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Basket Trials and the Evolution of Clinical Trial Design in an Era of Genomic Medicine

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Since the days of the ancient Greeks, the pathologic hallmarks of malignancy have been reflected in the language of oncology. Hippocrates was the first to use *carcinoma*—or crab—to describe the familiar invading sweep of tumor cells across tissue planes, and several hundred years later, Galen described the *oncos*—or swelling—of tumors from which the field of oncology takes its name. However, although the histopathology of malignancy has remained unchanged across several millennia, scientific advances of the modern era have begun to challenge earlier views of oncology, where patients were treated with an exclusive focus on the tissue of origin of a tumor. The translation of next-generation sequencing (NGS) into oncology practice has begun to demonstrate that although the primary site of origin of a tumor matters, so too does its genetic landscape.

The significance of classifying tumors based on defining genetic alterations has been particularly relevant for thoracic oncology. The development of tyrosine kinase inhibitors for patients harboring mutations in the epidermal growth factor receptor (*EGFR*) has been one of the success stories of translational research endeavors and has spurred efforts to identify other driver mutations in lung cancer.[1-3] National Comprehensive Cancer Network guidelines for non–small-cell lung cancer (NSCLC) now include genetic testing,[4] and the list of potentially actionable mutations continues to grow.[5] However, despite the tremendous promise of this new era of oncology, several challenges have emerged. First, a genetic classification and treatment strategy may not always follow the traditional boundaries of histopathology. Aberrant *HER2* signaling is well established in breast cancer but is also an oncogenic driver in a small subset of lung cancers.[6] Similarly, *BRAF* mutations are most often associated with melanoma[7] but can be found in hairy cell leukemia,[8] colon cancer,[9] lung cancer,[10] thyroid cancer,[11] and brain tumors.[12] Consequently, although we diagnose patients with lung cancer or breast cancer, the genetic makeup of a tumor may be just as important when considering treatment strategies. A lung tumor and a breast tumor with inappropriate activation of the same signaling pathways may share more molecular vulnerabilities with each other than with a lung or breast tumor lacking the same mutations. However, how are such patients to be identified and directed toward appropriate clinical trials? Even the most effective of targeted therapies fail to impress when evaluated in the wrong patient population, as illustrated by early trials with *EGFR* inhibitors in unselected patients.[13,14]

Furthermore, despite increasing recognition of the importance of genomic analysis in oncology practice, evaluating targeted therapies can present a formidable challenge when the mutations in question are rare and found across disease types. Some eminently targetable mutations may be so rare they are only discovered in the context of a negative trial. In recent reports, the mammalian target of rapamycin inhibitor everolimus caused extraordinary and durable efficacy for two specific patients, despite a lack of efficacy in bladder and thyroid cancers generally.[15,16] These exceptional responders were retrospectively found to harbor specific mutations in mammalian target of rapamycin signaling pathways, which rendered them uniquely sensitive to everolimus. If other patients with similar mutations can be identified, everolimus may well be the treatment of choice irrespective of tissue diagnosis. As our ability to probe the genome of an individual tumor continues to expand, so too must strategies for clinical trial design.

In the article accompanying this editorial, Lopez-Chavez et al[17] present the results of the CUSTOM (Molecular Profiling and Targeted Therapies in Advanced Thoracic Malignancies) trial, a so-called basket trial seeking to identify molecular biomarkers in advanced NSCLC, small-cell lung cancer, and thymic malignancies and to simultaneously evaluate five targeted therapies in patients grouped by molecular markers along with tumor histology. The five targeted therapies included erlotinib (*EGFR* mutations), the MEK inhibitor selumetinib (*KRAS*, *HRAS*, *NRAS*, and *BRAF* mutations), the AKT inhibitor MK2206 (*PIK3CA*, *AKT1*, and *PTEN* mutations), lapatinib (*HER2* mutations), and sunitinib (*KIT* and *PDGFRA* mutations). An attempt was made to evaluate each treatment in all three histologic subtypes, for a total of 15 study arms.

Basket trials are a new and evolving form of clinical trial design and are predicated on the hypothesis that the presence of a molecular marker predicts response to a targeted therapy independent of tumor histology. In the study reported by Lopez-Chavez et al,[17] the targeted therapies and actionable mutations were identified prospectively, with patients assigned in a nonrandomized way to a specific treatment arm. The intention of this design is to conduct several independent and parallel phase II trials. Of note, some trials also considered to have a basket design may start with the use of a targeted therapy in an unselected population followed by NGS in patients who respond to identify genetic biomarkers for subsequent prospective screening. Basket trials have generated an enormous amount of interest because

they implement a hypothesis-driven strategy incorporating precision medicine into clinical trials even for mutations that are rare or difficult to study solely within a disease-specific context. In early 2015, the National Cancer Institute (NCI) will be launching the NCI-MATCH (Molecular Analysis for Therapy Choice) trial, which plans to screen an estimated 3,000 patients, with enrollment of at least 1,000 patients, for a targeted drug combination, independent of tumor histology.[18] Similarly, to further evaluate the efficacy of treating tumors based on targets, the NCI-MPACT (Molecular Profiling-Based Assignment of Cancer Therapy) trial is randomly assigning patients with a mutation in a specific genetic pathway to either a targeted therapy for that pathway or a treatment not known to be pathway specific (ClinicalTrials.gov identifier NCT01827384).

The results of CUSTOM reveal the key strengths of the basket trial design: the ability to identify a favorable response to targeted therapy with a small number of patients and the ability to validate a clinical target. Only 15 patients with NSCLC and an *EGFR* mutation were enrolled onto the erlotinib treatment arm in this trial, but results demonstrated an overall response rate of 60%. This trial arm was closed early because of overwhelming published evidence of the efficacy of erlotinib, but the data nonetheless illustrate that with an appropriately paired target and therapy, large numbers of patients are not required to identify therapeutic efficacy. Among several emerging models for clinical trial design, a basket trial can be the proof-of-principle validation of a putative target. In future, novel targets may well be identified through an evaluation of exceptional responders before development of a basket trial. Indeed, an NCI-led initiative to identify and characterize exceptional responders for precisely this purpose is currently under way (ClinicalTrials.gov identifier NCT02243592).

The success of a basket trial depends in large part on the strength of the data linking the target and targeted therapy. For this trial design to work, two key conditions must be met: the tumor must depend on the target pathway, and the targeted therapy must reliably inhibit the target. Achieving both goals can be a matter of some complexity. In CUSTOM, the use of selumetinib as monotherapy did not achieve its primary end point in patients with *RAS* or *RAF* mutations. However, a 2013 phase II trial in patients with *KRAS* mutations demonstrated positive results using selumetinib not as monotherapy—despite KRAS activation of MAP kinase signaling—but rather in combination with docetaxel, highlighting that a functional in vivo response is not a certainty even with targeted therapies.[19] Preclinical evidence suggests that targeting MAP kinase signaling in *KRAS*-mutant lung cancers may depend on additional genetic aberrations, such as loss of key tumor suppressors.[20] As NGS technology continues to develop, basket trials may become more nuanced, with random assignment to specific trial arms based on both driver mutations and additional modifying mutations.

The challenges faced in CUSTOM also highlight concerns that will continue to shape clinical trial development in the genomic era. First, CUSTOM only succeeded in accruing to two of the planned 15 arms (erlotinib in NSCLC and selumetinib in NSCLC) because of feasibility issues with the low incidence of certain mutations in specific histology subtypes. In this sense, a basket trial that is completely independent of tumor histology may be more effective in truly addressing the efficacy of targeting a specific genetic aberration. The ongoing VE-BASKET trial evaluating the *BRAF* inhibitor vemurafenib in solid tumors and multiple myeloma is one example of this approach (ClinicalTrials.gov identifier NCT01524978).

In addition, despite growing interest in moving beyond histopathology in the development of targeted therapies, pathology does remain a clinically significant variable. The mutations evaluated in CUSTOM segregate along histologic lines, a reminder that—as is seen with *EGFR* mutations in NSCLC—the broader context in which a tumor develops can shape the rise of specific genetic mutations. Emerging data also indicate that the disease-specific context of a targetable mutation may determine whether the target represents a clinically valid end point. V600E *BRAF*–mutant melanoma or hairy cell leukemia can be exquisitely sensitive to *BRAF* inhibition, whereas many colon cancers with the same mutation are not.[7-9] As clinical trials evolve to integrate precision medicine, it is critical that enthusiasm for genetics does not push the still-valuable insights of histology out of the basket.

Finally, statistical considerations in novel clinical trial design will continue to play a central role. Ensuring that screening strategies reflect expected gene mutation frequencies will be a crucial calculation as basket trials move forward with ever more ambitious numbers of clinical arms, targeted therapy combinations, and complex collaborations. The upcoming NCI-MATCH trial is likely to involve more than 20 different drugs from 20 different pharmaceutical companies at as many as 2,400 clinical sites, highlighting the importance of thoughtful statistical design before trial activation. In addition, it is also important to consider the statistical issues surrounding the use of multiple comparators and the fact that given enough trial arms, there can be a statistically significant result by chance alone, whether or not the outcome is truly clinically valid.

Overall, tremendous advances in our understanding of cancer genetics have led to an exciting number of emerging targeted therapies. Clinical trial design must continue to evolve to take advantage of this ever-expanding body of knowledge. The basket trial is one way in which developing science is being integrated into clinical research in oncology. As with any other approach to translational medicine, the success of this strategy depends on the rigor of both preclinical development and preactivation trial design.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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REFERENCES

1. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004
2. Paez JG, Jänne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004
3. Hallberg B, Palmer RH: Crizotinib: Latest champion in the cancer wars? N Engl J Med 363:1760-1762, 2010
4. National Comprehensive Cancer Network: Clinical practice guidelines in oncology: Non-small cell lung cancer (version 3.2015). http://www.nccn.org/professionals/physician_gls/recently_updated.asp
5. Korpanty GJ, Graham DM, Vincent MD, et al: Biomarkers that currently affect clinical practice in lung cancer: EGFR, ALK, MET, ROS-1, and KRAS. Front Oncol 4:204, 2014
6. Ricciardi GR, Russo A, Franchina T, et al: NSCLC and HER2: Between lights and shadows. J Thorac Oncol 9:1750-1762, 2014

7. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-819, 2010

8. Tiacci E, Trifonov V, Schiavoni G, et al: BRAF mutations in hairy-cell leukemia. N Engl J Med 364:2305-2315, 2011

9. Prahallad A, Sun C, Huang S, et al: Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 483:100-103, 2012

10. Marchetti A, Felicioni L, Malatesta S, et al: Clinical features and outcome of patients with non–small-cell lung cancer harboring *BRAF* mutations. J Clin Oncol 29:3574-3579, 2011

11. Xing M, Alzahrani AS, Carson KA, et al: Association between *BRAF* V600E mutation and recurrence of papillary thyroid cancer. J Clin Oncol 33:42-50, 2015

12. Berghoff AS, Preusser M: BRAF alterations in brain tumours: Molecular pathology and therapeutic opportunities. Curr Opin Neurol 27:689-696, 2014

13. Niho S, Kubota K, Goto K, et al: First-line single agent treatment with gefitinib in patients with advanced non–small-cell lung cancer: A phase II study. J Clin Oncol 24:64-69, 2006

14. Crinò L, Cappuzzo F, Zatloukal P, et al: Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non–small-cell lung cancer (INVITE): A randomized, phase II study. J Clin Oncol 26:4253-4260, 2008

15. Wagle N, Grabiner BC, Van Allen EM, et al: Activating mTOR mutations in a patient with an extraordinary response on a phase I trial of everolimus and pazopanib. Cancer Discov 4:546-553, 2014

16. Wagle N, Grabiner BC, Van Allen EM, et al: Response and acquired resistance to everolimus in anaplastic thyroid cancer. N Engl J Med 371:1426-1433, 2014

17. Lopez-Chavez A, Thomas A, Rajan A, et al: Molecular profiling and targeted therapy for advanced thoracic malignancies: A biomarker-derived, multiarm, multihistology phase II basket trial. J Clin Oncol doi:10.1200/JCO.2014.58.2007

18. National Cancer Institute: Molecular Analysis for Therapy Choice (NCI-MATCH). http://deainfo.nci.nih.gov/advisory/ncab/164_1213/Conley.pdf

19. Jänne PA, Shaw AT, Pereira JR, et al: Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: A randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol 14:38-47, 2013

20. Chen Z, Cheng K, Walton Z, et al: A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. Nature 483:613-617, 2012

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