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Somatic Driver Gene Alterations are Associated with Predictive Anticancer Response and Prognostic Assessment in Pancreatic Ductal Adenocarcinoma

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The prognosis of Pancreatic ductal adenocarcinoma (PDAC) is extremely poor, and most patients with PDAC still receive palliative chemotherapy. There is an increased use of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) in the treatment of PDAC; however, it is noteworthy that there are few validated biomarkers of anticancer response, particularly in Asian populations. Using a cohort of 115 Korean patients, we identify genes associated with clinical features and drug sensitivities. Notably, we found SMAD4, a frequently mutated gene in PDAC patients, to be associated with a more favorable prognosis in response to FOLFIRINOX chemotherapy. Among the responders, 37 mutations, including SMAD4, with high variant allele frequencies, exhibited significant associations with the FOXO/SMAD signaling pathway and the DNA damage response (DDR). Importantly, somatic mutations in driver genes of the FOXO/SMAD signaling pathway were mutually exclusive with the loss of DDR pathway driver genes, suggesting distinct alternative mechanisms underlying FOLFIRINOX responsiveness. Among the mutually exclusive or co-occurring gene pairs, we identified a substantial hazard ratio and a positive prognosis associated with the FOXO/SMAD gene group-MDC1 (DDR gene) pair. This discovery not only underscores the established significance of DDR but also highlights the pivotal role of the FOXO/SMAD pathway in the mode of action of FOLFIRINOX. Considering the documented interactions among DDR, FOXO/SMAD pathways, and the hedgehog pathway, we propose an intriguing hypothesis regarding their intricate interplay, potentially strengthened by FOLFIRINOX's unique hedgehog inhibition, which may contribute to its effectiveness. Finally, we observed significant correlations between clinical features, such as the primary tumor location and metastatic progression, and SMAD4 mutations, resulting in a significantly improved prognosis with FOLFIRINOX compared to alternative chemotherapies like Gemcitabine and Abraxane. Together, these findings shed new light on the potential for development of anticancer therapy and prognostic prediction platform using the

personalized model of pancreatic cancer.