CCBIO Opinion

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Challenges in contemporary precision medicine

According to the NIH, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (NIH Precision Medicine Initiative). Targeted cancer therapy has been the poster child for precision medicine. In this regard, the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) clinical trial, the largest precision oncology trial to date with over 6000 patients enrolled, is a milestone[1]. NCI-MATCH demonstrated the utility of next-generation sequencing in clinical practice, showing that 38% of cancer patients have currently "actionable" mutations. However, the results of the trial also highlight the challenges: only a minority of patients experienced clinical benefit, and many tumors were resistant to targeted inhibition. Hence, there remains a need to understand how tumors acquire therapy resistance. This will likely involve novel combination treatments; indeed, a follow-up clinical study, NCI-ComboMATCH, will test drug combinations to increase responses.

An interesting observation from the NIH-MATCH trial was that in comparison with TCGA data, standard cancer treatments did not lead to a substantial increase in gene mutations, emphasizing the role of non-genetic mechanisms of acquired resistance. However, tumor clonal selection of cognate mutations that render targeted therapies ineffective (e.g. EGFR T790M) were highlighted by the investigators. Other likely mechanisms of resistance include modulation of molecular pathways within the cancer cells, including pathway reactivation, bypass and indifference[2].

Given the astonishing genetic and non-genetic heterogeneity of cancers, how do we move forward? Ideally, identification of genetic and non-genetic drivers of acquired therapeutic resistance will enable the development of novel combination treatment strategies that prevent the evolution of drug resistance. This is facilitated by advances in single-cell technologies such as single-cell RNA sequencing and imaging mass cytometry (IMC) that allow deep phenotypic characterization of tumors. The growing use of these techniques to analyze longitudinal on-treatment biopsy samples in concert with ever more sophisticated computational analysis is creating a new level in our understanding of the dynamic tumor immune microenvironment. A major challenge will be to develop robust next-generation predictive companion biomarkers incorporating this information for clinical application. It should be noted that a comprehensive epidemiological study of adverse effects associated with additional on-treatment biopsies is lacking, highlighting the necessity for innovative patient-derived organoid technologies to supplement longitudinal biopsy sampling[3-4].

In January 2021, the Norwegian Ministry of Health and Care Services provided a national action plan for clinical trials 2021-2025[5]. The main goals are that the number of clinical trials should double and that 5% of patients in the specialist health service are enrolled in clinical trials by 2025. This includes a focus to equip Norway for personalized medicine. Thus, IMPRESS-Norway is a nation-wide cancer study initiated in 2021 as a public-private partnership where industry partners provide medications approved by the Norwegian Medicines Agency for use outside standard indications. The aim is to allocate patients to approved medications based on the molecular profiles of their cancers. This includes establishment of a national genome-center with expertise in medicine, genetics, pathology, bioinformatics and ICT security, integrating therapy guidance through a virtual molecular tumor board[6]. This integration of diverse disciplines has been a major obstacle, and thus represents an important step towards the realization of precision medicine in Norway.

The IMPRESS-Norway study, based on the Dutch DRUP-initiative[7], seeks to harmonize with similar studies in the Nordic countries. These large projects build on the principles and lessons from NCI-MATCH and similar trials; IMPRESS-Norway includes a strategy to build a scientific rationale for novel phase II-III trials with a focus on rare cancers where alternative paths to conditional market approval are needed.

Potentially, this initiative can serve as a platform for future biomarker-based clinical trials. It is possible that the optimal clinical benefit is achieved when molecular diagnostic guided therapy is introduced first-line, and not in relapsed or refractory cancers as in the current version of IMPRESS-Norway.

We are optimistic that these initiatives and technological advances will encourage both creative approaches and rigorous testing necessary to guide clinical practice. However, in

most cases, the improved clinical benefit will be incremental but still of significant importance for the patient. Through integrated efforts from multiple disciplines, the concept of precision oncology can continue to expand. ••

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