Next-Generation Sequencing Standard of Care for Molecular Profiling

An update from the European Society for Medical Oncology (ESMO) Virtual Congress 2020

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Disclosure: Dr Quagliata is an employee of Thermo Fisher Scientific and holds stocks in this company.

Acknowledgements: Thermo Fisher Scientific gives acknowledgement to Jose Luis Costa, Amy Carrol, and Christina Bernasconi Ranft for their valued input.

Support: The publication of this article was supported by Thermo Fisher Scientific.

Citation: EMJ Oncol. 2020;8[1]:27-32.

Meeting Summary

Today, the need for robust and reproducible, but also timely, molecular testing to accurately identify treatment-eligible patients is largely acknowledged within the oncology community. This year's European Society for Medical Oncology (ESMO) annual congress, in its virtual debut, gathered healthcare professionals spanning a range of disciplines and stakeholder groups together to learn from over 200 invited speakers and approximately 2,000 e-abstracts. In the coronavirus disease (COVID-19) era, attention has been focussed on the importance of appropriate molecular testing as part of an integrated cancer care workflow aiming to effectively stratify patients and enable optimal treatment selection. Additionally, emphasis was placed on the unique challenges posed by the COVID-19 pandemic to cancer care. Throughout the event, it became clear that the medical community did not begin 2020 with full appreciation of how much a crisis such as COVID-19 would have on the capacity to rapidly reveal the fragility of the cancer testing ecosystem, highlighting the urgent need to integrate the siloed stakeholders who are so dependent upon it. A major question addressed by numerous speakers, with preliminary sets of data, was: "How does COVID-19 impact the prognosis of patients with cancer?"

With the usual workshops and satellite events, though only a few new product launches compared to previous years, the ESMO Virtual Congress 2020 was characterised by many presentations focussed on molecular biomarker testing. Overall, the ESMO 2020 meeting highlighted that there are vast gaps in current molecular diagnostics, with extremely marked geographical differences and a broken clinical diagnostic testing ecosystem that currently impedes patient access to precision therapy and better outcomes. While planning for new therapies associated with specific biomarkers is growing steadily, with approximately 100 new oncology drugs or combinations expected to be launched within 5 years, no widespread diagnostic solutions are currently available and the specialty will not be able to satisfy the mounting need for molecular testing in the near future unless a radical upheaval of the current situation occurs.

How Does COVID-19 Impact the Prognosis of Patients with Cancer?

Given that COVID-19 has posed unique challenges in cancer care, a number of speakers addressed, with evidence, the impact of COVID-19 on the prognosis of patients with cancer. It should be noted that the use of immunosuppressive agents, for example, was a real and understandable concern during the initial surge of COVID-19, given the potentially life-threatening consequences of inadequate immunity. Oncology professionals globally faced tough decisions on whether to stop treatment, change treatment regimens, modify doses, and in some cases, reverse previously planned treatment decisions. Patient-oriented aspects of oncology were forced to change because of COVID-19: bad news had to be relayed via video calls instead of in person and heart-breaking situations occurred whereby patients were not allowed visits from loved ones during a hospital stay, even at the end of their lives. Results from Europe's largest prospective dataset of patients with cancer and COVID-19 revealed an adverse impact of COVID-19 on prognosis, with a hazard ratio of 1.62 for mortality in patients with cancer versus without cancer.[1] In hospitalised patients with cancer and COVID-19, the mortality rate was higher in those with a history of cancer and on active treatment for cancer, at 44.3% and 42.3%, respectively, compared with 29.5% in patients without cancer. It is therefore mandatory to reduce the risk of COVID-19 exposure in patients with cancer.

COVID-19 Has Increased Pressure on Turnaround Times, from Sample Collection to Final Results

It is clear that the COVID-19 pandemic created a paradigm shift in all modern healthcare, with regulations, protocols, and mindsets having to be reworked in just a matter of months to keep pace with the virus.[2] As already highlighted during the 2019 annual ESMO meeting, it is imperative that exhaustive biomarker testing results are available within days for clinicians, and not weeks. The pandemic has further highlighted the need to timely generate and deliver molecular profiling results, with many institutions now facing increased pressure from COVID-19.[2,3] On one hand, institutions are urged to ensure safety during sample collection and adequate infrastructure sanitisation, inevitably inducing a delay to surgical procedures; on the other hand, they are required to promptly deliver results leading to important therapy-related decisions.[2-4] In this new scenario, it is clear that the sample testing send-out model is highly challenged. Building in-house sequencing facilities is going to be critical to ensure timely results, but also to generate the necessary independence that might prove pivotal during times when shipping biological specimens could add more challenges than benefits. Despite substantial efforts from major oncology stakeholders to prevent or reduce this behaviour, rushed decisions are common in routine practice. For example, contemplating the initiation of an immune-oncology drug regimen based on a fast immunohistochemistry test (i.e., programmed death-ligand 1 positivity >1%) before the mutational status of genes such as *EGFR* are eventually investigated. Such phenomena have been further exasperated by COVID-19, when pressure on physicians to initiate treatments is even higher, leading to several unappropriated decisions. Whether national healthcare systems will be willing, or in the position, to increase structural funding to support infrastructure expansion dedicated to molecular testing, including laboratories and specialised staff, remains to be seen. However, new technological, groundbreaking solutions are available on the market today, enabling molecular profiling at a speed compatible to immunohistochemistry, easing the burden of expediting results.

Tumour Tissue Sample Requirements and Test Success Rate Have Never Been More Critical

In addition to many discussions on the value of molecular testing, fewer but deeper debates have focussed on the importance of minimal tissue sample requirements to initiate the test (e.g., working with cytological specimens).[5] Drastically reducing the molecular test failure rates has turned out to be a basic requirement for any assay to be broadly introduced into routine

clinical practice during the pandemic, when avoiding a rebiopsy is an undisputable must. Preventing re-exposure to invasive procedures for patients with cancer, such as a rebiopsy, which is usually associated with medical risks and financial costs, has become a priority. The community is now more sensitive to this topic and careful checks for test requirements occur more than ever before. Assays that require minimal input and that have demonstrated a high success rate will be greatly beneficial.[6]

New Emerging Biomarkers Are Still on Hold: No News Is Bad News

Much awaited and more conclusive data regarding tumour mutational burden (TMB) were expected at ESMO this year. Unfortunately, several presented datasets indicated that tissue-TMB needs to be carefully re-evaluated as a biomarker for combination therapies, whereas the relationship for monotherapy has been confirmed in previous studies.[7] Among the unresolved critical points, the definition of a universal TMB cut-off value (TMB ≥175 mutations per exome) continues to appear unrealistic given that accumulating evidence suggests TMB to be highly tumour-type dependent. It now seems timely to look beyond TMB, identifying further predictors for checkpoint inhibitor response, including, for example, immune infiltration scores and T-cell receptor clonality.

New Opportunities for Early Stage Cancers: A Call on Molecular Testing at Diagnosis

Also at ESMO 2020, AstraZeneca took to the stage with their data from the ADAURA study.[8] The updated results from this trial, featuring Tagrisso® (AstraZeneca, Cambridge, UK) in the postsurgery or adjuvant setting, were promising and will continue to resonate enormously in the community. Extremely mature data presented at ESMO 2020 confirmed that Tagrisso generated an 83% reduction in the risk of postsurgery recurrence of non-small cell lung cancer (NSCLC). The study recruited participants with Stages IB, II, and IIIA NSCLC, who accounted for around 30% of the population presenting with this disease. Tumours at this stage can be removed with surgery but the cancer tends to recur for most patients; adjuvant cisplatin-based chemotherapy is the current standard of care but is a treatment that carries substantial toxicities. Tagrisso unequivocally demonstrated its successful treatment potential via the ADAURA study. Disease-free survival at 2 years was 89% with Tagrisso, compared to 53% in the control arm. Overall, these results pinpoint the future importance of determining the tumour mutational status at diagnosis, even in the early stages of NSCLC, as part of a board molecular profiling, in order to select the most appropriate treatment option for patients with lung cancer, as well as in the adjuvant setting.

New Treatment Options Highlights: More Targets Need Better Testing

Outside the NSCLC field, excitement for overall survival (OS) data presented for olaparib continues in males with metastatic castration-resistant prostate cancer and *BRCA1*, *BRCA2*, or *ATM* mutations.[7,9] The PROfound trial[9] was a prospective, multicentre, randomised, open-label, Phase III study evaluating the efficacy and safety of olaparib versus control (physician's choice of enzalutamide or abiraterone). The trial enrolled 387 patients with metastatic castration-resistant prostate cancer who had progressed on a hormonal agent and had a tumour mutation in one of 15 genes that play a role in the homologous recombination repair pathway; the trial has now reached substantial data maturity. OS was significantly longer with olaparib than control treatment in Cohort A (19.1 versus 14.7 months; hazard ratio: 0.69; 95% confidence interval: 0.50–0.97; p=0.0175), with a trend towards improvement in the overall population (17.3 versus 14.0 months; hazard ratio: 0.79; 95% confidence interval: 0.61–1.03; nominal p=0.0515). These results occurred despite approximately two-thirds of the patients in the control arm crossing over to olaparib following radiographic disease progression. The long-term safety of olaparib was as expected from previous studies

of its use. This substantial winning for olaparib, however, poses a real question regarding the readiness for *BRCA1, BRCA2*, and other *BRCA*-related testing. Overall, the very positive presented data might reach the bedside with substantial delay if the testing gap is not rapidly fulfilled.

Data on gene fusion were then presented, demonstrating the efficacy of pralsetinib (BLU-667) in patients with *RET* mutation-positive medullary thyroid cancer (MTC), with or without prior treatment, as presented in the ongoing Phase II extension of the registrational ARROW trial.[10] Notably, with the U.S. Food and Drug Administration (FDA) approval of selpercatinib (Retevmo; Eli Lilly and Company, Indianapolis, Indiana, USA) for the treatment of advanced and metastatic *RET* fusion-positive NSCLC, *RET* fusion-positive thyroid cancer, and *RET*-mutated MTC, physicians and patients are now offered with more options for *RET*-fusion management. More data is expected with the Phase III trials LIBRETTO-531,[11] conducted in treatment-naïve patients with advanced or mutated MTC, and LIBRETTO-431,[12] in treatment-naïve patients with metastatic NSCLC, each comparing selpercatinib as first-line therapy versus standard of care. Expected completion of these Phase III studies is in 2025–2026.

Regarding the open fight against resistance mechanisms, Janssen presented results from the Phase I CHRYSALIS trial,[13] which tested the combination of amivantamab (JNJ-6372), a bispecific antibody targeting *EGFR* and *MET*, with lazertinib, a third generation EGFR-tyrosine kinase inhibitor, in advanced NSCLC with *EGFR* exon 19 deletion or L858R mutation. In the presentations, given by key opinion leaders, Janssen showcased promising data; the CHRYSALIS study generated a compelling 36% response rate among 45 patients who were tyrosine-kinase inhibitor-refractory, at a median follow-up of 4 months.[14] Amivantamab and lazertinib have been designed to block numerous resistance mechanisms to EGFR inhibition, and ultimately provide hope that their combination can improve response rates. If successful, this new paradigm will push the need to address all clinically relevant *EGFR* alterations further, not simply the most common locations in exon 19 and 20, advocating for comprehensive molecular profiling.

Health Economics and Real-World Evidence: Better Stratification Means Better Outcome

With increasing numbers of next-generation sequencing (NGS) tests being performed clinically, and as means to screen for company-sponsored studies, there is a growing ability to source existing data in healthcare systems and claims databases. Translating NGS results into hard outcomes and quality of life measures in a real-world setting is becoming more relevant to clinical decision-making and provides evidentiary value for payors, ultimately affecting patient access. Real-world evidence has influenced guidelines for patient care and can be used to support regulatory approval. For example, a study from the British Columbia Cancer Center (BCCC)[15] on the treatment evolution of advanced NSCLC has determined the change in OS in advanced NSCLC with new treatment options that underwent molecular profiling for treatment decisions. Data were analysed from the BCCC from 2009, 2011, 2015, and 2017. While patient demographics have changed somewhat over time, the proportion of patients treated with systemic treatment remained consistent from 2009–2017. Notably, the impact of targeted therapy and immune checkpoint inhibitor on OS in each respective year significantly improved overall OS. Relative to the best supportive care, chemotherapy alone, any-line immunotherapy, and any-line targeted therapy demonstrated clear benefit in univariate and multivariate analyses ($p<0.001$). Notably, the benefit of immunotherapy on OS was comparable to the use of targeted therapy. These data clearly demonstrate the need for upfront NGS testing, which has the benefit of quantitative outcomes. These types of collaborative analyses should provide substantial pressure on national healthcare system stakeholders to increase access to NGS screening.

Whole Genome Sequencing In The Clinics: Not Ready for Prime Time

This year, the ESMO Translational Research session was divided into two parts. The first focussed on immunotherapy-related research

with presentations on intrinsic mechanisms of sensitisation to checkpoint inhibition and immune effector score in immunotherapy-treated patients with NSCLC. The second focussed on whole genome analysis of tumours and included presentations on validation of whole genome sequencing (WGS) in routine clinical practice and the evolution of metastatic tumours under therapeutic pressure. Both sections included talks from principal investigators affiliated with the Netherlands Cancer Institute, Amsterdam, the Netherlands.[16,17] The authors provided insights into the implementation of clinical-grade WGS (cWGS) in routine practice. In the WGS Implementation in standard cancer Diagnostics for Every cancer patient (WIDE) study,[18] cWGS was performed on a prospective cohort of 1,200 patients (with Stage IV solid tumours), and feasibility and clinical validity data (primary endpoints) of the first 600 patients were presented. Notably, cWGS was successfully performed in only 69% (414/602) of patients, with a technical success rate of 96% (414/433). Ineligibility for cWGS was mostly caused by an insufficient number of tumour cells (<20%) in the received biopsy (86% [145/169]). Median turnaround time for cWGS was 14 days, which the authors claim will decrease incrementally by continuous improvements to the clinical procedure and cWGS pipeline. Overall, cWGS identified a clinically actionable (routine practice and experimental) biomarker in 74% of all patients tested. Based on the first WIDE study data, the authors concluded that cWGS can be clinically feasible in routine molecular diagnostics in a comprehensive cancer centre and has added value by providing additional treatment options for most patients. Of note, successfully delivering results for only 69% of enrolled patients is far from being clinically acceptable and speaks for the need to recalibrate the realistic expectation of cWGS uptake for routine testing. The cost implications were not discussed by the authors, constituting a large barrier for widespread application of cWGS. While these proof-of-principle studies are pivotal for advancing cWGS and getting it closer to the clinic, cWGS is not yet ready for prime time.

Conclusion

To make precision medicine a reality, the widespread application of genome analysis as a feasible diagnostic solution, and not only as a privileged option for a few national healthcare systems, is a must, but the field is falling behind. Healthcare policymakers, medical institutions, manufacturers, clinicians, biomedical researchers, and patients' associations will have to push for NGS adoption through global initiatives, while also being able to deploy them at a local level. At ESMO 2020, a number of talks and abstracts referred to the real-world testing landscape and highlighted the impressive developments and progress within NSCLC testing. However, the effects of those testing developments on patient management are not as impressive from the clinical outcome perspective. The real-world NSCLC testing landscape tells a very different story underneath the surface; one that is suboptimal and unable to deliver treatments designed to improve the lives of enough patients at the right time. For instance, a clear example are peroxisome proliferator-activated receptor inhibitors, where the lack of drug prelaunch preparation on the biomarker diagnostic front is leading to low adoption rates and patient leakage.[19] Overall, the emerging need for the inclusion of new biomarkers with sufficient prelaunch runway, to enable appropriate preparation for laboratories, is paramount. Diagnostic laboratories and providers need time to achieve the standards required to offer the right test and interpretation at the right time for the launch of new treatments. Unprecedented technological solutions are now available to mitigate these issues, enabling fast and robust NGS testing, but will require a change of attitude towards molecular diagnostics to truly consider it as an integral part of the cancer-care workflow, deserving appropriate investment.

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