Inflection Point: Novel Treatment Options are Forcing Next-Generation Sequencing into Standard of Care for Molecular Profiling in Oncology

An Update from the
European Society for Molecular Oncology (ESMO) Congress 2019

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Meeting Summary

While precision medicine in oncology is eventually turning into reality outside the confined space of lung tumours, the approval of pan-cancer drugs, such as neurotrophic receptor tyrosine kinase (NTRK) inhibitors, is fostering the need for robust and reproducible molecular testing, in order to accurately identify treatment-eligible patients. At this year's European Society for Molecular Oncology (ESMO) congress in Barcelona, Spain, gathering >30,000 healthcare professionals spanning a range of disciplines and stakeholder groups, and >500 invited speakers, the latest update of clinical trial data showed the power of combining treatments, concurrently addressing multiple molecular pathways, and using both immune-oncology agents and targeted therapy. Similar to the 2018 congress, the integration of molecular data in the clinical management of cancer patients has been a major source of debate among specialists.

A number of workshops, satellite events, and new product launches at the ESMO congress were accompanied by dedicated companion diagnostic discussions. Most of the novel treatment options, either being new agents or therapeutic schemes, with sequential drug exposure and dosage adjustments, were complemented by presentations focussed on the need for adequate molecular testing. A few critical factors have emerged as being necessary for appropriate development and uptake of molecular profiling on a large scale in order to significantly impact patient outcomes.

Biomarkers Actionability

With a sustained number of new drugs or combination drugs entering standard of care this year, molecular testing should be constantly tailor based on those and should include the most updated relevant biomarkers to aid the best clinical decisions. In many panel discussions, a clear consensus was built around the need of triaging patient molecular and clinical data and to discuss in-depth the findings at local molecular tumour boards as a key element to enroot a truly personalised care model.

Conversely, a large and unresolved debate took place concerning to what extent molecular profiling should be used. Some major key opinion leaders advocated for the introduction of very

large next-generation sequencing (NGS) panel-based molecular testing including hundreds of genes, with many of those still having limited to no clinical actionability but holding the promise of increasing the patients' enrolling chances into clinical trials. On the other hand, a more consistent part of the audience was in favour of dedicated NGS panel-based tests covering clinically relevant genes (in the range of around 50) as being a more pragmatic and cost-effective approach.[1] The debate was further polarised between the standpoint of large academic centres versus community regional hospitals, having different resources both in terms of infrastructure and dedicated personnel. Given the complexity of cases to be analysed, it is evident that no one-size-fits-all solution exists because cancer type, molecular heterogeneity, the underlying clinical setting, and overall healthcare providers vary in terms of oncology patient support and management.[2]

Tumour Tissue Requirements along with Turnaround Times, from Sample Collection to Results, are More Critical than Ever Before

It is imperative that exhaustive biomarker testing results are available within days and not weeks before returning to the clinician. In fact, with many institutions now facing an increased pressure to deliver results leading to targeted therapy-related decisions, a clear trend in building in-house sequencing facilities to reduce time to result was at the forefront at this year's ESMO. Immuno-oncology agents are playing a pivotal role in underlining the need for fast testing procedure. In fact, a recurrent in practice scenario contemplates the initiation of an immuno-oncology drug regimen based on fast immunohistochemistry test results (i.e., programmed death-ligand 1 [PD-L1] positivity >1%) even before the mutational status of genes such as *EGFR* are known. Unfortunately, this fact leads to a number of mistreatments, especially for patients that after completing genomic testing turn out to be eligible for targeted therapy (e.g., *BRAF* positive melanoma).

In addition, in many of the discussions around molecular testing, the need for minimal tissue sample (i.e., working with cytological specimens) starting material and limited rejection rate (e.g., due to QNS) have turned out to be a basic requirement for any test to be broadly introduced into routine clinical practice. Any possible precaution should be taken in order to avoid a rebiopsy; anything that comes with associated risks, elevated costs and treatment delays, or when not applicable can lead to suboptimal therapy selection.

Molecular Testing Harmonisation

With many players and vendors now entering the molecular diagnostic field, the range of assays available on the market is steadily increasing; however, not all tests are born equal. In fact, there is a great need for harmonisation in nucleic acid testing in oncology. For instance, the range gene target number for molecular profiling across different assays and the absence of standard reference materials contributes to variability in test results among laboratories. A pivotal example is the recent unresolved issue related to the tumour mutational burden (TMB) assessment. Clinical studies have established TMB as a possible predictive biomarker for clinical efficacy of immune checkpoint inhibitors. However, there is a clear lack of standardisation for TMB estimation and reporting, something that is critical for ensuring reliability for its routine clinical implementation. An international effort to address this problem is currently lead by Friends of Cancer Research and Qualitätssicherungs-Initiative Pathologie GmbH (QuIP). Friends and QuIP aim to establish recommendations for achieving consistency in TMB estimation and reporting. Preliminary data from both stakeholders indicate several components to influence TMB estimation: preanalytical factors (e.g., input material quality/quantity), sequencing parameters (e.g., enrichment technologies), library preparation, bioinformatics (e.g., filtering of germline variants), as well as FFPE-induced deamination artefacts.

Such initiatives are necessary to assure that molecular testing can effectively enable true precision oncology by generating robust, reproducible, and meaningful data to inform treatment decisions.

Biomarkers for Immuno-Oncology Treatment Selection in Lung Tumour: An Open Debate

Nowadays, personalised oncology cannot be discussed without non-small cell lung cancer (NSCLC) as a pivotal example. With a fast-growing number of predictive biomarkers to be screened, but within the constraints of doing it in a tissue conservative manner, lung cancer represents both a great opportunity for new discovery and a challenging scenario for genomic profiling. Sequential testing algorithms are superseded by newer techniques such as NGS, being able to simultaneously look at a variety of biomarkers while only requiring low tissue input. In the field of immunotherapy, PD-L1 testing again played a major role at this year's ESMO congress as the most important biomarker to predict response to immune checkpoint inhibitors.[3] On the other hand, the controversial role of tissue TMB (tTMB) was not cleared up during the congress, with many conflicting data. The most debated study concerned the results from KEYNOTE-010 (tTMB available data for 253 patients) and KEYNOTE-042 (tTMB available data for 793 patients), including pembrolizumab versus chemotherapy in advanced NSCLC with mixed histology and a PD-L1 tumour proportion score (TPS) ≥1%.[4] tTMB status was defined with a cut-off point of 175 mutations/exome derived from a metanalysis of clinical trials across multiple tumour types. The chemotherapy arm showed no association with tTMB status; however, in the pembrolizumab arm a high tTMB value (i.e., TMB≥175) was associated with overall survival (OS), progression-free survival (PFS), and objective response rate. Conversely, Paz-Ares et al.[5] showed no association between tTMB and patient outcomes in pembrolizumab plus platinum-based chemotherapy for advanced untreated NSCLC with mixed histology. The patient cohort was composed of half of the patients of each of the KEYNOTE-021, KEYNOTE-189, and KEYNOTE-407 trials.

Overall, presented results indicated that tTMB requires careful re-evaluation as a biomarker for combination therapies, whereas the relationship for monotherapy has been confirmed in previous studies.[6] Among the unresolved crucial points, the definition of a universal TMB cut-off value (e.g., TMB ≥175 mutations/exome) seemed unrealistic, given that accumulating evidence suggests TMB to be highly tumour-type dependent. It was overall highlighted that further predictors for checkpoint inhibitor response need to be investigated, including immune infiltration scores and T-cell receptor clonality.

Overall, these results pinpoint the importance of determining the tumour mutational status at diagnosis as part of a board molecular profiling, in order to select the most appropriate treatment option for lung cancer patients.

Targeted Therapy Further Solidifies in Lung Tumour: Tyrosine Kinases Evolving Scenario

Outside the immunotherapy space, osimertinib was confirmed as an extremely effective option for first-line treatment of *EGFR*-mutated NSCLC based on the final data from the FLAURA trial,[7] moving the field forward from the original osimertinib scope as a third-line treatment for *T790M*-mutated patients. Improvement in PFS compared to first-generation EGFR-receptor tyrosine kinase inhibition was established, with a notable benefit especially in patients with brain metastases. Optimal sequencing regimens using tyrosine kinase inhibitors need to be further explored as resistance after osimertinib is observed and not yet fully understood. In the same study, ctDNA was analysed to monitor patients' disease progression. Mutational changes were visible before clinical progression was evident by monitoring for *T790M* or *C797S* resistance *EGFR* mutations during and after treatment.[7]

Outside EGFR, anaplastic lymphoma kinase positive NSCLC with active brain metastases now have an additional option given that the ASCEND-7 trial has confirmed ceritinib as a standard treatment option for those patients.[8] Of note, ASCEND-7 supports the activity of anaplastic lymphoma kinase inhibitors for brain metastases when administered prior to brain radiotherapy, thus allowing radiotherapy, along with its potential side effects, to be delayed.

Poly (ADP-Ribose) Polymerase Inhibitors move into First-Line in Ovarian and Breast Cancers: The Prominent Role of Breast Cancer Gene and Homologous Recombination Deficiency

Practice-changing Phase III trials were presented at the congress for newly diagnosed advanced ovarian cancers, wherein poly (ADP-ribose) polymerase (PARP) inhibitors are playing a major role. After the SOLO1 data presentation at ESMO 2018 in Munich, Germany, olaparib has demonstrated improved PFS in women newly diagnosed with high-grade advanced ovarian cancer with *BRCA1/2* mutation or homologous recombination deficiency (HRD).[9] The PRIMA/ENGOT-OV26/GOG-3012 trial highlighted that maintenance niraparib followed by platinum-based chemotherapy significantly extended PFS compared with placebo in the overall trial population (median: 13.8 months versus 8.2 months).[10] PARP inhibitors also elicit clear benefits to all newly diagnosed advanced ovarian cancers, independently from *BRCA1/2* status alone or in combination with chemotherapy or bevacizumab.[11] Olaparib plus bevacizumab significantly improved PFS compared with placebo plus bevacizumab in the overall population (median: 22.1 months versus 16.6 months), regardless of *BRCA* mutation status. However, in patients with *BRCA*-mutated tumours, olaparib plus bevacizumab was associated with superior PFS (median: 37.2 months versus 21.7 months), but with less benefit in patients with non-*BRCA*-mutated tumours (median: 18.9 months versus 16.0 months). Notably, there appeared to be no significant benefit for olaparib plus bevacizumab as maintenance regimen in patients with negative or unknown HRD status (median: PFS 16.9 months versus 16.0 months). However, the clinical validity of testing for HRD status needs to be comprehensively investigated.

In the BROCADE3 trial, Huggins-Puhalla et al.[12] showed that patients with advanced human *EGFR2*-negative breast cancer and germline *BRCA* mutation demonstrate significantly improved PFS with the addition of the PARP inhibitor veliparib to chemotherapy over placebo plus chemotherapy.

Yet another example highlighting the importance of a correct *BRCA* assessment, underlining the importance and the need to ramp up molecular diagnostics capabilities in the current scenario of patient management.[13]

Novelty in Colorectal Cancer: Beyond *BRAF V600E*

Most updated results from the BEACON trial[14] show unmatched OS in the second-line treatment of metastatic colorectal cancer (CRC) positive for *BRAF V600E* with a combo of three targeted agents, namely encorafenib, cetuximab, and binimetinib. The results of the randomised Phase III study based on 444 patients showed that the triplet combination was associated with markedly superior median OS (9.0 months versus 8.4 months) and objective response rate (26% versus 20%), compared with the doublet (encorafenib with cetuximab). Additionally, patients with *BRAF V600E*-mutated CRC benefited from surgery of liver metastases. In a retrospective series of 91 patients with *BRAF V600E*-mutated CRC and liver-only metastases, multivariate analysis found that surgery was associated with significantly longer OS and PFS than a chemotherapy-only strategy.[15]

Overall, the presented data emphasise the value of assessing *BRAF* mutations, not just *V600E*, outside the most commonly tested space of melanoma, and demonstrate the important predictive value of *BRAF* in patients with advanced CRC.

Biliary Tract Cancer: Time for Molecularly Informed Treatment Decisions

Biliary tract cancers, especially intrahepatic cholangiocarcinoma, often present (≤40% of cases) with fibroblast growth factor receptor (*FGFR*) 2 gene fusions along with isocitrate dehydrogenase-1 (*IDH1*) mutations. Pemigatinib, a FGFR inhibitor with compelling clinical efficacy in patients having *FGFR2* gene rearrangements or fusions, was presented at ESMO. Pemigatinib achieved an objective response rate of 35.5% and a median response duration of 7.5 months,

along with median PFS and OS of 6.9 months and 21.1 months, respectively.[16] Derazantinib and infigratinib, other FGFR inhibitors, further showed encouraging results in early-stage clinical trials (Phase IIa studies).

Patients with advanced cholangiocarcinoma presenting *IDH1* mutations and treated with IDH1 inhibitor ivosidenib in a Phase III clinical trial (ClarIDHy) showed some clinical benefit compared to placebo.[17] The Phase III trial confirms that targeting *IDH1* mutations in cholangiocarcinoma is a promising strategy, but the debate is open on whether results are clinically meaningful. Overall, *IDH1* mutations remain a highly interesting target for cholangiocarcinoma treatment.

The above-mentioned studies demonstrate that precision medicine in advanced cholangiocarcinoma has finally started to gain traction. Tumour profiling should be taken into consideration to decide upon treatment options and should become a new standard for patients diagnosed with advanced cholangiocarcinoma.

Prostate Cancer: *BRCA* Gene and Homologous Recombination Deficiency Status are Changing the Treatment Scenario

The PROfound study[18] results showed a clinically meaningful benefit in radiological PFS with olaparib in metastatic castration-resistant prostate cancer (mCRPC) with *BRCA1, BRCA2*, or ataxia-telangiesctasia mutated genes.[18] PROfound evaluated the efficacy and safety of olaparib versus enzalutamide or abiraterone in 387 patients with mCRPC who have failed prior treatment with a new hormonal agent and have a tumour mutation in one or more of 15 genes involved in the homologous recombination repair (HRR) pathway. Remarkably, the PROfound trial is the first positive Phase III biomarker-based (i.e., HRR) study in mCRPC.[19] Olaparib reduced the risk of progression by 66% ($p<0.0001$) in patients with alterations in *BRCA1, BRCA2*, or ataxia-telangiesctasia mutated gene by 51% ($p<0.0001$) in patients with alterations in any qualifying HRR gene.

As for ovarian and breast cancers, it is pivotal to rapidly equip molecular pathologists with the appropriate solutions to effectively test for HRR-related genes in order to inform treatment decisions.

Liquid Biopsy for Routine Testing: Towards Real-Time Disease Monitoring

Within the context of the FLAURA trial,[7] results presented at ESMO from an exploratory analysis using circulating tumour DNA (ctDNA) to monitor patients with *EGFR*-mutated NSCLC showed that early detection of disease progression is feasible, and that mutational changes can be detected in ctDNA before clinical progression is evident.[7] In detail, the detection of *ex19del, L858R*, or *T790M EGFR* mutations via plasma-derived ctDNA analysis was performed before, during, and after treatment. *T790M* or *C797S* resistance mutations were monitored during and after treatment. Notably, of the 122 patients who had their ctDNA monitored, progression according to ctDNA data preceded or occurred concurrently with manifest clinical disease progression in about 66% of patients, with a median lead time of 2.7 months. Acquired *EGFR C797S* or *T790M* resistance mutations were detected in 8% and 74% of patients with ctDNA progression in the osimertinib and comparator arms, respectively. Earlier awareness that resistance is present and prompt identification of the driving mutation might impact the overall therapy management process.[20]

Considering the fast-evolving technical progress enabling testing at increased sensitivity and specificity, liquid biopsy is emerging as a valuable diagnostic tool, including for minimal residual disease monitoring to determine treatment success in early-stage cancers. At the congress, several presented studies used liquid biopsies as an assessment tool in the prediction of prognosis for CRC. The IDEA FRANCE study investigated Stage III colon cancer and assessed the risk of 3-month adjuvant chemotherapy treatment versus 6-month standard treatment using ctDNA as a selecting factor, demonstrating the value of ctDNA analysis. However, the trade-off between monitoring a patient's individual mutations in a specifically designed single analyte liquid biopsy test

compared to using a broader NGS-gene panel comes down to difference in the assay sensitivity, a parameter that is vital for a proper minimal residual disease monitoring.[21] Overall, the utility of liquid biopsy for MDR detection has not been fully proved, but this year's data posed an important milestone toward this goal.

Molecular Diagnostics: Why Build an Interdisciplinary Approach

Molecular tumour boards (MTB) are an emerging entity in the field of oncology. A multidisciplinary approach enabling physicians to cope with individual patient history and to provide genotype matching opportunities is highly needed.[22] MTB is also a forum for continuing education and to increase oncologists' confidence in making treatment options while disseminating updates around molecular testing. The following specialists should be included in an MTB: oncologists, pathologists, geneticists and genetic counsellors, bioinformaticians, radiologists, and basic scientists to give insight on individual pathways and drug access specialists to provide information about ongoing clinical trials. The biggest challenges are that not all hospitals and practices have access to such a structure, and there is a lack of availability of fitting clinical studies in all geographic area.

Genomic testing increases the ability to find opportunities for patient treatment and generates a large amount of clinical data that can be used for translation research discoveries. To facilitate and aggregate such a mass of data, there is an increasing need to have software solutions that would facilitate NGS data interpretation to narrow down actionable mutations and help to focus MTB discussion. Furthermore, it is important that data collected by different stakeholders is accessible anywhere and that includes the outcomes of MTB discussions. This would also require an appropriate framework in regard to data sharing and acquisition, where major international associations, like ESMO and American Society of Clinical Oncology (ASCO), should play a prominent role in process governance.

Conclusion

While there has been a tremendous improvement around treatment availability as demonstrated during the ESMO congress, there is still a major hurdle hampering the prompt transfer of these therapies to patients: access to timely molecular testing results. For these drugs to benefit more patients, there needs to be a major paradigm shift in the way genomic patient tumour profiles are generated, interpreted, and provided to oncologists, particularly in the community hospital setting. It is now clear that in order to expedite access to the full arsenal of available targeted therapies, NGS will have to become mainstream.

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