PERSPETIVAS

THE "QUANTUM LEAP" CALLED PRECISION ONCOLOGY

UM "SALTO EM FRENTE" CHAMADO ONCOLOGIA PRECISÃO

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Cancer is among the most common cause of death worldwide.[1] Until last decades, the only treatment option available for advanced stages cancer patients was represented by radio-chemotherapy regimens. However, radio-chemotherapy treatments do not act exclusively on cancer cells, but on all cells that actively replicate. This phenomenon leads to severe collateral effects that significant affected patients' quality of life. In this setting, it has been highlighted the necessity for more specific therapies, able to improve patients' clinical outcome with a concomitant significant reduction of adverse events.[2] In this setting, the advent of precision medicine has dramatically changed the way advanced stages cancer patients are managed. A number of different targeted therapies, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (MoAbs), have been developed in the last years and represent an important arrow in the quiver of oncologists. In fact, respect to traditional radio-chemotherapy regimens, these latter feature the significant advantages to improve clinical outcomes while maintaining a high tolerability and manageability. In this setting, precision medicine is able to ensure the best treatment choice while do not harm at the same time. The hope of precision medicine is that in the near future any cancer patient will be treated with a specific drug tailored on the specific genetic change.[3] As an example, in advanced stages non-small cell lung cancer it has been demonstrated the positive predictive role of specific gene alterations, such as Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*) exon 2 p.G12C or V-Raf Murine Sarcoma Viral Oncogene Homolog B (*BRAF*) exon 15 p.V600E, for the administration of specific TKIs.[4-7] However, it should be borne in mind that when considering to adopt these novel drugs, it is fundamental to assess the molecular status of the clinical relevant genomic alterations.[8] In fact, the absence of the specific target is associated not only with an absent of clinical efficacy of targeted therapies, but also with a worsening of clinical conditions, the so-called "detrimental effect". The number of genetic alterations that should be tested in order to administer targeted treatments is rapidly increasing. However, several limitations may affect the correct analysis of the different clinical relevant biomarkers. First of all, advanced

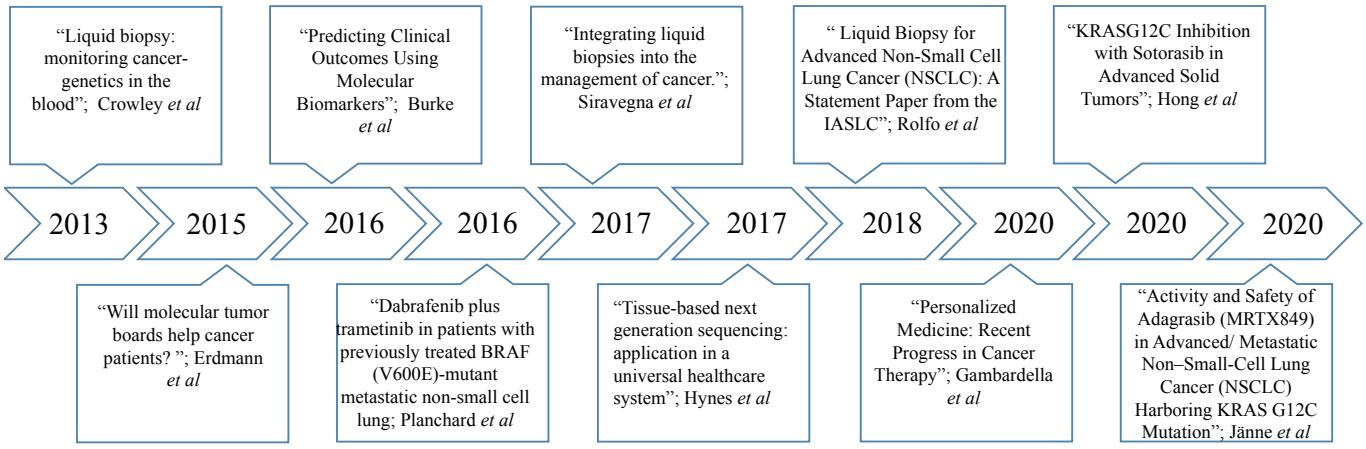

Fig 1. **A representative diagramm with some milestones papers focused on the precision oncology from 2013 to 2020.**

stages cancer patients do not always feature tissue samples availability for molecular purposes. In fact, in a not negligible percentage of advanced stages cancer patients, due to poor general conditions, it is not possible to perform wide histological resections. In this setting, small tissue samples (biopsies or cytological specimens) represent the only available starting material for morph-molecular purposes in a high number of advanced stages cancer patients.[9] In order to optimize the low input of nucleic acids, novel methodologies should be implemented in molecular predictive pathology laboratories. In particular, next generation sequencing (NGS) technology allows the analysis of different biomarkers for different patients, simultaneously.[10] In addition, in some circumstances, neither biopsies nor cytological specimens are available or features an inadequate results for molecular analysis. In this, and not only, setting, liquid biopsy represent a really powerful solution to overcome this limitation and to avoid to leave any patient behind.[11] From a clinical point of view, the term liquid biopsy represents a peripheral blood sample withdrawal. In this samples, circulating tumor DNA (ctDNA) is the most extensively studied. However, several other analytes may be of clinical interest, such as circulating tumor cells, ctRNA, tumor educated platelets, exosomes, etc.[12-13] In addition, besides blood samples, the term liquid biopsy includes other body fluids (such as saliva, urine, celebrospinal fluid, effusions, etc.) and supernatant, usually discarded after the preparation of cytological samples.[14-15]

In this fascinating scenario, it is fundamental a strict communication among the different healthcare figures to ensure the best management for advance stages cancer patients. For this reason, each institution should encourage the development of molecular tumor boards (MTBs). These latter are multidisciplinary group that include a wide range of medical professional figures (in particular, molecular pathologists, clinicians, surgeons, radiologists, genetists, bioinformaticians, biologists) implicated in the management of cancer patients. The discussion within the MTBs has the role to overcome the limited training in molecular biology of clinicians and the limited clinical knowledge of molecular pathologists.[16-17] The last but not least issue related to precision medicine and biomarker testing is related to costs and reimbursements. In particular, a well-resourced, reimbursement-based systems or the universal healthcare (UHC) organization systems may be employed. In the first case, insurances coverage can ensure the refund of broad tumor sequencing. In this setting

NGS is fully adopted as a "one-stop-shop" for the different clinical relevant biomarkers. In a UHC organization, instead, there are limitations of resources. For this reason, careful attention should be paid to ensure at least the molecular data that can represent the standard-of-care management of cancer patients.[18-19]

On the overall, the introduction of precision oncology and predictive molecular pathology in routine practice, starting from tissue or liquid biopsy based analysis, represents the most relevant "breaking in the wall" of the 20th century, leading to a real "quantum leap" in the diagnosis and treatment of cancer patients.

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