# Role of Real-World Evidence in Supporting and Validating Crossover Adjustments of Overall Survival in Oncology Trials: A Systematic Literature Review of Health Technology Assessments of Treatments for Selected Tumors

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## Conclusion

- This systematic literature review highlights the growing importance of real-world evidence in validating overall survival estimates in oncology trials affected by treatment crossover
- Randomized controlled trials remain the gold standard for evaluating treatment benefit; however, treatment crossover, restrictive eligibility criteria, and limited study duration can impact interpretability in the clinical setting and comparisons across trials
- Real-world evidence complements randomized controlled trials findings by providing external reference points that address crossover bias and support more credible long-term survival estimates
- Real-world evidence also improves the external validity and generalizability of cost-effectiveness analyses because it better reflects real-world treatment patterns and patient populations
- Overall, real-world evidence is playing a critical role in informing health technology assessments and guiding evidence-based health-policy decisions

## Plain language summary

- In various oncology trials, patients in the control arm change therapy to the investigational treatment upon disease progression, which can dilute the observed overall survival benefit of the treatment arm
- This systematic literature review examined how health technology assessments use real-world evidence to validate the overall survival estimates of comparator arms affected by treatment crossover
- Across submissions, diverse real-world evidence sources, including registries, electronic medical records, and secondary research, were used to support validation of comparator-arm overall survival estimates
- Real-world evidence contributed to validating long-term overall survival curves generated by fitting statistical models to real-world survival patterns
- Real-world data allowed decision-makers to validate whether trial survival results were realistic and reflective of routine practice
- Overall, the study shows that real-world evidence complements RCT findings by strengthening evaluations of oncology treatments and improving patient access when traditional trial data are difficult to interpret due to crossover

**References:** **1)** ICER: icer.org/assessment; **2)** HAS: Haute Autorité de Santé; **3)** IQWiG/ G-BA: www.iqwig.de; **4)** PBAC: www.pbs.gov.au/pbac-meetings; **5)** NICE: www.nice.org.uk/guidance; **6)** CDA/CADTH: www.cda-amc.ca; **7)** AIFA: Italian Medicines Agency; **8)** NCCN: www.nccn.org/professionals; **9)** AEMPS: Medicamentos de uso humano | AEMPS; **10)** FDA: www.fda.gov/advisory-committees; **11)** TA709: www.nice.org.uk/guidance/ta709; **12)** TA406: www.nice.org.uk/guidance/ta406; **13)** TA655: www.nice.org.uk/guidance/ta655; **14)** TA713: www.nice.org.uk/guidance/ta713; **15)** TA653: www.nice.org.uk/guidance/ta653; **16)** PC0262-000: www.cda-amc.ca/cemiplimab; **17)** CT19147: www.has-sante.fr/Keytruda; **18)** CT18206: www.has-sante.fr/tecentriq; **19)** CT17673: www.has-sante.fr/Keytruda; **20)** CT15941: www.has-sante.fr/Keytruda; **21)** CT19172: www.has-sante.fr/tukysa-tucatinib; **22)** CT16457: www.has-sante.fr/tecentriq; **23)** CT19944: www.has-sante.fr/enhertu

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## Introduction

- Treatment crossover in oncology trials is a well-recognized methodological complexity that impacts the interpretation of survival outcomes and subsequent health technology assessment (HTA) evaluations
- In addition to statistical adjustments, broader HTA-relevant considerations may play a significant role in guiding decision-making.
- These considerations include the use of real-world evidence (RWE) to complement randomized controlled trials, to support validation of counterfactual overall survival (OS) estimates, and assessment of long-term generalizability.
- Despite their importance, these approaches have not been systematically analyzed across various HTA contexts
- Validating crossover-adjusted OS estimates ensures that post-progression treatments and survival outcomes are reflective of real-world clinical practice

## Objective

- This systematic literature review (SLR) assessed how RWE supports validation of crossover-adjusted OS in HTA of clinical trials studying advanced/metastatic cancer of the lung (non-small cell, NSCLC), breast (BC), prostate, renal, colorectal (CRC), and gastrointestinal stromal tumors

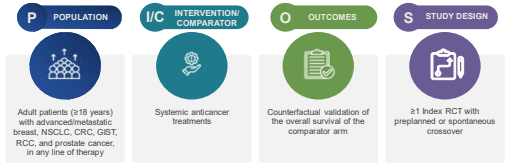
## Methodology

- HTA agency, regulatory authority, and clinical practice guideline websites were manually searched for published reports, including manufacturer submissions and final guidance, between January 1, 2013, and December 6, 2024:
  - *Health technology agencies:*
    - *Institute for Clinical and Economic Review (ICER) – United States (US)*[1]
    - *National Institute for Health and Care Excellence (NICE) – United Kingdom*[2]
    - *Haute Autorité de Santé (HAS) – France*[3]
    - *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); Federal Joint Committee (G-BA) – Germany*[4]
    - *Pharmaceutical Benefits Advisory Committee (PBAC) – Australia*[5]
    - *Canada's Drug Agency (CDA/CADTH) – Canada*[6]
    - *Agenzia Italiana del Farmaco (AIFA) – Italy*[7]
  - *Clinical practice guidelines:*
    - *National Comprehensive Cancer Network (NCCN) – US*[8]
  - *Regulatory bodies:*
    - *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Spain*[9]
    - *Food and Drug Administration - Oncologic Drugs Advisory Committee (FDA – ODAC) - US*[10]
- **Figures 1** and **2** outline the search strategy and inclusion criteria, respectively. The non-English HTA/regulatory documents (HAS, G-BA, AEMPS, and AIFA) were searched using keywords in their native language (e.g., crossover, cross over, cross-over, switch, croisé, permuté, wechsel, cruzado, cambi, etc.)
- All documents fulfilling eligibility criteria underwent a detailed assessment to capture information on the comparator drug/class similarity (RWE drugs aligned with trial comparators), intervention uptake (RWE reflecting investigation treatment use), external validity (RWE supporting long-term effectiveness), and characteristics and calibration (RWE used to match and calibrate trial populations)

**Figure 1: Search strategy used to identify HTA submissions**


AEMPS: Agencia Española de Medicamentos y Productos Sanitarios; AIFA: Agenzia Italiana del Farmaco; CDA/CADTH: Canada's Drug Agency; FDA-ODAC: Food and Drug Administration – Oncologic Drugs Advisory Committee; HAS: Haute Autorité de Santé; HTA: Health Technology Assessment; ICER: Institute for Clinical and Economic Review; IQWiG/G-BA: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/Federal Joint Committee; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee

**Figure 2: PICOS Criteria**

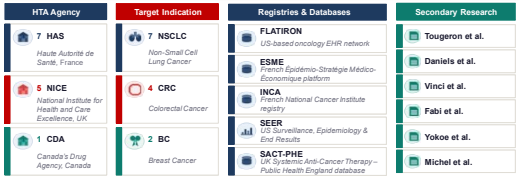



CRC: Colorectal cancer; GIST: Gastrointestinal stromal tumors NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; RCT: Randomized controlled trial

## Results

- Of 1,653 records screened, 162 product submissions permitting treatment crossover met the inclusion criteria; none of the product submissions to AIFA provided evidence of crossover
- Eleven product labels (FDA, AEMPS), four NCCN clinical practice guidelines, and 134 product submissions to HTA bodies lacked counterfactual validation of the OS estimate and were thus considered ineligible
- Thirteen submissions reported counterfactual validation of the OS estimate associated with the comparator arm using diverse real-world sources to support decision-making for payer archetypes relying on cost-effectiveness evaluation (**Figure 3**)

**Figure 3: RWE sources for validation of comparator arm OS across HTA agencies**




RWE: Real-world evidence; HTA: Health Technology Assessment; OS: Overall survival

- Overall, RWE sources comprise patients who received standard chemotherapy and excluded the treatment under investigation
- The validation of OS was accomplished through various real-world databases/registries or through secondary research based on real-world populations
- RWE was used to validate the extrapolated OS benefits using different parametric survival models and to determine generalizability for a longer time horizon

### NICE

- Five NICE HTA submissions reported the use of RWE to validate OS estimates for the comparator arm in clinical trials affected by treatment crossover
- These submissions also reported using RWE to validate the suitability of the comparator arm
- **Figure 4** summarizes the comparator-arm treatment, its comparison with RWE treatments, and the role of counterfactual validation

**Figure 4: Comparison of trial comparator with RWE treatments, and the role of validation**

| | Trial comparator | RWE Source | Comparator drug/class similarity | Intervention uptake | External validity | Generalizability |
|---|---|---|---|---|---|---|
| **TA709[11] (KEYNOTE-177; Pembrolizumab;MSI-H, dMMR, mCRC; 1L]** | Standard of Care | Tougeron et al. | ✓ | ✗ | ✓ | ? |
| **TA406[12] [PROFILE-1014; Crizotinib; mNSCLC; 1L]** | Pemetrexed + platinum | FRAME study | ✓ | ✗ | ✓ | ? |
| **TA655[13] [Checkmate-017; Nivolumab: SQ-mNSCLC; 2L]** | Docetaxel | NLCA dataset; SEER database | ? | ? | ✓ | ? |
| **TA713[14] (Checkmate-057 Nivolumab; NSQ-mNSCLC; 2L]** | Docetaxel | NLCA dataset | ? | ✗ | ✓ | ✓ |
| **TA653[15] [AURA; Osimertinib; mNSCLC, 2L]** | Platinum-based chemotherapy | SACT-PHE | ? | ? | ? | ✓ |

✓ Yes ✗ No ? Unknown/Unspecified

1L: First-line; 2L: Second-line; 3L: Third-line; CRC: Colorectal cancer; dMMR: Mismatch repair deficient; M: Metastatic; MSI-H: Microsatellite instability–high; NLCA: National Lung Cancer Audit Dataset; NSCLC: Non- small cell lung cancer; NSQ: Non-squamous; SACT-PHE: Systemic Anti-Cancer Therapy – Public Health England; SEER: Surveillance, Epidemiology, and End Results; SoC: Standard of care; OS: Overall survival; RWE: Real-world evidence

- Treatments in the RWE sources generally aligned with the trial comparator, with intervention uptake often unavailable or not permitted across most RWE sources. Two submissions did not report this information
- Most submissions employed counterfactual validation of the comparator arm's OS to support external validation of long-term estimates, while a smaller number applied it for generalizability or for both purposes

### CDA

- One CADTH/CDA submission of cemiplimab for first-line treatment of mNSCLC (programed death-ligand 1≥50%) reported use of RWE to counterfactually validate the comparator arm's OS, supporting the external validity of long-term OS estimates[16]
- However, information on the RWE source, treatment, and allowance of cemiplimab uptake was not reported in the submission (PC0262-000, EMPOWER-LUNG-1)[16]

### HAS

- Across the included HAS assessments, seven submissions reported validation of comparator-arm OS using RWE
- **Figure 5** summarizes the RWE sources, comparator-arm treatment, its comparison with RWE treatments, and the role of counterfactual validation

**Figure 5: Comparison of trial comparator with RWE treatments, and the role of validation**

| | Comparator | RWE Source | Comparator drug/class similarity | Intervention uptake | External validity | Characteristics and calibration |
|---|---|---|---|---|---|---|
| **CT19147[17] [Keynote-177; Pembrolizumab; MSI-H, dMMR, mCRC; 1L]** | Standard of Care | Tougeron et al. | ✓ | ✗ | ✓ | ? |
| **CT18206 & 18149[18] [IMpassion 130; Atezolizumab + nab paclitaxel; mTNBC; 1L]** | nab paclitaxel | FLATIRON and ESME | ✓ | ✗ | ? | ✓ |
| **CT17673[19] [Keynote-407; Pembrolizumab + carboplatin + paclitaxel; SQ- mNSCLC; 2L]** | Carboplatin + paclitaxel or nab-paclitaxel | SEER database | ? | ✗ | ✓ | ? |
| **CT15941[20] [Keynote-024; Pembrolizumab; mNSCLC; 1L]** | Standard of Care | FLATIRON | ✗ | ? | ✓ | ? |
| **CT19172[21] [HER2CLIMB; Tucatinib+ trastuzumab + capecitabine; HER2+, mBC; 3L+]** | Trastuzumab + capecitabine | Yokoe et al. | ✗ | ✗ | ✓ | ? |
| **CT16457[22] [OAK; Atezolizumab; mNSCLC; 2L]** | Docetaxel | INCA 2013 | ? | ? | ✓ | ? |
| **CT19944[23] [DESTINY BREAST-03; Trastuzumab deruxtecan; HER2+ mBC; 2L+]** | Trastuzumab emtansine | Daniels et al., Vinci et al., Fabi et al., Yokoe et al., Michel et al. | ✓ | ? | ✓ | ? |

✓ Yes ✗ No ? Unknown/Unspecified

1L: First-line; 2L: Second-line; 3L: Third-line; CRC: Colorectal cancer; dMMR: Mismatch repair deficient; ESME: Épidémiologie des Maladies de la Femme et de l'Enfant; HER: Human epidermal growth factor receptor; FLATIRON: Flatiron Health Database; TNBC: Triple negative breast cancer; BC: Breast cancer; M: Metastatic; MSI-H: Microsatellite instability–high; NSCLC: Non-small cell lung cancer; SEER: Surveillance, Epidemiology, and End Results; SoC: Standard of care; OS: Overall survival; RWE: Real-world evidence

- RWE was used to validate OS observed in trials, support long-term OS projections, and evaluate whether comparator arms reflected standard treatment pathways
- The similarity between treatments used in RWE sources and trial comparators varied across submissions. Three submissions reported comparable treatments, while treatments were non-similar in two submissions and unspecified in another two
- Information on whether patients received the investigational treatment in RWE sources was frequently missing or not permitted in four submissions, while three submissions did not specify this information
- RWE was used to interpret and calibrate long-term OS observed in the trial for the comparator arm, rather than to generate formal counterfactual models
- This approach strengthened assessments of clinical relevance, external validity, and alignment with real-world practice, particularly when treatment crossover or evolving standards of care limited interpretation of trial-based OS
- Collectively, these appraisals indicate that HAS draws on RWE to support clinical decision-making, confirm external validity, and maintain the credibility of long-term OS estimates in routine practice

### IQWiG/GBA & PBAC

- Counterfactual validation was not reported in any IQWiG/GBA and PBAC submissions

## Strengths & Limitations

- This represents the first comprehensive SLR to systematically explore how HTA bodies assessed approaches to address treatment-switching in company submissions, the varied approaches adopted by HTA bodies toward counterfactual validation, alongside the role of RWE in HTA decision-making
- The SLR was not limited to English-language publications and incorporated studies in native languages, including German, French, Spanish, and Italian, thereby minimizing selection bias
- Considerable heterogeneity in HTA frameworks, evidence requirements, and reporting practices across agencies limits direct comparability of findings and the generalizability of conclusions across jurisdictions