Investigator's choice comparator arms: A review of their use and appraisal in health technology assessment

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Background and objective

- RCTs using comparator arms in which treatment is determined by physician's choice or IC are increasingly common, particularly in indications where standard of care is heterogenous (1)
- Regulators in both the US and EU have voiced their support for IC trial designs in these situations, conditional on all treatments in the IC arm having regulatory approval (2)
- This study sought to review current practice in the utilisation and assessment of such trials in HTA

Methods

- NICE technology appraisals with a final draft guidance between 2022 and 2024 were searched for variations of the terms "investigator's choice" and "physician's choice". Appraisals were screened to determine whether RCTs with IC arms represented the pivotal trial
- For NICE appraisals identified, equivalent submissions assessed by the CADTH in Canada, G-BA in Germany, and HAS in France were identified via searches of relevant agency websites
- Information was extracted on whether treatments in the IC arms were considered representative of clinical practice and on analytic approaches used to estimate comparative efficacy/safety

Results

Of the 291 NICE assessments screened, 5 estimated comparative efficacy/safety based on data from RCTs with an IC arm. Equivalent assessments in other countries of interest were identified in all but one case (talazoparib for the treatment for HER2-negative breast cancer) in which there was no assessment identified in Canada

Disease areas

- All assessments evaluated technologies in oncology indications, including uveal melanoma, breast cancer, prostate cancer, and mesothelioma **(Table 1)**
- Technologies were used to treat patients with advanced disease or in either biomarker-defined or pre-treated populations

Table 1. Technologies and disease areas of identified submissions

Technology	IC arm comparators	Disease area
Tebentafusp	Dacarbazine OR ipilimumab OR pembrolizumab	Advanced (unresectable or metastatic) uveal melanoma
Talazoparib	Capecitabine OR eribulin OR gemcitabine OR vinorelbine	HER2-negative advanced breast cancer with germline BRCA mutations
Olaparib	Enzalutamide OR abiraterone	Previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer
Sacituzumab govitecan	Eribulin OR vinorelbine OR gemcitabine OR capecitabine	Unresectable triple-negative advanced breast cancer after 2 or more therapies
Nivolumab with ipilimumab (N+I)	Cisplatin plus pemetrexed OR carboplatin plus pemetrexed	Untreated unresectable malignant pleural mesothelioma

IC arm design

- For 3/5 technologies (talazoparib, sacituzumab govitecan, N+I), the IC arm involved a choice between chemotherapies only (**Table 1**). For the remaining technologies, the IC arm included a mix of chemotherapies and immunotherapies (tebentafusp), or hormonal therapies only (olaparib)
- For 4/5 technologies, IC of treatment was determined pre-randomisation, with the timing of choice between cisplatin or carboplatin unclear in the trial comparing N+I with IC

Representativeness of the IC arm to clinical practice

- In 13/19 (68%) assessments, HTA bodies stated that the IC arm did not capture all relevant comparators (**Table 2**). However, this was not considered an issue for most HTA agencies because the comparators were noted to have low prevalence of use, have off-label use only, or were relatively new to the market
- At least 1 HTA body stated that the IC arm included comparators with little relevance to clinical practice for 3/5 technologies, and that relevant comparators were excluded from the IC arm for 4/5 technologies
- There was limited discussion on representativeness of the percentage of patients receiving therapies deemed relevant in clinical practice, although concerns regarding overrepresentation of some therapies were raised in 2 assessments (NICE, N+I; CADTH, sacituzumab govitecan)

Table 2. Relevance of the IC arm comparators to clinical practice in each country

Technology	Excludes relevant comparators (Yes/No)	Includes irrelevant comparators (Yes/No)
Tebentafusp	**England**: Yes (N+I) **Canada**: Yes (N+I, nivolumab) **France, Germany**: No	**All countries**: No
Talazoparib	**England, Germany**: No **France**: Yes (carboplatin or cisplatin)	**France**: No **England, Germany**: Yes (gemcitabine)
Olaparib	**England**: Yes (cabazitaxel) **Canada:** Yes (docetaxel, cabazitaxel, radium-223) **France**: Yes (chemotherapy) **Germany:** No	**England, Canada**: Yes (all comparators) **France, Germany**: No
Sacituzumab govitecan	**All countries**: No	**England, Germany**: Yes (gemcitabine) **Canada, France**: No
Nivolumab with ipilimumab	**England**: No **Canada, France, Germany:** Yes (bevacizumab)	**All countries**: No

Methods used to estimate comparative effectiveness/safety

- In some cases, comparative effects were estimated through unadjusted analysis of the RCT data, despite concerns over a lack of representativeness
- Where ***irrelevant comparators were included in the IC arm***:
  - German assessments requested post hoc analysis excluding irrelevant comparators (talazoparib, sacituzumab govitecan)
  - In NICE assessments of talazoparib and tebentefusp, the manufacturer chose to proactively present this post hoc analysis
  - In other cases, a similar post hoc analysis was not requested, and it was assumed the irrelevant comparators had no impact on efficacy
- Where ***IC arms excluded relevant comparators***:
  - NICE and CADTH assessments of talazoparib and tebentafusp, and CADTH and assessments of N+I included ITCs to estimate comparative effects
  - Unanchored ITCs were used to compare tebentafusp with N+I in the NICE assessment, because of the lack of a common comparator arm
  - Anchored ITCs were conducted in other cases
    - NMAs were conducted for the CADTH and HAS assessments of N+I, with the whole IC arm used to connect N+I to the network
    - For olaparib, Bucher comparisons were submitted for CADTH and NICE assessment, although differences in the absence of exactly matching control arms required an assumption of equivalent efficacy across these control arms
    - No ITC was submitted for G-BA assessment
- Where ***the comparator mix was considered unrepresentative***:
  - Sensitivity analysis was conducted for the NICE assessment of N+I, which re-weighted the trial to reflect an alternative comparator mix
  - In other cases, equivalent efficacy across treatments in the IC arm was assumed

Conclusions

- HTA bodies regularly raise concerns that IC arms do not fully reflect clinical practice but appear to be generally accepting of evidence derived from trials in such cases
- Where feasible, analyses excluding comparators deemed irrelevant should be planned, particularly in Germany, and ITCs conducted where there is a concern that relevant comparators are excluded
- IC trials should be designed so physician's choice is determined pre-randomisation because it enables comparators to be excluded without breaking randomisation and enables individual treatments in the IC arm (in addition to the pooled IC arm) to be used as anchors for ITCs

Abbreviations: BRCA, breast cancer gene; CADTH, Canadian Agency for Drugs and Technologies in Health; EU, European Union; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HER2, human epidermal growth factor receptor 2; HTA, health technology assessment; IC, investigator's choice; ITC, indirect treatment comparison; N+I, nivolumab + ipilimumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RCT, randomised controlled trial; US, United States

References

1. Olivier T, et al. Reporting of Physicians' or Investigators' Choice of Treatment in Oncology Randomized Clinical Trials. JAMA Netw Open. 2022;5(1):e2144770; 2. Mckendrick J, et al. SA22 Does the Use of Investigator-Choice Comparator Arms in Oncology Clinical Trials Influence Payer Assessments Outcomes? Value Health. 2024;27(6):S399-400

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