DO THE GUIDELINES IN ONCOLOGY NEED TO EVOLVE?

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Therapeutic guidelines in oncology, such as those from the National Comprehensive Cancer Network (NCCN) or the European Society for Medical Oncology and the European Cancer Organisation (ESMO/ECCO), are designed as tools intended to help oncologists to manage their patients according to the best available clinical data. In the metastatic setting, these guidelines are based upon individual clinical trials and/or meta-analyses, as well as upon the opinion of key experts. Nevertheless, these important tools are often not fully applicable in clinical practice because they suffer from many drawbacks. These drawbacks are not only related to the design of the clinical trials supporting these guidelines, but also to patients' characteristics and the studies' eligibility criteria, the evolution of tumour biology over time, and finally the mechanism of action of the therapeutic interventions. These issues will be detailed in the sections following.

Most of the available clinical trials in metastatic research involve first and second-line therapies but rarely much more. Consequently, beyond these therapeutic lines, the available guidelines are either not available, or based on scanty data or expert opinions. Moreover, most clinical trials have included a highly selected homogeneous population of patients with good performance status, who are compliant, have volunteered, and are able to understand the principles of clinical trials necessary to give a proper consent. Overall, these patients' profiles are not representative of the whole population of patients seen routinely in clinical practice. This means that the translation of published data to daily clinical practice can be potentially misleading. The patients who are seen in clinical practice are extremely different on various levels from those seen in clinical research, starting from age and performance status, and ending at the level of tumour extension and biology. Consequently, the tumour response, patient outcome, and treatment tolerability observed in reality may be very different and less positive from the results obtained from clinical trials. Additionally, in clinical research as well as in clinical practice, nothing is static but rather globally, every parameter, patient or disease-related, may quickly change and therefore guidelines agreed to at one time should be updated regularly.

Guidelines, as previously mentioned, are often based on Phase III clinical trials, but the landscape and methodology of clinical trials are changing rapidly. For example, the frontier between Phase I, II, and III has become less stringent. The drugs and therapeutic approaches to development are very variable ranging from cytotoxics, to the new formulations of cytotoxics (like antibody drug conjugates), to molecular-targeted agents, and finally to new immunotherapeutics. The clinical research for each of these categories might be different and the result obtained (ranging from outstanding to borderline clinical significance) will have different interpretations and powers and thus influence the strengths or limitations of the guidelines. Therefore, the guidelines should evolve in parallel to reflect this move in clinical research methodology and on the mechanisms of action of available therapies.

In conclusion, the guidelines currently cover a selection of patients who are largely unrelated to what is seen in clinical practice and do not take into account the evolution of tumour biology, the therapeutic classes under experimentation, and the need to adapt to rapidly evolving clinical research methodology. Future guidelines should not only include the lines of therapy but also important patient characteristics, tumour biology subtyping, the availability of biomarkers if any, and the presence or absence of companion diagnostics etc., with the ultimate aim of adequately taking into account real clinical practice.