UNIVERSITÀ DEGLI STUDI DI PADOVA

# PROJECT

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| Tutor's Name | Sara De Martin |
| Cotutor's Name | Daniela Gabbia |

| 1) Project title |
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| Investigating novel immunotherapy strategies to treat liver cancer |
| 2)Abstract (max 500 words) |
| In the last years, checkpoint blockade has become a major focus in the immunotherapy of the two main primary form of cancer affecting the liver, i.e., hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Antibodies inhibiting checkpoints, such as anti-programmed death (PD)-1 and PD-L1, are a novel class of inhibitors suppressing tumours by modulating the interaction between immune and tumour cells. In particular atezolizumab, a monoclonal antibody inhibiting PD-L1, is able to restore T-cell–mediated antitumor activity. Interestingly, atezolizumab in association with bevacizumab has been recently approved for advanced or unresectable HCC, and several clinical trials involving atezolizumab and other checkpoint blockade inhibitors are currently ongoing in HCC and CCA patients, with conflicting results in terms of safety and tolerability, and overall response rate. However, several limitations of immune checkpoint blockade monotherapy have been emerged, leading to a tremendous interest in developing combination immunotherapy strategies, including dual immune checkpoint blockade, or combination with chemotherapy or other immunomodulatory agents. With this project, we aim at testing different strategies to improve the efficacy of PD-L1 inhibition *via* the combined restoration of T cells and other immune cell (NK cells, APC cells) response against liver cancer. Beside targeting NK and APC cells by different approaches (stimulation by therapeutic ILs, or antibodies), we will take advantage of innovative formulations designed and prepared by our collaborators.<br>This combined, PD-L1-based, approach could lead to:<br>1) increased efficacy,<br>2) efficient delivery to the tumour site since the overexpression of PD-L1 characterizes liver tumours.<br>To improve the translational value of this project, we will also perform an immunohistochemical study on liver biopsies of HCC and CCA patients, to obtain new insights into the role of HCC and CCA aetiology in tumour development. Such approach will allow to unravel whether different liver diseases lead to different immune phenotypes in the tumour microenvironment during HCC and CCA progression, and this might open the road to the personalization of HCC and CCA therapy, leading to an increase of efficacy in selected patients. |