Trial suggests total neoadjuvant therapy for locally advanced rectal cancer is safe

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Results from the first experimental arm using veliparib as part of total neoadjuvant therapy (induction chemotherapy followed by chemoradiotherapy and surgery; TNT) in patients with locally advanced rectal adenocarcinoma on the NRG Oncology Phase II clinical trial NRG-GI002 were recently presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. Results were reported on the primary endpoint of pathological regression via the neoadjuvant rectal cancer (NAR) score, a short-term clinical trial surrogate endpoint.

After treatment with a combination chemotherapy regimen called mFOLFOX6, researchers combined veliparib, a poly (ADP-ribose) polymerase (PARP) inhibitor or a drug that kills cancer cells by blocking a protein called PARP, with another chemotherapy drug named capecitabine, and radiotherapy in patients who had locally advanced Stages 2 or 3 rectal cancer. Patients on the control arm got the same therapy with the omission of veliparib. In the first experimental arm of NRG-GI002, veliparib was added to radiotherapy and chemotherapy treatment regimens because PARP inhibitors, like veliparib, have been shown to enhance the effectiveness of radiotherapy by interfering with a patient's DNA repair mechanisms and thus killing or reducing tumor cells or the amount of normal tissue that needs to be removed. Results from the overall study demonstrate that the TNT approach of therapy is safe and associated with high rates (>90%) of chemotherapy completion. However, the addition of veliparib did not demonstrate a significant improvement in reducing the amount of cancer present at the time of surgery. The primary endpoint of the mean Neoadjuvant Rectal (NAR)

Score (lower number reflects more downstaging) was 12.6 for the control arm and 13.7 for the experimental arm (p=0.69). There were numerically more patients who achived a pCR with veliparib, though (22% vs. 34%; p=0.14). This first experimental arm results demonstrated that the addition of veliparib was associated with more short-term side effects and reduced completion of chemoradiation (85% vs. 70%; p=0.026). The most common, grade 3 and 4 side effects that were experienced on the first NRG-GI002 experimental arm included diarrhea and cytopenias. Importantly, these side effects did not appear to negatively impact short term patient outcomes.

"NRG-GI002 is intended to serve as a platform to test novel agents, such as veliparib, or other novel hypotheses using a total neoadjuvant treatment for rectal cancer as part of a phase II clinical trial platform," stated Thomas J. George, MD, FACP, of University of Florida Health Cancer Center and lead author of the abstract for NRG-GI002. "The goal of this study was to build upon the encouraging results seen with veliparib in the phase I trial that produced few dose-limiting toxicities. Our randomized phase II trial combined 400mg PO BID veliparib with chemoRT followed by surgery to observe improvement in patients' NAR score that would translate into improved disease free and overall survival. Unfortunately, we did not see an improvement with the use of veliparib. However and very importantly, we have now established that TNT can be safely and successfully delivered to patients with locally advanced rectal cancer. This ensures all patients get the treatments they need and gives us many opportunities to further improve care for this group of patients."

Future direction on this trial includes continued analysis of secondary endpoints and biomarkers to determine which specific patients achieved benefit from the addition of veliparib and why. An ongoing second experimental arm is observing the impact of the monoclonal antibody pembrolizumab in combination with capecitabine and radiotherapy after

induction mFOLFOX6 to determine if immunotherapy is also a safe, effective option for treating locally advanced rectal cancer. This second arm has completed enrollment with results eagerly awaited. Additional arms are in active development with the goal of improving outcomes for patients with this disease.

More information: George TJ, Yothers G, Hong TS, Russell MM, You YN, Parker W, Jacobs SA, Lucas PC, Gollub MJ, Hall WA, Kachnic LA, Vijayvergia N, Wolmark N. NRG-GI002: A Phase II Clinical Trial Platform using Total Neoadjuvant Therapy (TNT) in Locally-advanced Rectal Cancer (LARC): First Experimental Arm (EA) Initial Results. Abstract presented at the annual meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL.

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