Methodological Divergence and Policy Impact of HTAs for Immune Checkpoint Inhibitors in NSCLC

HTA10

Anschutz

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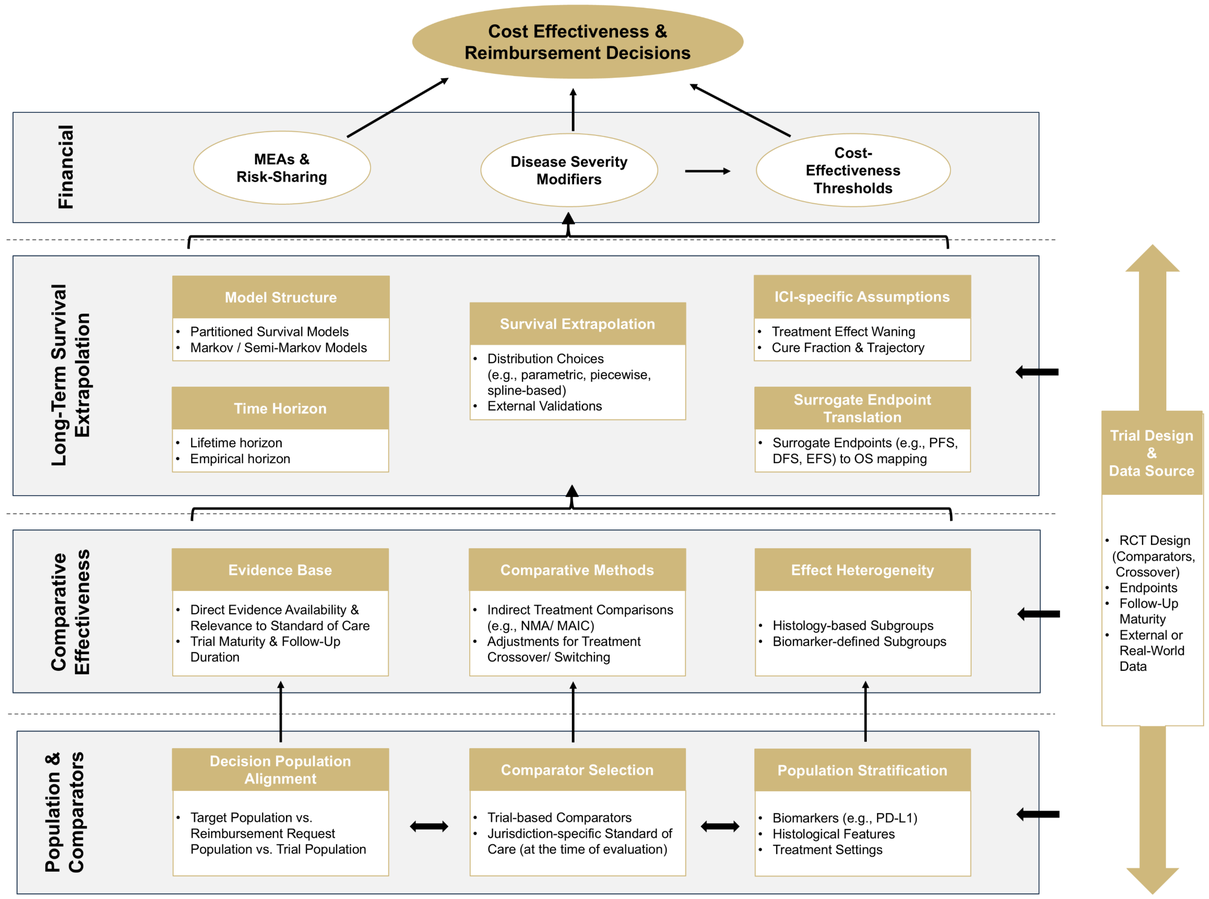
BACKGROUND

- Immune checkpoint inhibitors (ICIs) have transformed the treatment of non-small cell lung cancer (NSCLC) across early- and advanced-stage disease. However, they pose persistent challenges for health technology assessment (HTA), including high prices, immature survival data, heterogeneous patient response, and uncertainty about long-term treatment effects.[1-2]
- Previous studies have documented cross-country variation in HTA outcomes for oncology drugs but have primarily focused on final reimbursement decisions rather than underlying methodological drivers.[3-4]
- Little empirical work has systematically compared how HTA agencies operationalize uncertainty through methodological choices within appraisals.

METHODS

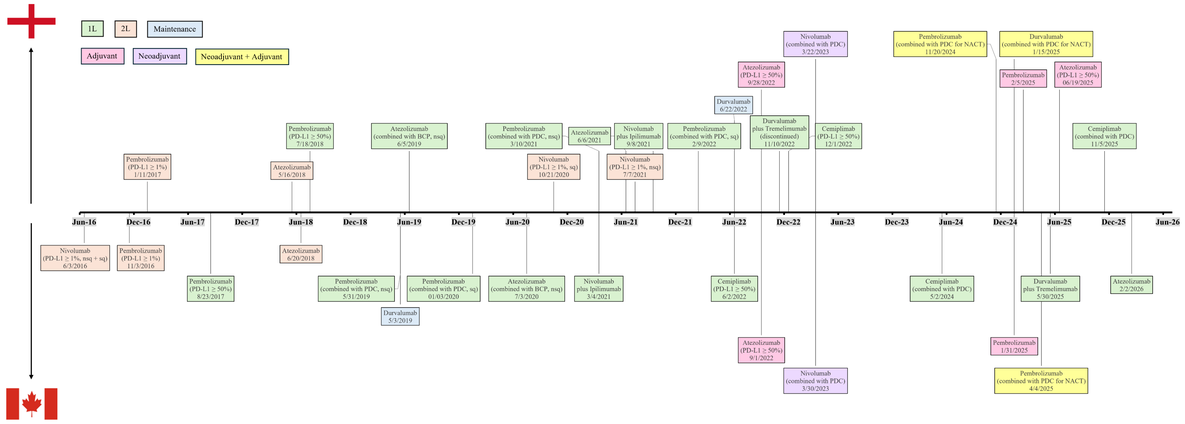
- We conducted a descriptive, comparative review of HTA appraisals for ICIs used in early- and advanced-stage NSCLC through February 2026 across two HTA bodies:
  - National Institute for Health and Care Excellence (NICE), England
  - Canada's Drug Agency, known as L'Agence des édicaments du Canada (CDA-AMC)
- All appraisals were anchored to the same pivotal randomized controlled trials where overlapping drug-indication pairs existed.
- Data extracted from each appraisal included characteristics of the referenced randomized clinical trials, the chosen comparators, cost-effectiveness conclusions, and details regarding modeling settings and assumptions, including but not limited to: modeling methods, time horizon, utility values, survival extrapolations, treatment duration, effect waning, and cure.
- Synthesized findings descriptively to identify:
  - Methodological convergence and divergence across agencies
  - Associations between modeling choices, cost-effectiveness results, and final recommendations

Figure 1 Evidence-to-Decision Pathway in NSCLC



Abbreviation: MEA = managed entry agreement; NMA = network meta-analysis; MAIC = matching-adjusted indirect comparison; RCT = randomized clinical trial; PFS = progression-free survival; DFS = disease-free survival; OS = overall survival; PD-L1 = programmed death ligand-1

Figure 2 Timeline of HTA appraisals for ICIs in NSCLC in NICE and CDA-AMC



Abbreviation: PDC = platinum-doublet chemotherapy; BCP = bevacizumab, carboplatin, paclitaxel; nsq = non-squamous; sq = squamous; NACT = neoadjuvant chemotherapy

RESULTS

- Across 35 appraisals, overall concordance in cost-effectiveness conclusions was 50%. NICE issued positive recommendations substantially more often than CDA-AMC (83% vs. 41%).
- Divergence accumulated across sequential methodological layers rather than arising from a single modeling choice **(Figure 1)**:
  - Rapidly evolving standards of care and strategic population definitions led to frequent misalignment between trial comparators and HTA-preferred benchmarks **(Figure 2)**.
  - NICE adopted more flexible, exploratory approaches using evidence from indirect treatment comparisons in survival extrapolations and scenario analyses, despite uncertainty due to sparse network and trial heterogeneity. In contrast, CDA-AMC applied stricter evidentiary thresholds, often emphasizing residual uncertainty.
  - NICE progressively evolved and formalized its handling of long-term ICI effects, moving toward explicit treatment effect waning (TEW) and flexible cure scenario analyses, whereas CDA-AMC applied more conservative, trial-anchored approaches that evolved more cautiously.
- NICE decisions frequently relied on confidential PAS and end-of-life modifiers, whereas CDA-AMC evaluated cost-effectiveness at list prices with fewer downstream flexibilities.

DISCUSSION

- HTA divergence for ICIs in NSCLC reflects cumulative methodological discretion rather than disagreement over clinical evidence, with differences emerging sequentially across population framing, comparative effectiveness methods, and most prominently – long-term survival modeling assumptions.
- NICE and CDA-AMC have both evolved their approaches to handling uncertainty, particularly regarding TEW and cure, but have done so along distinct institutional trajectories.
- Evidence harmonization alone is insufficient to prevent divergence in HTA outcomes without alignment on how uncertainty and long-term effects are modeled.

References

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