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EDITORIAL

Approval of new drugs in oncology – a changing pattern

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Patients with advanced malignancies have high-unmet medical needs, which bring requests for early availability of new innovative treatments. Calls for expedited trial formats and rapid regulatory assessment his challenges the established drug development and evaluation process based on randomized, comparative trials with an increasing number of innovative, biomarker-driven, and non-randomized designs.

In this issue of Acta Oncologica, Hatogai et al. reviewed Japanese approvals of new drugs in oncology during 2006–2019 and report an increasing number of approvals based on single-arm clinical trials [1]. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) acts as the regulatory agency. The authors reviewed PMDA reports for 202 eligible oncology drugs of which 43 (21%) were based on single-arm clinical trials. Interestingly, the proportion of approvals based on single-arm studies increased over time with mean 4.3 annual approvals in recent years. For comparison, Davis et al. did in a retrospective cohort study on cancer drugs approved by the EMA during 2009–2013 identify 48 drugs for 68 indication with 8 (12%) approved based on single-arm studies [2].

Hatogai et al. demonstrate that single-arm studies are over-represented in hematology and orphan drug settings [1]. This is also supported by Tenhunen et al. who reviewed EMA approvals 2010–2019 and herein identified 22 single-arm trials of which half had an orphan indication [3]. Further, single-arm studies more often have biomarker-driven indications and use response-related outcomes [1,3]. Though the single-arm studies apply shared methodologies, fixed endpoints are often lacking, which is motivated in studies with a limited number of highly selected patients where a water-fall plot supplemented with data on duration of benefit may be preferable. Further, new efficacy measures such as molecular profiles determined based on liquid biopsies are likely to be developed.

The increasing biomarker-driven approvals reflect a changing oncology treatment landscape where biologically stratified subgroups define and individualize treatment strategies. The 'biomarker-related' terminology used by Hatogai et al. does in my opinion define the area more correctly than the more commonly used denomer 'precision medicine'. These developments are also reflected in a high number of ongoing basket trials and umbrella trials. Whereas the basket trials test a targeted intervention for various histopathological diagnoses with a shared biological marker, the umbrella trials evaluate multiple targeted interventions in various subgroups of a single disease. The agility and flexibility of modern trial design hold promise for definition of new diagnostic subgroups and therapeutic possibilities also in rare molecular or diagnostic subgroups with high-unmet clinical needs.

Among the new drug indications reported by Hatogai et al., solid tumors with the rare NTRK gene fusions may be the most spectacular [1]. In infantile fibrosarcomas and rare subset of other solid tumors, larotrectinib, and entrectinib prove highly active to the point that comparative studies are not judged necessary for clinical implementation. Other approvals, e.g., immune check point inhibitors for tumors with defective mismatch repair may, however, need further comparative studies to define responsive tumor subsets.

The future of drug development in oncology is exciting and provides new hope for effective treatment in rare subgroups and challenges clinical management through increasing complexity. As a 'close to retired' clinician reflecting on the changing current practices, I am envious of all my younger colleagues. They will, in addition to chemotherapy, radiotherapy, endocrine treatment, and immunotherapies contribute to the further development of biomarker-driven oncology and harvest the fruits of the increasing insights in the molecular basis of cancer to the benefit of our patients. With non-randomized and innovative trial designs and rapid evaluation and clinical use also comes responsibilites for consideration of modern trial design, definition of relevant endpoints, development of regulatory guidance, and follow-up of real-world effects.

Disclosure statement

No potential conflict of interest was by reported the author.

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