1993 : GNS561, A NEW ORAL CLINICAL-STAGE SMALL MOLECULE COMBINED WITH A PD-1 INHIBITOR 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 inhibits TGF-β1 maturation. As TGF-β1 signaling significantly upregulates PD-1 in the context of T-Cell Receptor engagement (1), anti TGF-β1 signaling properties of GNS561 are assumed to be beneficial to enhance PD-1 inhibitors activity in HCC.

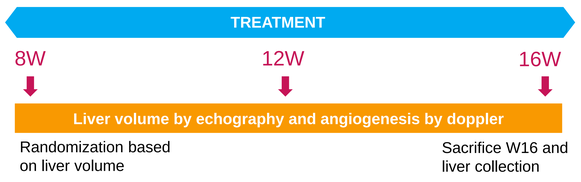
Thus, a combination of GNS561 with a PD-1 inhibitor was tested in the ASV-B transgenic mouse model of HCC.

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 functional immune system which is needed to study checkpoint inhibitors.

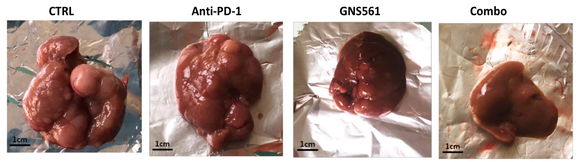
A Study Design

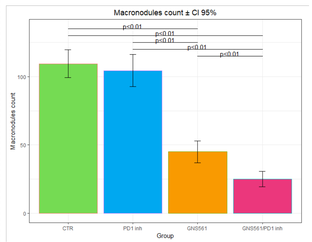
- CTRL (n=10)
- PD-1 inh 10 mg/kg twice a week i.p. (n=10)
- GNS561 50 mg/kg 5 days/week p.o. (n=10)
- GNS561 + PD-1 inh same dose and schedule (n=10)



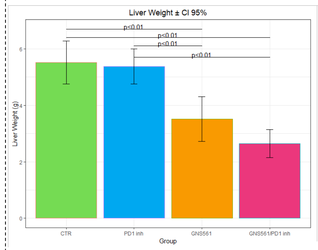
Results

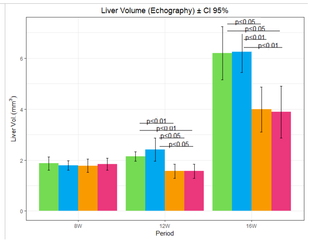
B GNS561 alone or in combination with a PD-1 inhibitor rapidly decreases the tumour burden in ASV-B mice livers



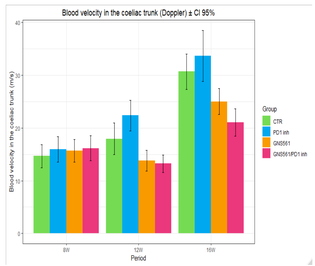


Group	Macronodules count		Liver weights (g)	
	Mean	% Decrease Compared to CTRL	Mean	% Decrease Compared to CTRL
CTRL	109.4	na	5.54	na
Anti-PD-1	104.4	-4.60%	5.37	-3.10%
GNS561	45.1	-59%	3.51	-37%
Combo	25.2	-77%	2.65	-52%

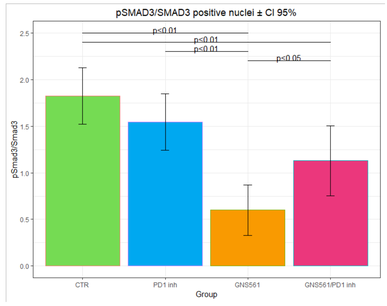


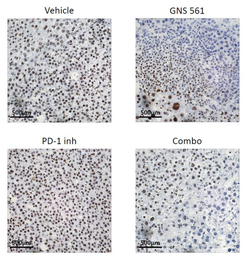


C GNS561 alone or in combination rapidly decreases the blood velocity in the coeliac trunk from W12



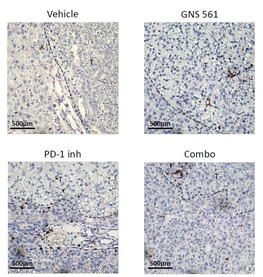
D GNS561 alone or in combination with a PD-1 inhibitor inhibits TGF-β1/SMAD signalization pathway (inhibition of SMAD3 phosphorylation)

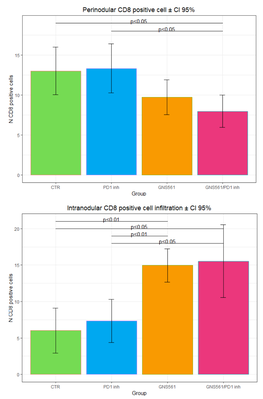




Representative pictures of pSMAD3 expression in liver at sacrifice (W16)

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





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 carcinoma and potentialy other cancers.

References & Contacts

1. B. Park et al, TGF-β1-Mediated Smad3 Enhances PD-1 Expression on Antigen-Specific T Cells in Cancer. Cancer discovery. 10.1158/2159-8290. CD-15-1347. (2016)

Conflicts of interests: PH, MR, CS, SB, CA and ER are employed by Genoscience Pharma, that is the sponsor of the study. PH, CS, SB, CA and ER are shareholders of Genoscience Pharma.

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