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Does the use of investigator-choice comparator arms in oncology clinical trials influence payer assessment outcomes?

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Introduction and objectives

Investigator-choice comparator (ICC) clinical trials refers to studies in which the treating physician or investigator has the discretion to choose the specific comparator treatment for each patient, often from a set of given options. This approach is supported by regulators in both the US and the EU if a single reference treatment cannot be identified and all ICC options have regulatory approval.

The National Institute for Health and Care Excellence (NICE) assesses evidence and decides about the appropriateness and relevance of comparators, considering factors such as established NHS practice and existing NICE guidance. However, there is little specific guidance on how to deal with establishing clinical and cost-effectiveness when an ICC arm is included in the trial.

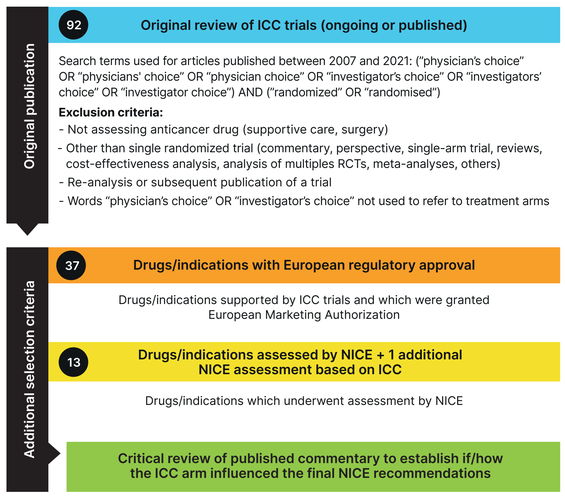
The objective of this work was to establish whether the use of an ICC influenced recommendations by NICE.

Methods

A published literature review of studies conducted between 2007 and 2021 identified 92 oncology randomized trials with an ICC arm.[1] Identified articles reported trials of anticancer interventions that included the phrases "physician's choice" or "investigator's choice" within the title or the abstract.

This study was selected as the basis of the research as it provided a comprehensive recent list of published and ongoing relevant clinical trials. Drug/indications with European regulatory approval and a subsequent NICE assessment were identified (Figure 1).

Figure 1: Methodology for the selection of clinical trials for review

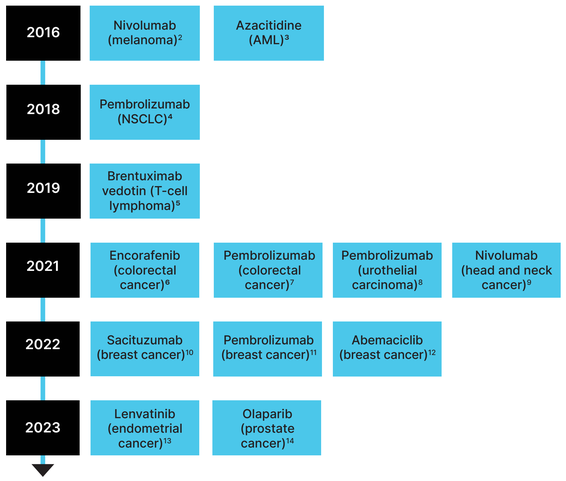


Results

Of the 92 trials identified, 12 were the basis of a European regulatory approval for the given drug/indication that was then assessed by NICE between 2016 and 2023. An additional trial was identified that did not meet the search criteria but which did have an ICC arm (described as a "conventional care arm"), and that drug/indication was added to the analysis.

- Four of the NICE assessments were re-assessments for that drug/indication where additional data may have been considered.
- In 8 assessments, the ICC focused on a choice of chemotherapy (or standard systemic therapy), most commonly stating 2-3 choices of therapy.

Figure 2: Oncology drugs assessed by NICE



Of the trials for the 13 drug/indications, the majority (10, 77%) of the treatment comparisons were based on a trial with a comparison of a single intervention with an ICC arm. Three drug/indications had trials with more complex study designs:[6,11,12]

- Encorafenib (colorectal cancer):[6] cetuximab element was common across all 3 treatment arms
- Pembrolizumab (breast cancer):[11] the ICC element was common to both intervention and comparator arms
- Abemaciclib (breast cancer):[12] the ICC element was common to both intervention and comparator arms

Overall, 12 drug/indications had a trial design where the patients were randomized to the intervention or comparator arms and then the choice of ICC was made; however, in one case,[3] the ICC element was selected prior to patients being randomized to either the pre-selected ICC or the intervention.

Table 1: ICC details and NICE HTA outcomes

Drug Indication	ICC details	NICE HTA outcome
Nivolumab (melanoma)[2]	Dacarbazine or paclitaxel combined with carboplatin	Recommended in full
Azacitidine (AML)[3]	Intensive (anthracycline + cytarabine) chemotherapy or low-dose cytarabine chemotherapy or BSC	Not recommended
Pembrolizumab (NSCLC) (re-assessment)[4]	Platinum-based chemotherapy: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel	Recommended with restrictions
Brentuximab vedotin (Tcell lymphoma)[5]	Oral methotrexate or oral bexarotene	Recommended with restrictions
Encorafenib (colorectal cancer)[6]	Cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil, and irinotecan)	Recommended in full
Pembrolizumab (colorectal cancer)[7]	Intravenous mFOLFOX6 or intravenous FOLFIRI or intravenous weekly cetuximab	Recommended with restrictions
Pembrolizumab (urothelial cancer) (re-assessment)[8]	Chemotherapy: paclitaxel, docetaxel, or vinflunine	Not recommended
Nivolumab (head and neck cancer) (re-assessment)[9]	Single-agent systemic therapy (methotrexate, docetaxel, or cetuximab)	Recommended with restrictions
Sacituzumab (breast cancer)[10]	(Eribulin), vinorelbine, capecitabine, or gemcitabine	Recommended in full
Pembrolizumab (breast cancer)[11]	Chemotherapy: nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine-carboplatin	Recommended with restrictions
Abemaciclib (breast cancer)[12]	Standard-of-care endocrine therapy of physician's choice	Recommended in full
Lenvatinib (endometrial cancer)[13]	Chemotherapy: doxorubicin or paclitaxel	Recommended in full
Olaparib (prostate cancer) (re-assessment)[14]	Enzalutamide or abiraterone	Recommended in full

"Not recommended" (n=2)

- Azacitidine (AML):[3] ICC components were not the major driver of the NICE outcome; analyses vs each individual ICC component were presented and discussed.
- Pembrolizumab (urothelial carcinoma):[8] concern about lack of comparison with BSC as an element of usual care—this appeared to partly influence the NICE outcome.

"Recommended with restrictions" (n=5)

- In all cases, NICE questioned whether the ICC choices available to or made by investigators as part of the ICC arm would align with UK clinical practice.[4,5,7,9,11]
- In one case[7] this was of real concern, given the omission of some clinically relevant comparators from the ICC arm.

"Recommended in full" (n=6)

- In only two cases, NICE criticized that the ICC arm did not reflect clinical practice and noted that this appeared to be a significant issue.[6,14]

In four assessments, the ICC arm was of significant concern to NICE (Table 2).

Table 2: NICE comment/criticism of ICC

Encorafenib (colorectal cancer)[6]	• The ICC arm included two specific combinations not used in the NHS, and therefore was not reflective of UK clinical practice (according to clinical experts). • NICE concluded that the ICC components were not clinically equivalent, raising concern about conclusions drawn with a "blended" comparator. • Lack of direct comparative studies with two specific NHS-relevant treatments were noted. • However, treatment was recommended without any restrictions.
Pembrolizumab (colorectal cancer)[7]	• ICC components were not considered to reflect NHS clinical practice. • High use of one ICC element (70% patients) was expected to influence estimation of overall clinical benefit (given potential differential efficacy between ICC components). • Lack of comparative data vs each element of ICC was noted; pooled ICC arm data were considered appropriate to use to determine clinical efficacy. • Treatment was recommended with restrictions.
Pembrolizumab (urothelial cancer)[8] (re-assessment)	• The ICC arm in the original trial did not include BSC, which was considered a relevant comparator for UK clinical practice. • Subgroup analyses of trial data excluded the element of ICC, which was not used in UK clinical practice (recognizing risk of bias and also lack of power for this comparison). • Main drivers of the decision were factors not sufficiently addressed by data collected through the drug's inclusion in the Cancer Drugs Fund.
Olaparib (prostate cancer)[14]	• The ICC arm led to some patients in the trial population receiving treatment that was inconsistent with UK clinical practice (ie, prior use of both ICC components). • Supported by clinical experts, it was concluded that treatment was effective vs ICC despite this not reflecting UK clinical practice. • Treatment was recommended in full.

Overall, no pattern directly highlighted a specific relationship between the use of an ICC arm and the outcome of the NICE assessment.

Conclusions

ICC arms in clinical trials are becoming more common and can provide flexibility in the comparator arm by allowing clinicians to choose the best treatment for each patient based on their specific need and condition, which may be considered to best reflect real-world clinical practice.

NICE has recommended unrestricted or restricted access for several treatments with pivotal trials that included ICC arms, despite raising concerns about the generalizability and representativeness of the choices. Analyses of the NICE decisions do not support a direct link between the use of an ICC and NICE outcomes. The review of HTAs has also highlighted some key challenges to this study design, most commonly around whether the choice of specific ICC components was appropriate, which can provide insight for manufacturers when designing their trials.

As more data become available, the influence of ICC on assessment outcomes should be further explored in the UK and other markets.

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. TA384 (Feb 2016); 3. TA399 (Jul 2016) 4. TA531 (Jul 2018); 5. TA577 (Apr 2019; 6. TA668 (Jan 2021); 7. TA709 (Jun 2021); 8. TA692 (Apr 2021); 9. TA736 (Oct 2021); 10. TA819 (Aug 2022); 11. TA801 (Jun 2022); 12. TA810 (Jul 2022); 13. TA904 (Jun 2023); 14. TA887 (May 2023)

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