Molecular profiling of recurrent and metastatic salivary gland cancer to personalise cancer therapy

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Background: Recurrent and metastatic salivary gland cancer (RM-SGC) is an orphan disease with no standard drug therapies. Recent progress has been delivered through molecular profiling, identifying mammary analogue secretory carcinoma as a subtype of SGC characterised by the ETV6-NTRK3 gene fusion which shows dramatic and durable response to the pan-TRK inhibition. We describe the Manchester Experimental Cancer Medicine Centre experience of molecular analysis in RM-SGC demonstrating...
the potential clinical utility and the challenges for the delivery of personalised therapy in this setting.

Methods: Between October 2015 and July 2017, 106 molecular analyses were completed for 73 patients with RM-SGC. We sought to identify clinically significant molecular abnormalities to provide a scientific rationale for prioritising patients to specific molecularly targeted clinical trials. Patients were consented to pre-screening for specific studies and offered molecular profiling by next generation sequencing (NGS). The NGS panels included a targeted panel (24 cancer-associated genes) to identify single nucleotide variants and small insertions/deletions; and a panel sequencing the entire exonic regions of 315 cancer-associated genes and common rearrangements in 28 genes. Publically available whole exome sequencing (WES) datasets were interrogated to identify previously reported genomic alterations in histopathological subtypes of RM-SGC.

Results: Histopathological subtypes were: adenoid cystic carcinoma (76.5%), adeno-carcinoma (12.7%), myoepithelial carcinoma (3.6%), acinic cell carcinoma (3.6%), mammary analogue secretory carcinoma (1.8%) and muco-epidermoid carcinoma (1.8%). Of 42 patients screened for TRK1/TRK2/TRK3, ROS1 or ALK gene rearrangements and 22 patients for c-MET amplification, the analysis was successful in 95% of cases. However, no positive results were identified. Combining the 24 and 343 gene NGS panels, actionable alterations were detected in 31% of patients (11/36) including BRAF, PIK3CA, NOTCH1 and TP53. Analysis of publically available WES data from 60 patients with adenoid cystic carcinoma identified DNA damage/checkpoint signalling alterations in 27% of patients. As such, 4 patients in our cohort with adenoid cystic carcinoma were treated within trials targeting DNA damage response pathways.

Conclusions: Results from molecular pre-screening within clinical trials have the most direct clinical applications. However, specific alterations were not common in this patient group. Therefore, a large number of patients need to undergo profiling to be matched to clinical trials. Broader molecular profiling with NGS panels has a detection rate of 31% for clinically actionable tumour associated genetic alterations in our limited dataset. The clinical relevance of these results is often less clear and should ideally be discussed through a molecular tumour board. The main challenge in the clinical application of the findings was the availability of suitable matched clinical trials. To determine the clinical benefit of broad genomic profiling in this patient group, further large scale collaborative analyses will be performed in a larger patient cohort aiming to match patients with molecularly targeted therapies within prospective studies.

Clinical trial identification: NCT0258267, NCT02520752 and NCT02626234.

Legal entity responsible for the study: The Christie NHS FT.

Funding: Supported by Roche Products Ltd. through provision of Foundation Medicine tumour profiling service.

Disclosure: All authors have declared no conflicts of interest.