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Precision oncology for upper GI cancers – Where are we heading?

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Upper Gastrointestinal cancer, including esophageal and gastric cancers, have an increasing tumor incidence and mortality rate worldwide. Despite significant improvements in radiotherapy, chemotherapy, and targeted therapy over the last decade, upper GI cancers are still characterized by high recurrence rates and a dismal prognosis. Thus, there is an urgent need for new diagnostic and therapeutic approaches. Recent technological advances and the accumulation of molecular and clinical data are moving toward the use of precision medicine in this field now. Precision medicine is a concept that aims to include the patient's living environment along with the patient's clinical data (as well as molecular imaging techniques and bioinformatics technology) into account to optimize diagnostic and therapeutic approaches. Although, prospective use of comprehensive genomic profiling has been increasingly used to identify actionable target in oncology, so far NGS analysis led to only modest results, as actionable alteration, found in approximately 40% of patients only lead to matched therapy in only 20% of patients with only about 10% of these having an objective response [1].

In the current issue Cassier et al. [2] report on the outcome of molecular screening for actionable alterations in patients with advanced gastroesophageal cancers who were prospectively enrolled in the French *ProfiLER 01* program [3]. They correctly conclude that molecular screening needs to be implemented early during disease management requiring better and more focused tumor sampling to allow distinct histopathological diagnosis and broad molecular analyses which they argue should be implemented at the earliest possible time point to allow the use of molecularly guided therapy up-front, including in the preoperative setting. Furthermore, they recognize that access to matched therapy currently remains the greatest bottleneck, although the number of approved targeted agents is constantly increasing.

Standard of care is in terms of diagnostic testing in upper GI-cancers is screening for HER2, EBV, MSI, and PDL-1/CPS score. The observation that dMMR /MSI cancers respond exceptionally well to immunotherapy, led to the histology-agnostic approval of Pembrolizumab in these cancers. Bases on further analyses of the Keynote-158 trial and the observation that an increased tumor mutational burden (TMB^{high}) can predict response to immunotherapy beyond dMMR/MSI cancers led to the label extension of Pembrolizumab in TMB^{high} cancers. This highlights the clinical significance of identifying hypermutated tumors for immunotherapy treatment in addition to the reported distinct genetic alterations in the work by Cassier et al.

Indeed, precision oncology including broad sequencing analysis will define modern therapy strategies in upper GI-cancers. Nevertheless, firstly it will be as important to understand the basic biology of these cancers. Multiple trails on upper GI cancers, including the current analysis, inadequately combine squamous cancer and adenocarcinoma in the same analysis or response evaluation. In 2017, molecular data from The Cancer Genome Atlas Research Network showed that histological subtypes of human esophageal adenocarcinoma (EAC) and esophageal squamous cancer (ESCC) are distinct in their molecular characteristics [4]. Furthermore, analysis of EAC and gastric adenocarcinoma could not clearly distinguish these two cancers. In addition, research from a preclinical mouse model and distinct human studies suggests that gastric progenitor cells give rise to EAC [5, 6]. Thus, medical treatment does not depend so much on the localization of the tumor (esophageal *vs* gastric) but more on the histology (adenocarcinoma *vs* squamous cell carcinoma), arguing against a combination of EAC and ESCC in clinical trials, as unfortunately still done in ongoing phase III drug approval studies and in the current *ProfiLER 01* analysis. In terms of precision oncology, there are distinct molecular subtypes in EAC and GC [7, 8] with the need to be treated with respect to their molecular profile (*i.e.* MSI, CIN, EBV, genomic stability, PDL-1, Her2/-neu) as also suggested by Cassier et al. Precision medicine in this case allows by genomic analysis to realize that otherwise indistinguishable tumors indeed have discrepant biology and require distinct therapies. Nevertheless, precision oncology aims to treat cancers not only based on histologically defined entities but also entity-agnostically based on their molecular profile.

The diagnosis and evaluation of genetic alteration (mutation, fusion, alterations, pathway activation) is complex, so that interdisciplinary and cross-sectoral networks such as the *ProfiLER 01* program in France or the German Consortium for Translational Cancer Research (DKTK) are necessary to identify patients with rare alterations [9]. Such need for

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interdisciplinary and intersectoral collaboration becomes even greater when alterations are present for which there are no cross-tissue approvals and thus comparatively low evidence for therapies outside such approvals. In the future it will be essential to improve our collaboration in national and even international networks to provide all patients with access to modern diagnostics and precision oncological treatment and to carry out this treatment in an evidence-based manner [10]. In such a network, the complexity of the NGS data-analysis process could be improved with a systematic and easily interpreted system necessary for detecting specific genomic alterations and genotype-matched therapeutic options with clinical practice. In that way, precision oncology programs or molecular tumor boards can serve as important screening platforms for innovative clinical trials. Although it would be impossible to completely prepare a treatment plan for each individual case, more suitable treatment based on the unique genomic changes could be adapted. Using network data, the currently insufficient access to targeted therapies after identification of druggable targets by molecular profiling may be overcome. Moreover, for upper GI cancers, there is an urgent need for preclinical models to identify and select suitable target for therapy. Recent developments utilizing patient-derived organoids (PDOs) may be an alternative individualized cancer model to test and identify effective therapy for individual patients with currently available drugs in a timely manner.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C. Massard, et al., High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 trial, Cancer Discov. 7 (6) (2017) 586–595.
[2] P.A. Cassier, et al., Precision medicine for patients with gastro-oesophageal cancer: a subset analysis of the ProfiLER program, Transl. Oncol. 15 (1) (2021), 101266.
[3] O. Tredan, et al., Molecular screening program to select molecular-based recommended therapies for metastatic cancer patients: analysis from the ProfiLER trial, Ann. Oncol. 30 (5) (2019) 757–765.
[4] N. Cancer Genome Atlas Research, et al., Integrated genomic characterization of oesophageal carcinoma, Nature 541 (7636) (2017) 169–175.
[5] K. Nowicki-Osuch, et al., Molecular phenotyping reveals the identity of Barrett's esophagus and its malignant transition, Science 373 (6556) (2021) 760–767.
[6] M. Quante, et al., Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia, Cancer Cell (2012).
[7] N. Cancer Genome Atlas Research, Comprehensive molecular characterization of gastric adenocarcinoma, Nature 513 (7517) (2014) 202–209.
[8] M. Secrier, et al., Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance, Nat. Genet. 48 (10) (2016) 1131–1141.
[9] A. Mock, et al., Community-driven development of a modified progression-free survival ratio for precision oncology, ESMO Open 4 (6) (2019), e000583.
[10] B.C. Westphalen, et al., Conceptual framework for precision cancer medicine in Germany: consensus statement of the Deutsche Krebshilfe working group 'Molecular Diagnostics and Therapy', Eur. J. Cancer 135 (2020) 1–7.