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nvmo

Using Non-Randomized Trials to Assess the Clinical Value of Systemic Anti-Cancer Treatments: Viable or not?

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BACKGROUND

Non-randomised trials (NRTs) have become increasingly relevant for the appraisal of new systemic anti-cancer treatments (SACTs) in rare indications. However, randomised controlled trials (RCT) still remain the gold standard for assessing their efficacy and safety, not least due to many SACTs failing in the RCT phase after promising NRT results.

After market authorisation, clinical benefit of a new SACT is assessed to facilitate healthcare decision-making. In the Netherlands, the Committee for Evaluating Oncological Drugs (CieBOM) provides recommendations on the suitability of SACTs for use in clinical practice. To this end, the so-called PASKWIL criteria are applied.

In 2021, CieBOM developed PASKWIL criteria suitable for NRTs ("NRT-PASKWIL criteria"). Objective response rate (ORR) and duration of reponse (DoR) are considered for assessment. Applicable ORR and DoR thresholds must both be met for a positive recommendation:

- ORR >40% (lower confidence interval [CI] bound) and DoR >4mo *or*
- ORR >30% (lower CI bound) and DoR >8mo *or*
- ORR >20% (lower CI bound) and DoR >12mo

However, NRT results are less robust than RCT results. Hence, it is questionable whether evidence from an NRT is sufficient for conclusive assessments of an SACT's clinical value.

AIM

Through applying the NRT-PASKWIL criteria, we investigated whether and how NRT results can be used to assess the clinical value of new SACTs, and whether the assessment outcomes differ from each other.

METHODS

1. Match

We selected recommendations by CieBOM on new EMA-approved SACTs issued from January 2015 to December 2017. The underlying trials were phase III RCTs. Reassessments, adjuvant therapies, or recommendations based on phase II RCTs were excluded.

We searched for potential matching NRTs by conducting a narrative review.
Matching requirements:

- NRT tested same treatment for same indication and same treatment line
- NRT preceded respective RCT regarding enrolment period
- NRT results reported min. one outcome of interest (ORR with CI, DoR, PFS)
- Publication of NRT results before RCT results

2. Apply

We applied the NRT-PASKWIL criteria to the results of the matching NRTs.

Additional scenarios to determine how clinical value assessments would change upon application included:

- different ORR/DoR thresholds:
  lower CI ORR >40%/>30%/>20% *or* DoR >4mo/>8mo/>12mo;
  median ORR ≥60%);
- addition of progression-free survival (PFS) threshold (median >6mo).
  PFS was considered if reported ORR/DoR data was insufficient for an assessment and – in an alternative scenario – if PFS was a primary endpoint.

3. Compare

Finally, we compared the NRT-based assessment outcomes to the respective CieBOM recommendations.

RESULTS

Matching

44
CieBOM recommendations issued between Jan 2015 and Dec 2017 (RCT-based)

37 (84%)
eligible recommendations

13 (35%)
matching NRTs found

Application

Assessments based on NRT-PASKWIL criteria:

2 (15%) positive | **6 (46%)** negative | **5 (38%)** not assessable

Changing ORR / DoR thresholds…
… led to more positive assessments compared to the base case, but no considerable changes for non-assessable studies

Removing DoR, applying ORR ≥60% threshold…
… allowed assessment of all NRT results; but 4 out of 5 non-assessable results received negative assessment

Applying PFS threshold if ORR/DoR reporting was insufficient…
… considerably reduced the number of non-assessable NRT results
… facilitated two / three preliminarily positive and one preliminary negative assessment

Comparison

RCT-based vs. NRT-based assessments

⊕ **10** vs **2**
⊖ **2** vs **6**
? **1** vs **5**

Assessments matched

⊕ **2**
⊖ **1**
? **1**

Assessments contrasted

RCT ⊕ / NRT ⊖ **4**
RCT ⊕ / NRT ? **4**
RCT ⊖ / NRT ? **1**

Legend:
⊕ Assessment positive | ⊖ Assessment negative | ? Treatment not assessable

Take-Home Messages

The possibility to assess the clinical value of NRT-tested SACTs depends on consistent and conclusive reporting of the results relevant to the assessment criteria.

Limited available publications and inconsistent data reporting hamper the viability of NRTs as an alternative to RCTs to assess the clinical value of an SACT.

NRT-based assessments should be seen as only preliminary due to uncertainty of the results, and thus be considered with caution.

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