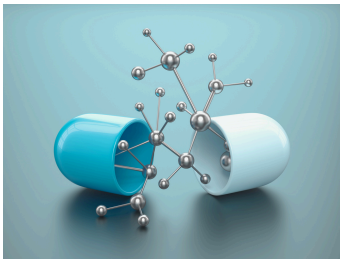

SCIENCE BREAKTHROUGH

MOLECULAR MEDICINE FOR THE GENERAL ONCOLOGIST

Through our BSMO newsletters and flashes, we aim to improve our knowledge of molecular biology and NGS by publishing a series of small articles that will update or improve your understanding of this very hot topic. We will put a specific focus on practical important aspects for daily oncological practice.
Like NGS, this effort is multidisciplinary and, involves several experts in the field : Dr Philippe Aftimos (medical oncologist at Institut Jules Bordet), Dr Brigitte Maes (pathologist at Jessa Ziekenhuis), Dr Vasiliki Siozopoulou (pathologist at Cliniques universitaires Saint-Luc), Dr Léon Van Kempen (pathologist at UZ Antwerp), coordinated by Dr Cédric Van Marcke (medical oncologist at Cliniques universitaires Saint-Luc).

Clinical interpretation of next generation sequencing data

by Cédric Van Marcke, Cliniques Universitaires Saint-Luc

In the previous newsletters, we reviewed the concept of NGS, the different types of genomic alterations and how they act differently on proto-oncogenes and tumor suppressor genes. We then discussed which patients should get tested, by which type of NGS panel, and on which material. Lastly, we introduced the main concepts of interpretation of the variants, to consider their pathogenicity (i.e, their impact on the protein function) and their actionability (i.e, the existence of evidence of association with response to a treatment).

Here, we will provide more details regarding the landscapes of clinical actionability.

Histology-specific vs tissue-agnostic biomarkers for treatment

For decades, cancer management has primarily relied on the specific histology of the tumor, and the tissue in which it originated. Treatment approaches are for the vast majority of tumor types still organ- and histology-specific.
In the last years, tissue-agnostic biomarkers (thus of pertinence across different tumor histologies) have emerged, due to the wide applicability of NGS and the exponential development of more efficient targeted therapies. Nevertheless, most biomarkers remain histology-specific, probably due to lineage-specific differences in pathways activities.

Tissue-agnostic biomarkers

As of today, five biomarkers are considered to predict high odds of response to a targeted therapy, no matter the tumor type.

Tissue-agnostic biomarkers	Approved targeted therapy	Approximate pan-cancer prevalence	Most frequently concerned tumor types
Mismatch repair deficiency (dMMR) or microsatellite instability (MSI)	Pembrolizumab, dostarlimab	3%	Endometrial (30%) Colon (20%) Stomach (20%)
NTRK fusions	Larotrectinib, entrectinib	< 1%	90-100% : mammary-analogue secretory carcinoma of the salivary glands ; secretory carcinoma of the breast ; infantile fibrosarcoma 10-15% : thyroid cancer ; spitzoid tumor ; KIT-negative GIST 5% : brain tumors ; sarcomas ; ampullary cholangiocarcinomas ; KRAS-negative pancreatic cancer <1% : others

RET fusions	Selpercatinib	< 1%	thyroid cancer and NSCLC (5%), anal cancer and brain tumors (2%)
BRAF V600E mutation	Combined dabrafenib and trametinib	2%	Thyroid cancers (40%) ; melanoma (30%) ; colorectal cancer (20%)
HER2 overexpression (IHC 3+)	Trastuzumab deruxtecan	2-5%	Oesogastric cancer (12%) ; breast cancer (10%) ; salivary/vaginal/endometrial/bladder (4%)

Based on recent data from the RAGNAR and NCI-MATCH studies, FGFR1-4 fusions and mutations (but not amplifications) could be considered as histology-agnostic biomarkers for erdafinitib, a selective FGFR1-4 inhibitor.

Of note :

- *the HER2 overexpression is an immunohistochemical biomarker, with in situ hybridization positivity serving as a proxy. A pan-tumor method of HER2 assay remains required.*
- *Screening for MSI across all tumor types can be performed through NGS, providing sufficient microsatellite regions are covered by the panel. In a study of almost 200.000 samples, the discordance rate between NGS and IHC to assess microsatellite status was of only 0.3%.*

Histology-specific biomarkers

Most biomarkers considered predictive of response to a targeted treatment have only proven so in a specific cancer type. Hence, the association weighing the evidence must take the tumor context into consideration: the triad histology – gene abnormality – targeted therapy allows to estimate the level of clinical actionability.

Nevertheless, this evidence only refers to a specific molecule of targeted treatment, and not necessarily to a specific class of targeted treatment. We provide here two seminal examples :

- *PIK3CA mutations are frequent across many cancer types (10% altogether). PI3K inhibitors have gradually evolved towards more specific inhibitors of the alpha subunit of the protein, and now even to the mutated isoform. The first generation PI3K inhibitors (like taselisib) did not lead to any objective response in PIK3CA-mutated cancers. More specific inhibitors (like inavolisib or STX-478) appear more effective, and at the same time less toxic.*
- *HER2 mutations are frequent across many cancer types (3% altogether). In the SUMMIT basket trial, First-generation tyrosine kinase inhibitors like neratinib leads to objective responses in some tumor types (mainly breast and biliary tract cancers), but none in other tumor types (colorectal, bladder, gastro-oesophageal cancers). However, other treatment classes targeting HER2, like the antibody-drug conjugate trastuzumab deruxtecan, achieve higher efficacy, across most tumor types (DESTINY-PanTumor02 trial). Careful consideration of the clinical ontext remains mandatory, as some tumor types and specific mutations (eg, gastro-oesophageal cancer, enriched in mutations in the juxtamembrane domain of the protein) are associated with disappointing responses.*

Thus, future more potent tyrosine kinase inhibitors or different treatment classes should lead more biomarkers to be considered as actionable, in specific histologies or even in a tissue-agnostic setting.

In the next newsletter (May), we will publish a final article and discuss the beneficial impact of applying the global framework of precision oncology at a population level of metastatic cancer (comprehensive testing early in the disease, dedicated targeted treatment with an effective compound). Then, we will elaborate on how clinicians should organize as a team to reduce the risk of missing a clinically actionable target.

References

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