Evaluation of the role of clinical unmet need in HTA decision-making of oncology trials without demonstrated overall survival benefits due to treatment crossover

HTA 6

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Conclusion

- Across NICE, CDA, and HAS, unmet need was widely recognized but rarely drove reimbursement; decisions were largely determined by cost-effectiveness and clinical effectiveness evidence, even where overall survival benefits did not reach statistical significance
- Unmet need was inconsistently defined across HTA agencies, reflecting differences in appraisal frameworks and payer archetypes; in G-BA, endpoints beyond overall survival, including morbidity, safety, and HRQoL, played a critical role where crossover diluted survival benefits
- Overall, unmet need strengthened the case for reimbursement only where sufficient added clinical benefit or cost-effectiveness versus the standard of care was demonstrated

Plain language summary

- In some oncology trials, patients in the control group switch to the experimental treatment after disease progression, making it challenging to measure true survival benefits
- Unmet need is context-specific, varying across health systems; while NICE, HAS, and CDA require convincing clinical or cost-effectiveness evidence, G-BA positively recommended interventions without clear survival advantages where improvements in symptoms, quality of life, or safety were demonstrated
- Unmet need strengthens the case for reimbursement but rarely works alone; some interventions targeting unmet need were not recommended due to uncertain or limited evidence, highlighting that strong clinical or economic justification remains essential

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) TA531: www.nice.org.uk/guidance/ta531
12) TA512: www.nice.org.uk/guidance/ta512
13) TA866: www.nice.org.uk/guidance/ta866
14) TA709: www.nice.org.uk/guidance/ta709
15) TA786: www.nice.org.uk/guidance/ta786
16) TA770: www.nice.org.uk/guidance/ta770
17) TA887: www.nice.org.uk/guidance/ta887
18) A16-62: www.iqwig.de/en/a16-62
19) A21-36: www.iqwig.de/en/a21-36

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Introduction

- Crossover from the control arm to the investigational therapy is routinely incorporated into placebo-controlled randomized oncology trials, often occurring upon disease progression, at the request of investigators or patients, or due to ethical considerations
- Traditional statistical methods, including intention-to-treat analysis, may produce biased overall survival (OS) estimates, potentially underestimating the magnitude of the true treatment effect
- Considerations of disease burden, unmet medical need, and health-related quality of life (HRQoL) are playing an increasingly important role in payer and HTA resource-allocation decisions
- Evidence suggests that HTA committees may issue positive recommendations even in the absence of a demonstrated OS benefit, provided the submission addresses a recognized unmet medical need and aligns with the relevant payer archetype (clinical or cost effectiveness)

Objective

- This systematic literature review (SLR) assessed how HTA bodies have given precedence to clinical unmet need, allowed reimbursement, and provided favorable appraisal even in the absence of OS benefit
- It further highlights the extent to which unmet need and other contextual factors influence HTA decision-making beyond traditional efficacy endpoints

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:
- <u>*Health technology agencies:*</u>
  - *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]
- <u>*Clinical practice guidelines:*</u>
  - *National Comprehensive Cancer Network (NCCN) – US*[8]
- <u>*Regulatory bodies:*</u>
  - *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 PICOS criteria, respectively
- The Non-English HTA documents (HAS, G-BA) were searched using keywords in their native language (e.g., crossover, cross over, cross-over, switch, croisé, permuté, wechsel, cruzado, cambi, etc.)
- All documents meeting the predefined eligibility criteria were subjected to a thorough and systematic assessment to identify, extract, and compile key information relevant to the objectives of the study

Figure 1: Search strategy used to identify HTA submissions

Figure 2: PICOS Criteria

BC: Breast cancer; CRC: Colorectal cancer; GIST: Gastrointestinal stromal tumor; HTA: Health technology assessment; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; PC: Prostate cancer; RCT: Randomized controlled trial

Results

- Of 1,653 records screened, 147 product submissions allowing treatment crossover were included; Searches yielded no submissions from AIFA
- Of these, 79 submissions were assessed under cost-effectiveness-based archetypes (NICE n=32; CDA n=20; PBAC n=26; ICER n=1), and 68 under clinical-effectiveness-based archetypes (IQWiG/G-BA n=42; HAS n=26)
- Eleven product labels (FDA, AEMPS) and four NCCN clinical practice guidelines were ineligible due to a lack of reported unmet medical need

NICE

- Across seven of 32 NICE submissions, unmet need was defined by limited effective therapies for treatment-naïve patients, later-line settings, and specific patient subgroups.

Figure 3: Rationale behind reimbursement decisions with recognized unmet medical need across NICE submissions

TA531[11] (mNSCLC, PD-L1 +ve, 1L+) Pembrolizumab	• Limited effective treatment options for people with this condition • Met the life expectancy and life extension criteria to be considered a life-extending & end-of-life treatment
TA512[12] (aRCC, 1L+) Tivozanib*	• Need to offer tivozanib to people who do not tolerate existing treatments • Lack of effective treatment options with better tolerance
TA866[13] (mCRC, 3L+) Regorafenib	• Treatments giving improvements in quality of life & extensions to length of life are considered important • Committee agreed that people with mCRC who have had previous treatments, have an unmet clinical need
TA709[14] (MSI-H/dMMR, mCRC, 1L+), Pembrolizumab*	• Same treatment was offered whether their CRC has high MSI or DNA MMR deficiency • The committee concluded that there is an unmet need for treatments for this condition
TA786[15] (HER-2 +ve, mBC, 3L+) Tucatinib	• Tucatinib can cross an intact blood-brain barrier and treat brain metastases • The committee concluded that there is a high unmet need for anti-HER2 treatment after second-line
TA770[16] (PD-L1, TPS ≥ 50%, mNSCLC 1L+), Pembrolizumab	• High unmet need due to lack of other treatment options available and because this indication are likely to have a very short life expectancies
TA887[17] (BRCA+ve, mPC, 2L+), Olaparib	• Lack of therapies which extend survival and help them to maintain or improve their quality of life • The committee concluded that there is an unmet need for new treatments for this indication

- ***Unmet need did not influence reimbursement decisions by NICE***
- ***Positive reimbursement decisions*** *were consistently driven by favourable cost-effectiveness, with the incremental cost-effectiveness ratio (ICER) as the primary determinant*

*High crossover rate with statistically non-significant ITT OS; 1L+: First-line and beyond; 2L+: Second-line and beyond; 3L: Third-line and beyond; BC: Breast cancer; BRCA: Breast cancer gene; CRC: Colorectal cancer; dMMR: deficient mismatch repair; HER: Human epidermal growth factor receptor M: Metastatic; MSI-H: Microsatellite instability-high; NSCLC: Non- small cell lung cancer; PD-L1: Programmed death ligand-1; RCC: Renal cell carcinoma; TPS: Tumor proportion score; PC: Prostate cancer

CADTH/CDA

- Across 20 CDA submissions, unmet medical need was frequently recognized as an important contextual factor, with appraisals noting gaps in available treatments or limitations of current care
- Technologies lacking sufficient clinical effectiveness or cost-effectiveness often still received "do not reimburse" or "reimburse with conditions" recommendations, even in unmet-need populations
- This reflects CDA's emphasis on evidence-based value, where unmet need informs but does not supersede requirements for robust clinical and economic justification

IQWIG/GBA

- Only two of the 42 product submissions to IQWIG/GBA referenced unmet need, which was characterized by the absence of effective therapies **(Figure 4)**

Figure 4: Rationale behind reimbursement decisions with recognized unmet medical need across IQWIG/GBA submissions

[A16-62][18] (ALK +ve, mNSCLC, 2L+) Crizotinib	• Indication of considerable added benefit, considering the advanced disease stage and situation in which patients have already received AKL-specific therapy • OS benefit not proven • Considerable added benefit for morbidity, HRQoL and safety outcomes
[A21-36][19] (MSI-H/dMMR, mCRC, 1L+) Pembrolizumab	• Indication of minor additional benefit, recognizing the unmet need for a first-line monotherapy, where patients previously depended solely on chemotherapy-based regimens • OS benefit not proven • Considerable added benefit for safety outcomes

- **Positive decisions** from G-BA are primarily driven by clinical effectiveness
- IQWiG does not apply a formal framework to assess unmet need; however, the G-BA may qualitatively consider unmet need as a supportive context when determining the extent of additional benefit.

1L+: First-line and beyond; 2L+: Second-line and beyond; ALK: Anaplastic lymphoma kinase; CRC: Colorectal cancer; dMMR: deficient mismatch repair GBA: Federal Joint Committee; IQWIG/GBA: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; M: Metastatic; MSI-H: Microsatellite instability-high; NSCLC: Non- small cell lung cancer

- In the submission for anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer previously treated with crizotinib (A16-62), no OS benefit was shown; however, considerable benefit existed in morbidity, safety, and quality of life (QoL)
- In the submission for first-line microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer (A21-36), no OS, morbidity, or QoL benefit was demonstrated, although safety outcomes showed considerable added benefit
- These cases highlight IQWiG/G-BA's recognition that crossover can mask true treatment benefits in OS analyses, necessitating consideration of alternative non-OS endpoints, unmet need as supportive elements in determination of additional benefit

HAS, PBAC & ICER

- Unmet need was reported in all product submissions to HAS (n=26); however, decision-making was primarily driven by clinical added benefit
- Unmet medical need was not reported in any of the ICER (n=1) and PBAC submissions (n=26)

Strengths & Limitations

- This SLR provides the first systematic evaluation of how HTA bodies characterize unmet need and the extent to which it informs decision-making in cancer clinical trials affected by treatment switching
- Heterogeneity in HTA methodologies and payer archetypes; HTA bodies across countries use different appraisal frameworks, evidence thresholds, and criteria for unmet need, making direct comparison difficult and limiting the generalizability of findings