Immune-remodeling effects of lenvatinib plus anti-PD1 in a murine model of hepatocellular carcinoma

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1. INTRODUCTION

- Lenvatinib is approved as first-line therapy for advanced hepatocellular carcinoma (HCC).
- Immune checkpoint inhibitors are showing promising results, but only ~20% of the patients respond.
- Phase Ib data in combination with pembrolizumab, an anti-PD1 checkpoint inhibitor, is promising (ORR: 46% by mRECIST per IIR, median survival: 22 months).
- This combination is currently assessed in phase III vs. lenvatinib alone.

2. HYPOTHESIS AND AIMS

Lenvatinib has immune-modulating potential and its combination with anti-PD1 checkpoint inhibitors might improve its anti-tumoral effect in HCC.

The aims of the study are:

- To investigate the anti-tumoral effect of the combination of lenvatinib +/- anti-PD1 therapy.
- To identify the immune effects of lenvatinib alone or in combination with anti-PD1 therapy.
- To define potential biomarkers of response to the combination therapy.

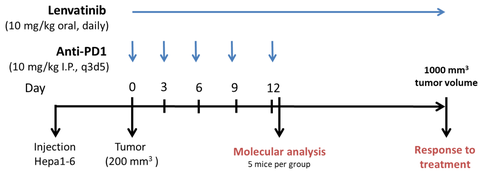
3. METHODS

We generated a syngeneic HCC model by injecting Hepa1-6 cells in C57BL/6J mice (n=59). Animals were randomized to receive:

1. Placebo
2. Lenvatinib
3. Anti-PD1
4. Combination therapy

Flow cytometry, immunohistochemistry and transcriptomic analyses were performed in tumor and blood samples from 20 animals sacrificed at day 13.

The rest of the mice were monitored to measure tumor growth and response to treatment.



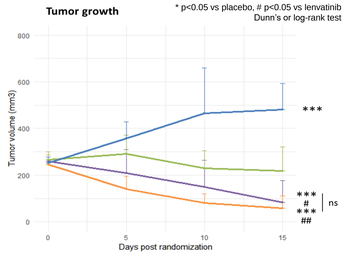
We generated a molecular signature capturing the transcriptomic changes induced by the combination therapy.

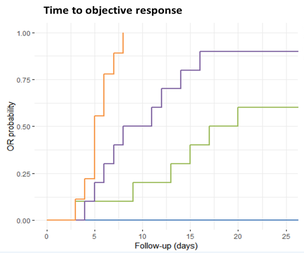
This signature was then assessed in a cohort of 228 human HCC to identify patients that would be ideal targets of the combination treatment.

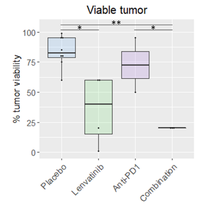
4. RESULTS

Anti-tumoral effect of lenvatinib plus anti-PD1 combination

- Mice treated with lenvatinib, anti-PD1 or combination therapy presented a decrease in tumor growth. Response to treatment was faster in the combination arm compared to the other treatments.
- Histological analysis showed a reduction in tumor viability in the combination arm.

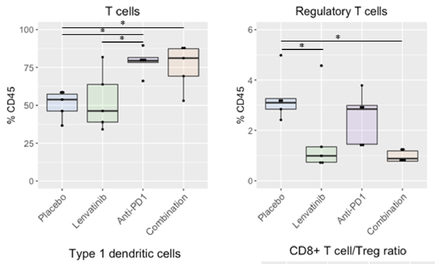


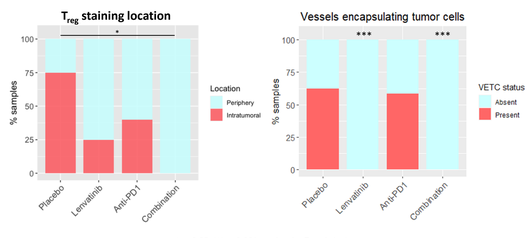


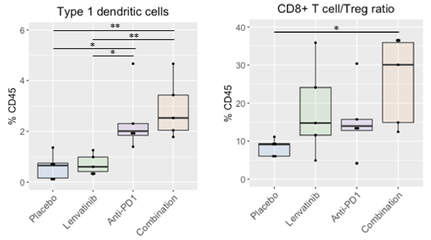


Immune cell population and microenvironment analysis

- Tumors from animals treated with anti-PD1 and combination therapy presented increased T cell and dendritic cell infiltration.
- Mice receiving lenvatinib and combination therapy showed a reduction in regulatory T cell infiltrate (T_{reg}), T_{reg} intratumoral location, and tumor vasculature.
- Only the combination treatment was able to significantly increase the CTL to T_{reg} ratio, associated with immune activation.
- No changes in circulating immune cells were detected.





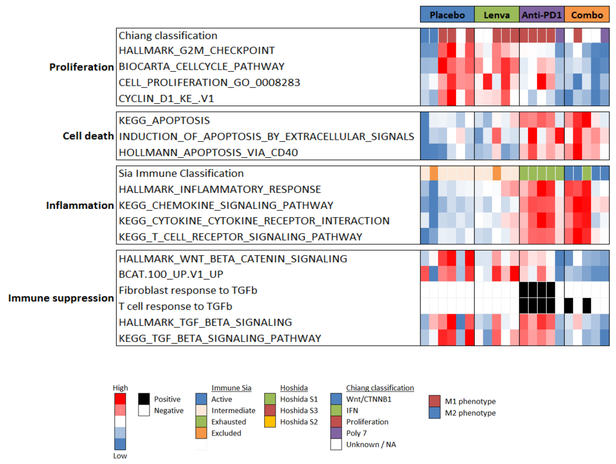


* p<0.05, *** p<0.001 vs placebo Dunn's test

* p<0.05, ** p<0.01 Tukey test

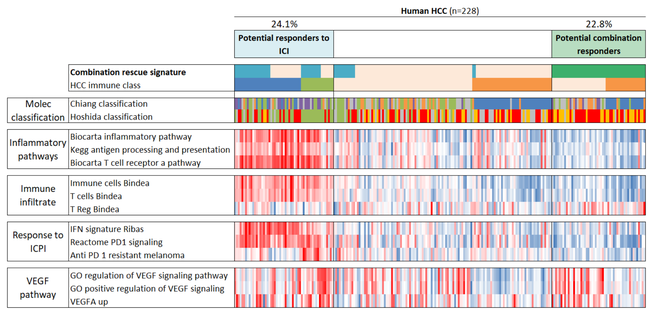
Gene expression profile

- The combination therapy induced a reduction in cell proliferation and increased apoptosis signaling.
- All treatments increased the inflammatory signaling in the tumor.
- Only the combination group presented gene signatures associated to an activated immune infiltrate.



Identification of potential responders to combination therapy

- 22.8% (52/228) of human HCC patients presented the combination rescue signature, along with reduced pro-inflammatory signaling, high T_{reg} levels and VEGF signaling. These tumors could harbor primary resistance to anti-PD1 but potentially benefit from the booster effect of the combination treatment.
- 24.1% (55/228) of the cohort belonged to the HCC immune class, previously proposed as a marker of primary response to ICI.
- Altogether, ~50% human HCC could respond to the combination treatment.



5. CONCLUSIONS

- The combination treatment showed anti-tumoral potential and reduced the time to objective response compared to monotherapies.
- Lenvatinib exerted an immunomodulatory effect on the tumor infiltrate characterized by a reduction of T_{reg} infiltrate and inhibition of immunosuppressive pathways. Its combination with anti-PD1 favored the generation of an activated immune profile.
- The obtained gene signature could be a tool for identifying ideal candidate patients to combination therapy.

6. DISCLOSURE

This study was supported by a research grant from EISAI.

7. CONTACT INFORMATION

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