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Quantifying the Benefits of Genome-Driven Oncology

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Summary

The excitement surrounding genomically selected cancer therapy has led many to question whether this treatment paradigm is living up to its initial promise. The MOSCATO study suggests that a genome-driven strategy for cancer therapy improves outcomes in a significant minority of patients who undergo molecular screening.

Genomically selected treatment has demonstrated unequivocal benefit and has thus been incorporated into routine management of at least seven different solid tumors as well as several types of leukemia. In total, 11 genomic biomarkers are part of health authority prescribing indications including *ALK*, *BCR-ABL1*, *BRAF*, *BRCA1*, *BRCA2*, *EGFR*, *ERBB2*, *KIT*, *PDGFRA*, *PDGFRB*, and *ROS1* (1). Moreover, a growing list of promising investigational biomarkers are being actively pursued in clinical trials. What remains to be answered, therefore, is not whether genome-driven oncology can work but rather what proportion of cancer patients will ultimately benefit from this approach and for how long.

To answer this crucial question, several drug development centers have launched broad genomic screening programs to facilitate hypothesis-driven enrollment onto precision oncology studies (2). The utility of this strategy will be best demonstrated by the successful development of new treatments targeting specific alterations, in particular those that would otherwise be challenging, if not impossible, to evaluate without broad screening efforts that can identify rare alterations present in multiple tumor types. Nevertheless, the significant human and financial resources required for this research has led some to question whether this investment is warranted (3,4). Practical impediments to directly quantifying the benefits of genome-driven oncology have made it difficult to address these concerns with the rigor that we have become accustomed to in evidence-based practice. This is because patient heterogeneity, the genomic profiling techniques applied, matching criteria used, drugs selected, and reliability of access to these drugs can all have profound implications on the measured impact of precision medicine.

The SHIVA study was the first modern attempt to evaluate the broad utility of precision oncology. These French investigators specifically sought to answer whether histology-

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agnostic, matched targeted therapy is superior to unmatched treatment in patients who have failed standard-of-care (5). Adult patients with refractory metastatic solid tumors were randomized to targeted drugs with one of 10 regimens containing 11 prespecified agents or physician's choice. While SHIVA ultimately reported equivalent outcomes between targeted and physician's choice therapy, serious methodological shortcomings limit the relevance of these findings. Critically, the targeted therapies evaluated in this study were chosen from a limited list of agents commercially available in France at the time, and included 3 anti-hormonal agents as well as several drugs now understood to have limited selectivity or potency against the targets to which they were matched. Moreover, the biological rationale underlying some of the matches was dubious. For example, everolimus was matched to alterations in the PI3K pathway despite the general paucity of biologic or clinical data supporting these alterations as predictive biomarkers (6). Finally, SHIVA was not designed to test for benefit of matched targeted therapy within a given disease or specific set of variants, the way these drugs would ultimately be used, and therefore did not exclude the possibility that one or more of the biomarker-drug pairs may have been efficacious. Therefore, while certainly well intentioned, the methodologic shortcomings of SHIVA have left the original question of the benefits of genome-driven oncology largely unanswered.

In this issue of *Cancer Discovery*, Massard and colleagues return to the question of whether genome-driven therapy improves patient care by evaluating outcomes from a comprehensive molecular profiling effort embedded within one of the leading drug development centers in Europe (7). In the Molecular Screening for Cancer Treatment Optimization (MOSCATO) trial, advanced cancer patients who did not have a genomic alteration qualifying them for an approved targeted therapy were offered profiling via next-generation DNA and RNA sequencing, CGH array, and FISH. Unlike the SHIVA trial, patients were not randomized to receive matched or unmatched therapy. Instead, results were used to guide enrollment to ongoing phase I/II clinical trials of targeted therapy available at the center. Using this single-arm observational study design, patients were considered to have met the primary endpoint (ie: achieved benefit) if their progression free survival (PFS) on genomically targeted therapy exceeded the PFS achieved on the immediate prior line of therapy by at least 30%. This clever endpoint helped to mitigate the challenge of measuring clinical benefit in a heterogeneous population by using each patient as their own control. Expecting that in the absence of efficacy 15% of patients would have a PFS ratio exceeding the prespecified cutoff of 1.3 (null hypothesis), the study ultimately met its primary endpoint by finding that 33% of patients with actionable alterations who matched to therapy exceeded this metric.

The MOSCATO trial also provides valuable insight into the rate of actionable alterations in the advanced solid tumor population as well as the ability to utilize this information. In total, 49% of patients for whom molecular profiling was successful were found to have at least one potentially actionable alteration and approximately half of these patients, or 24% overall, were matched to targeted therapy. This match rate is noteworthy because it substantially exceeds the experience of previously reported comparable efforts and demonstrates definitively that these screening programs can be used to successfully drive accrual to precision oncology studies when supported by the appropriate clinical infrastructure and study portfolio (2,8).

In our view, it is not surprising that the MOSCATO trial was positive, while SHIVA was not. Unlike SHIVA, which applied questionable off-label use of a limited set of approved therapies, MOSCATO primarily evaluated purpose-built inhibitors designed to target the identified alterations. Additionally, the biomarker-drug pairings were generally more selective and based on stronger clinical or preclinical rationale. As a result of these and other design decisions, MOSCATO ultimately supports the assertion that patients may benefit from tumor profiling and subsequent treatment with appropriately matched targeted therapies. The MOSCATO experience also demonstrates how measuring the impact of genome-driven oncology may be better accomplished within the context of a “real-world” drug development program than through the conduct of therapeutic studies whose explicit intent is determining whether this approach “works”.

MOSCATO is a landmark trial in the growing debate over the utility of genome-driven oncology. The results are encouraging and provide evidence-based support for continued pursuit of this treatment paradigm. Despite this positive result, MOSCATO again demonstrates the challenges of measuring and assigning value to this overall treatment approach. Their primary endpoint of a PFS ratio >1.3 makes use of the population-level phenomenon that PFS is generally lower with each subsequent line of therapy; however, this is not always the case at the individual patient level so the true baseline (null) rate is not expected to be 0%. Furthermore, patients with a very short PFS on prior therapy may have a PFS ratio >1.3 despite minimal absolute benefit, whereas patients with very long PFS on prior therapy may be perceived to have not benefited despite prolonged disease control or even response to matched therapy. Moreover, while 33% of patients with actionable alterations matched to therapy appeared to benefit from targeted treatment, this equated to only 8% of all patients successfully profiled. This overall rate was undoubtedly impacted by the fact that approximately half of patients with actionable alterations were not successfully matched to therapy. Unlike SHIVA which was itself a therapeutic study, matching patients in MOSCATO required the availability of a spot on a relevant therapeutic study open at the center. Additionally, many of the patients enrolled to the dose escalation portion of Phase I studies likely received subtherapeutic doses of the study drugs. Lastly, patients with a genomic alteration for which an approved therapy exists for their tumor type were not included in the study, an entirely understandable decision that nevertheless significantly underestimates the utility of sequencing by excluding therapy already known to confer benefit. Nonetheless, MOSCATO clearly demonstrates that the majority of patients who undergo comprehensive genomic screening still do not derive direct benefit. As researchers in this field we must acknowledge this reality while simultaneously hoping that improving knowledge, profiling, and drugs will raise this proportion over time.

The results of MOSCATO raise several important questions. For example, could similar results have been achieved with a more focused profiling effort that might be more easily adopted in the community? Nearly all the clinically actionable alterations identified in MOSCATO would be detectable by targeted hybrid capture next-generation sequencing alone, a technology that is capable of identifying all classes of genomic alterations. These data suggest that the more expansive and orthogonal information provided by whole exome sequencing and CGH arrays, respectively, may add little incremental value as an initial screen. One important exception may be the detection of fusions, which can be missed by

DNA-based hybrid capture technologies. Screening strategies may therefore benefit from supplementation with targeted RNA sequencing, especially in tumors without an identified driver on DNA sequencing. Similarly, 16% of patients with an actionable target clinically deteriorated before the results could be utilized for a match. We need to better understand how test turnaround time affects this type of attrition and optimize our workflows accordingly to compensate. Continuing to refine our operational approaches, biomarkers, and drugs, should improve the number of patients who benefit from to genome-driven oncology.

Perhaps the most important outstanding question is how we should define success in this field. For the first time since the advent of this approach to treating cancer, we are beginning to see the emergence of genomic biomarkers that may predict for response irrespective of cancer type, suggesting broad sequencing across tumor histologies will be necessary to identify these patients. For example, preliminary experience targeting *NTRK* fusions indicates that they confer exquisite sensitivity in a histology agnostic manner (9). Similarly, next-generation sequencing can identify patients with mismatch repair deficiency, a profile that predicts for dramatic and durable response to checkpoint inhibitors across tumor types and is estimated to be present in up to 3% of all cancer patients (10). We are rapidly approaching a time when as a community we must decide to either embark on broad sequencing across tumor histologies or accept missing these exceptional responses. Even setting these more dramatic examples aside, MOSCATO suggests that as many as 50% of patients may harbor potentially targetable alterations and that based on current approaches around 30% of these patients, or 15% overall, may benefit from matched targeted therapy by their definition. At a minimum, MOSCATO provides reason for continued optimism for the scientists, physicians, and patients working together to translate genome-driven oncology into improved outcomes for cancer patients.

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