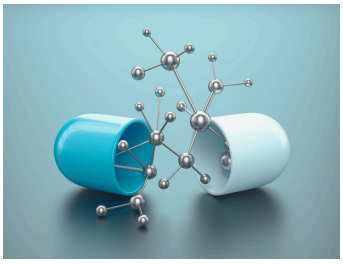

BSMO SPECIAL SERIES #2

MOLECULAR ONCOLOGY IN DAILY LIFE

BSMO aims 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).

Practical considerations for NGS : Who should get tested, and how?

The first article in this series (read BSMO newsletter May 2024)introduced some overarching concepts:

- Different types of gene aberrations are relevant for tumor development/progression.
- The gene function and classification has to be taken into account for a correct interpretation.
- Several sequencing technologies have to be considered, depending on the question to be answered.

Large pan-cancer collaborative efforts like TCGA, ICGC, Project Genie have demonstrated that :

- Tumor genome profiling can further subdivide organ-based tumor histologies into more homogeneous, molecular subgroups.
- Those subdivisions can highlight significant prognostic and/or predictive biomarkers.
- Most tumor-driving alterations are context-dependent (i.e., specific to a histology).
- Some tumor-driving alterations are agnostic biomarkers (i.e., critical events for tumor development that can be found across all tumor types).

Thus, these invaluable efforts allow to delineate which cancer patients should benefit from the genomic profiling of the tumoral sample and which targets should be considered.

Who should benefit from an NGS test?

Localized disease

Locoregional solid tumors, amenable to curative treatments, should be offered tumor NGS if the test would potentially provide:

- A strong prognostic value that could lead to treatment adaptation (escalation/de-escalation).
- Strong predictive value that could lead to specific treatment options.
- Key arguments to further characterize the cancer diagnosis.

Main examples (non-exhaustive) :

- Endometrial cancer (searching for POLE and TP53 mutations, in parallel to microsatellite instability).
- GIST and NSCLC at higher risk of relapse (searching for KIT and EGFR mutations, respectively).

However, in the current clinical practice, most locoregional solid tumors do not require a genome profiling test, due to a lack of sufficient clinical evidence.

Metastatic disease

The situation dramatically differs when considering metastatic solid tumors. Here, we will mainly focus on the impact of NGS on treatment allocation, not on diagnostic impacts. Virtually all tumor types carry subgroups expressing an agnostic biomarker amenable for specific treatment options at the metastatic stage, albeit at (very) low frequencies. This concept will be developed in a future newsletter.

Clinical considerations can help delineate who could benefit from testing:

- Life expectancy of > 6 months.
- Good general health to consider a systemic treatment (ECOG performance status ≤ 2).

Which NGS test in which situations?

Small panels upfront

Tumors with a **high probability of displaying a specific driving genomic abnormality** will benefit from a (small) targeted panel. In such cases, there is, in first intention, no added value of a broad, comprehensive genomic profiling (CGP test).

Main examples (non-exhaustive list) :

- melanoma and BRAF V600 mutations
- GIST and KIT mutations
- glioma and TERT or IDH1 mutations

Sequential CGP for selected wild-type tumors

Furthermore, the absence of frequently encountered genomic events can help delineate a **subgroup of cancers enriched in (very) rare driving events**. Thus, CGP testing should be offered for some tumor types when smaller targeted panels are negative. This approach is considered more cost-effective than upfront CGP testing in those situations, as the expected number of sequential CGP tests is limited.

Best examples :

- pancreatic cancer without a KRAS mutation (< 10% of cases)
- colorectal cancer without a KRAS/NRAS/BRAF mutation (± 50% of cases)

CGP upfront, at diagnosis of metastatic disease

CGP as the first genomic NGS test (i.e., at diagnosis of the metastatic disease), or exhaustive tumor profiling by DNA ± RNA targeted panels, should be considered for several tumor types, if inter-patient genomic heterogeneity is the rule and several actionable driving events can be highlighted.

Main examples (non-exhaustive list) :

- triple-negative breast cancer
- non-small cell lung cancer
- cholangiocarcinoma
- salivary gland cancer
- glioblastoma
- renal cancer
- gastric cancer

It is also mandatory to consider a **CGP test for a cancer of unknown primary** (CUP), as it allows in up to 30% of cases to define the tissue of origin and tailor treatment options, tissue- or biomarker-specific.

CGP during the metastatic disease course

CGP is probably also the most cost-effective test to consider **upon resistance to a targeted treatment** (e.g, NSCLC and resistance to an EGFR inhibitor, frequently due to the acquisition of a secondary mutation, amplification or fusion in the same or in a different gene).

Finally, CGP is frequently considered in later lines **when standard treatment options are exhausted**. However, testing in this situation **generally leads to disappointing results** in real-life situations for many reasons:

- Genomic instability and persistent oncogenic events have gradually led to the accumulation of multiple distinct subclones. Targeting a specific biomarker could thus only lead to the exhaustion of a specific subclone without improving survival outcomes.
- Genomic testing is then rarely performed on a recent biopsy. An archival biopsy, obtained months to years ago, does not represent the current disease.

Thus, if CGP is considered in later lines, **obtaining a recent biopsy should be the rule**.

In the next newsletter, we will further discuss some analytical aspects: how to interpret the pathogenicity and clinical actionability of the variants?