Single-arm trials improve early access to rare cancer drugs

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Although randomised clinical trials (RCTs) remain the gold standard for evaluating the benefit/risk of cancer drugs, single-arm trials (SATs) can provide invaluable opportunities to speed up cancer drug development and approval, in particular for drugs with dramatic activity and strong biological rationale in small populations with high unmet need, Dr. Jorge Martinalbo, Scientific Officer at the European Medicines Agency (EMA) reported at the ESMO 2016 Congress today.

"Drug approval requires demonstration of a positive benefit/risk ratio, usually based on evidence from randomised clinical trials (RCTs). Nevertheless, in certain instances such as very rare cancers or molecular subgroups, or when preliminary evidence shows dramatic efficacy in settings of high unmet medical need, RCTs may not be strictly required for regulatory approval," he said.

There is limited regulatory guidance about the circumstances under which SATs can provide sufficent evidence for EU authorisation. The EMA and ESMO have recently started a collaboration to define evidence requirements that can satisfy market access decision-makers, patients and clinicians, and facilitate access to innovative cancer drugs.

As part of this effort, Dr Martinalbo analysed the role of SATs in 263 applications for initial approval or indication extension for cancer drugs reviewed by EMA between 1995-2014. Martinalbo explained that: "around 20% of cancer drug approvals in the EU in the last 20 years were based on evidence from SATs, and more than half of the initial

authorisations for haematological malignancies. Almost one-third of targeted drugs used in biomarker-restricted populations were approved on the basis of response rate. Perhaps surprisingly, regulatory review times and success rates for initial approvals based on SATs are similar to those based on RCTs. Altogether this reflects the flexibility of regulatory requirements for approval, supported by early access tools like conditional and exceptional circumstances authorisations used in almost half of the initial approvals based on SATs."

There are, however, further decisions at national and regional level before patients can have access to new cancer drugs, that take into account economic criteria2. "The increased uncertainty inherent to evidence from uncontrolled trials can pose challenges to subsequent health technology assessment (HTA) and price and reimbursement decisions at a national level, potentially compromising effective access to patients," Martinalbo explained.

This was one of the key topics in a recent workshop3 jointly organised by the EMA and ESMO, where a wide range of stakeholders including clinical scientists and drug developers in academia and pharmaceutical industry, regulators, patient representatives and HTA bodies discussed the evidence requirements and particular challenges for cancer drug approval and reimbursement decisions based on SATs.

"The workshop allowed us to realise the diversity of views and the challenges in developing an evidence framework that could satisfy all stakeholders. We identified certain methodological areas such as innovative endpoints, external controls and basket trials which provide opportunities to improve evidence generation, and together with ESMO we are currently establishing core groups to further elaborate on them. We understand that approval decisions affect everyday clinical practice, and the workshop clearly showed us the immense opportunities offered by a close collaboration with ESMO," concluded Martinalbo.

Commenting on the abstract, Dr Denis Lacombe, EORTC Director General who has a vast experience in clinical research, said: "The retrospective study performed by European regulators analysing the role played by SATs between 1994 and 2015 brings light to the actual regulatory impact of SATs in Europe. It certainly illustrates the evolution of regulatory sciences as new designs and new end-points challenge the methodology of clinical research, now based on well documented knowledge on both mechanisms of action of new drugs and biology of diseases. However, robustness of databases on which new treatments are made available to cancer patients should not be compromised."

Dr Lacombe explained that: "Randomised clinical trials and SATs can't be considered alternatives to each other. SATs bring less robust data to patients, with ethical and societal implications, further impacting HTA and reimbursement decisions. In absence of benchmarking traditionally provided by RCT, the decision process remains uncertain. In addition, there is no justifiable reason why certain groups of patients would be treated based on less robust data."

Dr Lacombe concluded: "Clinical researchers must develop new solutions that span from proof of concept to effectiveness, constantly taking the challenges to bring solid evidence to patients and not too easily compromising towards easier routes such as SATs which should be limited to situations where strong biological evidence emerges in absence of relevant existing therapeutic strategies and/or unmet needs. Discussing SATs outside of a complete transformation of clinical research may jeopardise appropriate recognition of SATs where they may be useful and is certainly a disservice to patients."

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