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Cancer researchers publish landmark "basket study"

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Researchers from Memorial Sloan Kettering Cancer Center (MSK) have announced results from the first published basket study, a new form of clinical trial design that explores responses to drugs based on the specific mutations in patients' tumors rather than where their cancer originated.

Published in the *New England Journal of Medicine*, the early phase II study, led by MSK Physician-in-Chief and Chief Medical Officer José Baselga, MD, PhD, looked at the effect of vemurafenib (Zelboraf) in multiple nonmelanoma BRAFV600-mutated cancers in 122 patients from 23 centers around the world. Vemurafenib previously has been proven to treat BRAFV600-mutated melanoma. People with lung, colorectal, and ovarian cancers were among those included in the study as well as people with rare diseases, such as Erdheim-Chester disease. Until this point, the efficacy of vemurafenib in nonmelanoma cancers has remained unexplored despite significant therapeutic potential.

"This study is the first deliverable of precision medicine. We have proven that histology-independent, biomarker-selected basket studies are feasible and can serve as a tool for developing molecularly targeted cancer therapy," said Dr. Baselga, the study's senior author. "While we can—and should—be cautiously optimistic, this is what the future of precision medicine looks like."

Basket studies permit the detection of early signals of activity across multiple tumor types simultaneously, while allowing for the possibility that tumor lineage might influence drug sensitivity. The first to follow

this model, this new study aims to explore treatment responses among tumors based on their mutation types and to identify promising signals of activity in individual tumor types that could be pursued in subsequent studies. The results will ultimately guide researchers in looking for different drug targets or developing therapies that combine vemurafenib with complementary treatments.

Basket studies also have the ability to greatly increase the number of patients eligible to receive certain drugs. The mixed efficacy seen in this study proves that drugs can reach patients beyond the current approved use but, expectedly, do not work for everyone. As a pioneering trial, this data demonstrates the promising benefits of basket studies and the need for more work to be done with these types of trials.

The findings illustrate the preliminary clinical efficacy of vemurafenib in multiple nonmelanoma BRAFV600-mutated cancers. Of the 122 trial participants, clinical activity was observed in various tumor types. Preliminary vemurafenib activity was observed in non-small cell lung cancer as well as Erdheim-Chester disease and Langherhans cell histiocytosis. Response rate and median progression-free survival in non-small cell lung cancer was 42 percent and 7.3 months, respectively. In Erdheim-Chester disease and Langherhans cell histiocytosis, response rate was 43 percent; despite median treatment duration of 5.9 months, no patients progressed during therapy. Anecdotal responses were seen in anaplastic pleomorphic xanthoastrocytoma, anaplastic thyroid cancer, cholangiocarcinoma, salivary duct cancer, ovarian cancer, clear cell sarcoma, and colorectal cancer (cetuximab combination only).

"This kind of study is a beneficial way to do rare tumor research because it allows us to open the study to patients with diseases that are completely underrepresented in clinical trials in general, such as anaplastic thyroid cancer and glioblastoma," said David Hyman, MD, the study's first author and Acting Director of Developmental Therapeutics

at MSK. "By broadening eligibility, we are translating potential benefits to as large a patient population as possible."

This clinical trial is the first in an impending wave of such studies focused on cancer-related mutations identified through the huge amounts of genomic data generated in recent years. It highlights the importance of further investigation into precision medicine, a promising area that has recently received attention from President Obama and the National Cancer Institute, among others. Last May, MSK launched an initiative in this space—the Marie-Josée and Henry R. Kravis Center for Molecular Oncology—that works to transform cancer care through genomic analysis of patient-derived tumors. Currently the center is analyzing 410 of the most important cancer genes in thousands of patients.

"We now have the landscape of all the most frequent cancer-causing mutations in the majority of tumor types, and we know there are a number of genes that are frequently mutated in some tumors and less frequently in others," explained Dr. Baselga. "The next step is exploring appropriate drug combinations, knowing that these cells have a finite number of pathways."

Full findings from the study can be found in the August 20 issue of the *New England Journal of Medicine*.

More information: "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations." *NEJM*. DOI: 10.1056/NEJMoa1502309

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