFTM†**	ITT	**RPSFTM**	RPSFTM	ITT
Crizotinib: NSCLC (1L)	Crossover to crizotinib	*RPSFTM*	ITT	ITT	**RPSFTM**	*RPSFTM TSE IPE*	RPSFTM **TSE** IPE	**RPSFTM**	No HTA

Key: Positive impact | No impact | Negative impact | *Unknown acceptance / impact* | **Most appropriate method by HTAB** | Inappropriate method by HTAB | *Use case rejected*

Conclusions:

- Adjusting OS data to account for subsequent treatments can overcome limitations of confounded ITT-analyses, as was accepted by several HTAB in our analysis.
- However, in our sample there was overall no HTAB consensus on use cases, which method to apply for a specific switching mechanism, or what impact adjusted OS can have on final decisions.
- Adjusted OS data positively impacted several HTA outcomes, highlighting the value of selecting, justifying, and reporting appropriate methods.
- Among our country sample, only PBAC and NICE provide detailed guidance. While EU JCA documentation does not currently incorporate latest research on OS adjustment methods, there is an opportunity to improve consistency and reliability in the assessment of OS adjustment methods for HTA decision-making across Member States.

References: (1) IQWiG General Methods v8 (2025); (2) IQWiG Treatment Switching in Oncological Studies (2018); (3) G-BA Rules of Procedure (2025); (4) G-BA Dossier Module (2025); (5) HAS Transparency Committee doctrine (2023); (6) HAS-CEESP doctrine (2021); (7) HAS Choices in methods for economic analysis (2020); (8) AIFA Guidelines (2020); (9) CAPF Guide to the Economic Evaluation of Medicines (2023); (10) ZIN Guideline for Economic Evaluations (2024); (11) CTG Guidelines (2025); (12) AOTMiT Guidelines for HTA (2016); (13) INFARMED Pharmacotherapeutic assessment methodology (2021); (14) TLV Handbook (2025); (15) NoMA Submission Guidelines (2024); (16) Danish Medicines Council Methods Guide (2021); (17) NCPE HTA Guidelines (2019); (18) NICE TSD 24; (19) NICE TSD 16; (20) SMC Guidance to Submitting Companies (2022); (21) PBAC guidelines (2016); (22) CDA Methods Guide for HTA (2025); (23) CDA Guidelines for the Economic Evaluation of Health Technologies (2018); (24) HTA CG Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in JCA (2024); (25) IQVIA Market Access Insights™

Abbreviations: EU JCA – European Union Joint Clinical Assessment; HTD – Health Technology Developer; ICER – Incremental Cost-effectiveness Ratio; IPCW – Inverse Probability of Censoring Weights; ITT – Intention-to-Treat; MBC – metastatic breast cancer; mCRC – metastatic colorectal cancer; mUC – metastatic urothelial carcinoma; NSCLC – non-small cell lung cancer; OS – Overall Survival; PFS – Progression-free Survival; PPS – Post-progression Survival; RCT – Randomised Controlled Trial; RPSFTM – Rank Preserving Structural Failure Time Model; SMR/ASMR – [Added] Clinical Benefit rating; SoC – Standard of Care; TSE – Two-Stage Estimation; Tx – Treatment

Poster presented at ISPOR Europe 2025, 9-12 November 2025 | Glasgow, Scotland, United Kingdom

Disclosures: This research is part of an alliance and was funded by AstraZeneca and Daiichi Sankyo Europe GmbH.
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