Poster 899: GNS561, A NEW ORAL CLINICAL-STAGE SMALL MOLECULE COMBINED WITH ANTI-PD1 SHOWED REMARKABLE ANTI-TUMOR EFFECTS IN A TRANSGENIC IMMUNOCOMPETENT HEPATOCELLULAR CARCINOMA MOUSE MODEL (ASV-B)

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Background

Lysosome has been described as a target of interest for cancer therapy. GNS561, a new oral lysosomotropic small molecule currently studied in a Phase Ib/IIa international clinical trial, displays a meaningful activity against several tumor types, specifically in primary and secondary hepatic lesions.

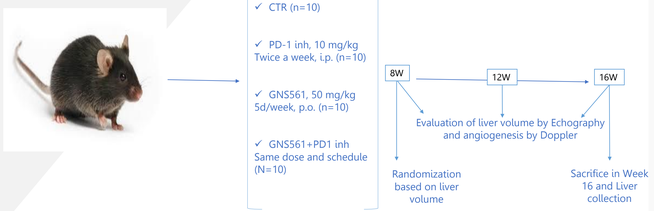
GNS561 shows an intrinsic anti-tumoral activity and inhibits in vitro TGF-β1 signalization pathway through inhibition of the phosphorylation of SMAD2/3 as well as the inhibition of TGF-β1 maturation.
As TGF-β1 signaling selectively through SMAD3, significantly upregulates PD-1 in the context of T-Cell Receptor engagement (B. Park, "TGF-β1-Mediated Smad3 Enhances PD-1 Expression on Antigen-Specific T Cells in Cancer. Cancer discovery. 6. 10.1158/2159-8290.CD-15-1347. (2016)), GNS561's anti TGF-β1 signaling properties are hypothesized to be beneficial to enhance PD-1 inhibitors activity in HCC.

Checkpoint inhibitors are more and more studied in hepatocellular carcinoma (HCC) with difficulties to prove benefits on the survival, thus, a combination of GNS561 with a PD-1 inhibitor was tested in the ASV-B transgenic mouse model of HCC.

Methods

Transgenic mouse model: ASV-B is a transgenic mouse model (C57BL/6J) that spontaneously develops a reproducible stage defined HCC, with hyperplasia at week (W) 8, followed by nodular stage at W12, then diffuse carcinoma stage at W16-20. Transgene consists in the fusion between the antithrombin promotor and the T oncogene of SV40, on the Y chromosome.
One of the advantage of this model is that it keeps a fonctionnal immune system which is needed to study checkpoint inhibitors.

Study Design:



Results

1 GNS561 alone or in combination with a PD-1 inhibitor rapidly decreases the tumour burden in ASV-B mice livers

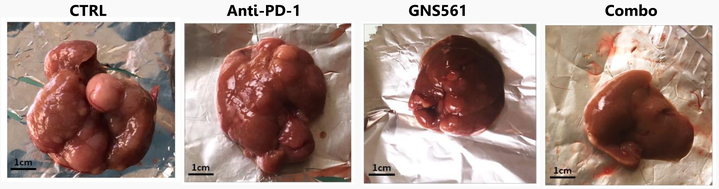


Figure 1: Representative livers from ASV-B mice treated with the vehicle, the murin PD-1 inhibitor, GNS561 or a combination of GNS561 and the PD-1 inhibitor

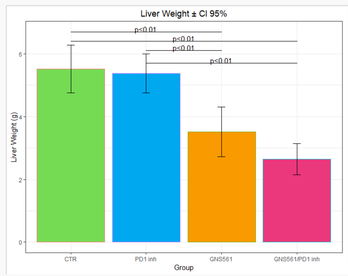


Figure 2: GNS561 alone or in combination decreases the liver weights at sacrifice

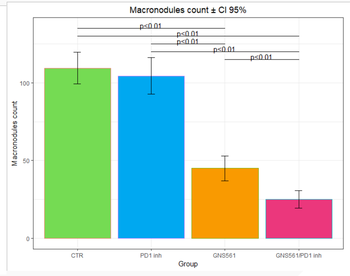


Figure 3: GNS561 alone or in combination decreases the number of liver macronodules at sacrifice

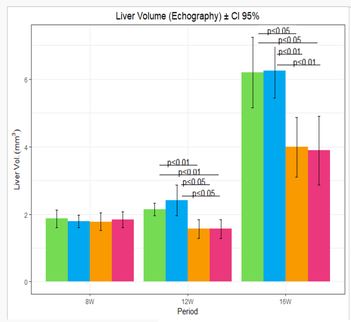


Figure 4: GNS561 alone or in combination rapidly decreases the liver volume from W12

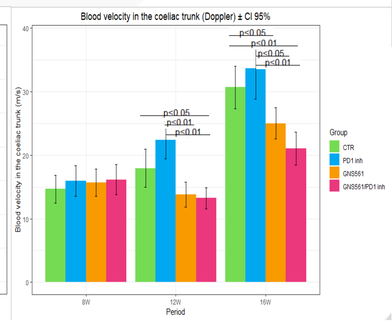


Figure 5: GNS561 alone or in combination rapidly decreases the blood velocity in the coeliac trunk from W12

2 GNS561 alone or in combination with a PD-1 inhibitor inhibits TGF-β1 signalization pathway via the inhibition of SMAD3 phosphorylation

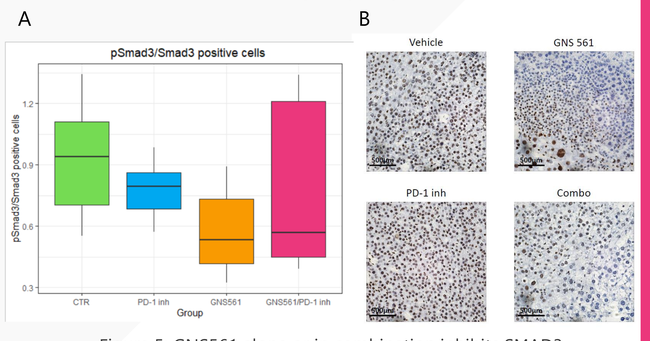


Figure 5: GNS561 alone or in combination inhibits SMAD3 phosphorylation

3 GNS561 alone or in combination with a PD-1 inhibitor allows a better recolonisation of CD8 positive cell in the tumour territory

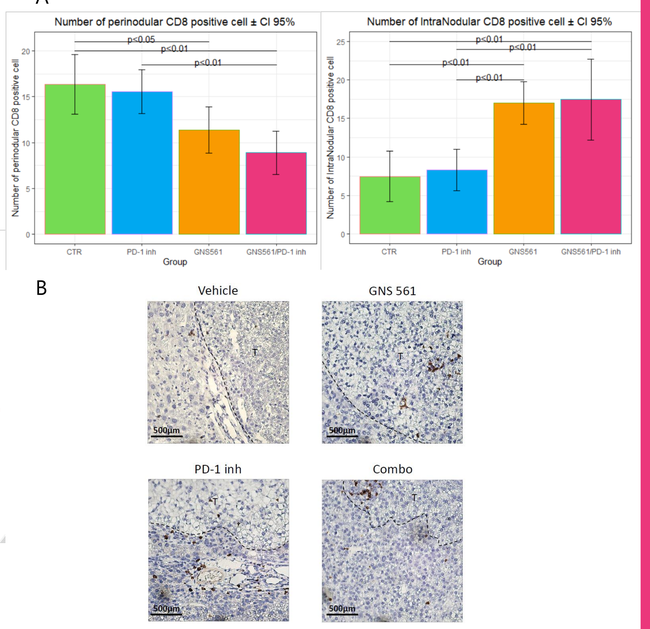


Figure 7: GNS561 alone or in combination increases the number of CD8⁺ cells in the tumour (A and B)

Conclusion

GNS561 alone or in combination with a PD-1 inhibitor shows a significant anti-tumoral activity with a dramatic decrease in the number of macronodules, liver volume and weight as well as a decrease in the blood velocity in the coeliac trunk.

Moreover, it is shown that in vivo, GNS561 inhibits the signalization pathway of TGF-β1 by inhibiting the phosphorylation of SMAD3 and helps CD8 positive cell to recolonize the tumoral territories.

Thus, a combination of GNS561 with a PD-1 inhibitor could be of great interest in the treatment of hepatocelullar carcinomas and potentially other cancers.

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