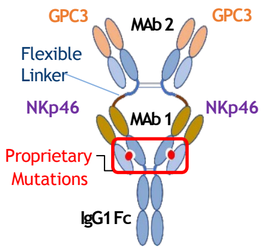
1074 Reversal of resistance to PD-1 checkpoint blockade in Hepatocellular Carcinoma by NY-303, a GPC3 NK cell engager, inhibiting Wnt-GPC3-beta catenin signaling.

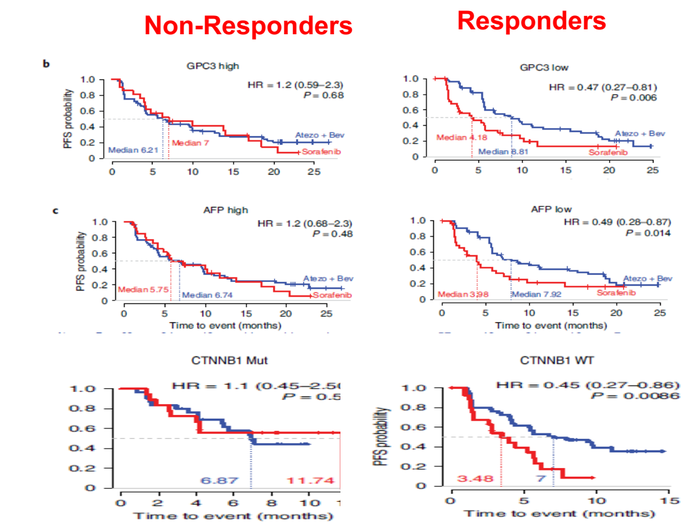
Vishal Khairnar1, Wei Li1, Armin Rath2, Jean Kadouche2, Dan Chiche2, Daniel Teper2, Ofer Mandelboim3 and Tony Arulanandam1. (1) Cytovia Therapeutics, Natick, MA, USA , (2) Naya BioSciences, Miami, FL, USA, (3) Hebrew University Medical School, Jerusalem, Israel .

Introduction & Background

A retrospective biomarker analysis of the Phase III and Phase Ib clinical trials with PD-1 checkpoint plus angiogenesis inhibitor combinations (Atezolizumab + Bevacizumab) in Hepatocellular Carcinoma patients (HCC) (IMbrave150 and GO30140 studies respectively) have identified that increased expression of biomarkers GPC3, AFP and activated beta-catenin are associated with resistance to PD-1 checkpoint blockade [1]. Vice versa decreased levels are associated with response to PD-1 checkpoint blockade and increased progression free and overall survival in responder patients. Having demonstrated previously that our NY-303 NK cell engager bispecific antibody targeting GPC3+NKp46 can mediate potent killing of HCC tumors with concomitant increase in NK cell infiltration of HCC tumors and reduction in HCC biomarker AFP levels we set out to evaluate if NY-303 could down modulate-cell surface GPC3 and inhibit Wnt- beta-catenin signaling and beta-catenin activation resulting in increased immune infiltration, thereby–rendering HCC patients sensitive to PD-1 checkpoint blockade.



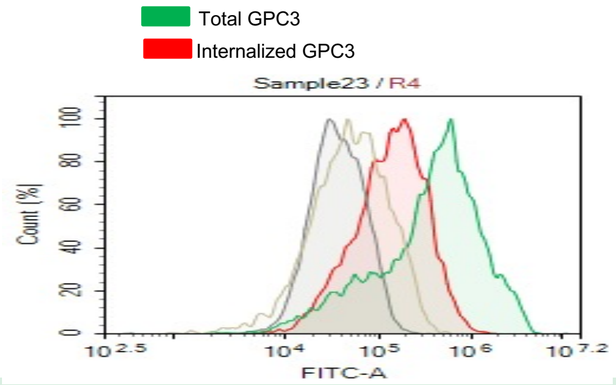
NY-303 Uniquely Positioned to Address PD-1 Checkpoint Refractory Patients in HCC.



Retrospective biomarker analysis in Atezo + Bevacizumab refractory HCC patients (PFS: HR >1.0) were associated with GPC3 high, AFP high and CTNNB1 mutations (activated β-catenin) and HCC disease progression. Responder patients (PFS: HR < 0.5) were associated with GPC3 low, AFP low and CTNNB1 WT (non-activated β-catenin) levels. [1] A Xu et al Nat Med 2022

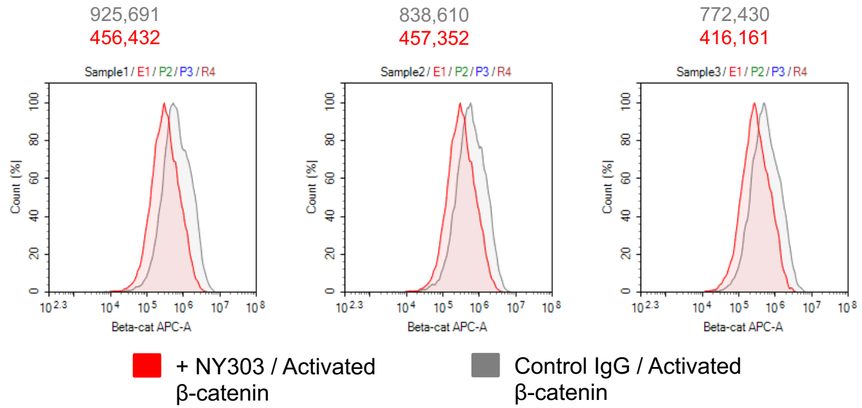
Results & Methods

NY-303 Induces GPC3 Internalization in HCC Tumors.



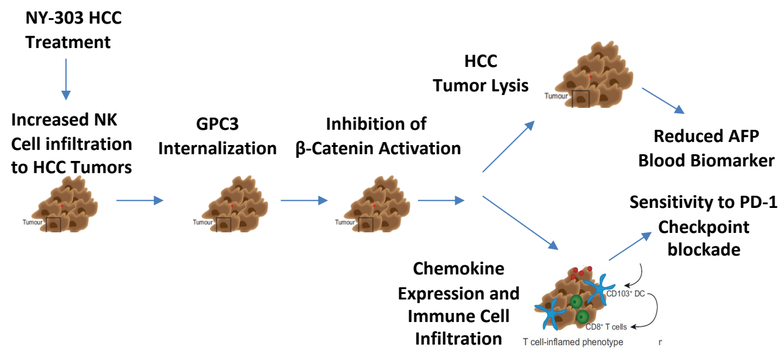
PBNK Cells were co-cultured with HCC tumors (Hep3B) in the presence of NY-303 (10 ug/ml) or hIgG1 isotype control for 6 hrs. HCC tumors were treated with 0.2M Glycine Buffer or control Buffer to evaluate GPC3 internalization. Cells HCC tumors were stained with NY-303-AFP or control IgG1-AFP labeled antibodies and analyzed GPC3 expression by Flow cytometry.

NY303 Inhibits Wnt/beta catenin signaling and beta-catenin activation.



PBNK Cells were co-cultured with HCC tumors (Hep3B) in the presence of NY-303 (10 ug/ml) or hIgG1 isotype control for 6 hrs. HCC tumors were fixed, permeabilized and stained with a beta-catenin antibody that selectively recognizes activated form of β-catenin and analyzed by Flow cytometry.

NY-303 Mechanism of Action for Increased Immune Cell Infiltration and HCC Tumor Killing Phase 1/2A Clinical Trial



NY-303 treatment facilitates NK cell infiltration from blood to HCC tumors and GPC3 down-modulation followed by inhibition of Wnt-beta catenin signaling. This results in inhibition of beta-catenin activation and thereby increasing chemokine expression and immune cell infiltration to HCC tumors making these tumors/patients sensitive to PD-1 checkpoint blockade and turning the tumor from “cold” into “hot”.

Conclusions

NY-303 has the Potential to Reverse PD-1 Checkpoint Resistance in HCC Patients and Provides a Strong Rationale for Testing NY-303 in PD-1 Refractory Patients.

- NY-303 Mediates potent killing of HCC tumors via multiple mechanisms including NK redirected Killing, ADCP and Complement fixation.
- NY-303 induces GPC3 down-modulation in HCC Tumors and inhibits β-catenin activation.
- NY-303 mediated inhibition of β-catenin activation can reverse immune exclusion and increase immune cell infiltration to tumors in HCC patients that are refractory to PD-1 checkpoint blockade.
- These results suggest NY-303 has the potential to reverse PD-1 checkpoint resistance in HCC patients and provides a rationale for NY-303 sequencing and combination treatment with PD-1 checkpoint blockade in HCC.
- The data further support clinical development of NY-303. The Phase 1/2A clinical studies will assess safety and early efficacy in HCC patients using clinical endpoints like time to progression and a validated HCC disease biomarker AFP. Start of the Phase 1 is planned for H1 2025.

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