1463 ADDITION OF LOSARTAN TO FOLFORINOX AND CHEMORADIATION DOWNREGULATES PRO-INVASION AND IMMUNOSUPPRESSION ASSOCIATED GENES IN LOCALLY ADVANCED PANCREATIC CANCER

[1]Rakesh Jain, [1]Yves Boucher, [1]Jessica Posada, [2]Spencer Rosario, [1]Liqun Gu, [1]Ashwin Kumar, [1]Heena Kumra, [1]Mari Mino-Kenudson, [1]Nilesh Talele, [1]Dan Duda, [1]Dai Fukumura, [1]Jennifer Wo, [1]Jeffrey Clark, [1]David Ryan, [1]Carlos Fernandez-del Castillo, [1]Theodore Hong, [3]Mikael Pittet, [1]Sonu Subudhi*. *[1]Massachusetts General Hospital, Boston, MA, USA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [3]University of Geneva, Geneva, Switzerland*

Background Adding losartan to FOLFIRINOX (FFX) chemotherapy followed by chemoradiation (CRT) resulted in 61% R0 surgical resection in our phase II trial in patients with locally advanced pancreatic cancer (LAPC). Here we identify potential mechanisms of benefit by assessing the effects of neoadjuvant losartan+FFX+CRT versus FFX+CRT on the stromal tumor microenvironment.

Methods We performed a gene expression analysis of RNA extracted from pancreatic cancer tissue sections and immunohistochemistry (IHC) for cancer cells and immune cells using archived surgical samples from patients treated with losartan +FFX+CRT (**NCT01591733**), FFX+CRT (**NCT01591733**) or surgery upfront, without any neoadjuvant therapy. We then assessed whether certain gene sets could stratify the overall survival (OS) of patients.

Results Neoadjuvant losartan+FFX+CRT and FFX+CRT increased the expression of genes linked to vascular normalization, transendothelial migration of leukocytes, T cell activation and cytolytic activity, and dendritic cell (DC) related genes versus no neoadjuvant treatment. In comparison to FFX +CRT, losartan+FFX+CRT downregulated pro-invasion, immunosuppression, and M2 macrophages-related genes, and upregulated genes associated with tumor suppression, including the p53 pathway. Furthermore, immunostaining revealed significantly less residual disease in lesions treated with losartan +FFX+CRT versus FFX+CRT. Losartan+FFX+CRT also reduced $CD4^{+}FOXP3^{+}$ regulatory T cells in PDAC lesions with a complete/near-complete response. OS was associated with DC and antigen presentation genes for patients treated with FFX+CRT, and with immunosuppression and invasion genes or DC– and blood vessel-related genes for those treated with losartan+FFX+CRT.

Conclusions Adding losartan to FFX+CRT reduced pro-invasion and immunosuppression-related genes, which were associated with improved treatment outcomes in patients with LAPC. We have shown in murine models of pancreatic ductal adenocarcinoma that the angiotensin receptor 1 blocker losartan improves the delivery and efficacy of cytotoxic agents. Our phase II trial – stemming from our preclinical findings – in patients with LAPC showed that losartan plus FFX chemotherapy followed by CRT led to high rates of complete surgical resection. Here, we identified the potential mechanisms of benefit of neoadjuvant losartan+FFX+CRT. We show that both losartan+FFX+CRT and FFX+CRT improved the expression of genes linked to vascular normalization, transendothelial migration of leukocytes, T cell activation, cytolytic activity and dendritic cell maturation, effects mediated by chemotherapy. In addition, losartan+FFX+CRT downregulated immunosuppression and pro-invasion-related genes, likely mediated by losartan. These findings suggest that losartan potentiates the benefit of FFX+CRT by reducing immunosuppression and invasion, and thus, may help overcome resistance to immunotherapy.

Ethics Approval The study was approved by institutional review board (IRB) of Mass General Brigham (IRB protocol number: 2022P001372).

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1463