AACR poster # 4499

The peptide-drug conjugate sudocetaxel zendusortide (TH1902) potentiates anti-tumoral activity of the anti-PD-L1 checkpoint inhibitor and induces immune cell infiltration in a B16-F10 syngeneic melanoma model

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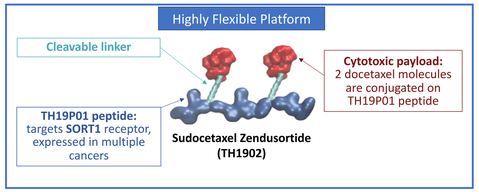
Introduction

SORTILIN (SORT1) RECEPTOR IN CANCER

- Sortilin receptor (SORT1) is preferentially expressed in many cancers compared to healthy tissues, which makes it an attractive target for cancer drug development.
- SORT1 is a scavenger receptor involved in the internalization of peptides into cells via the endosomal/lysosomal pathway (cellular shuttle system).
- SORT1 is known to be highly expressed in various tumor types such as TNBC (59%), invasive ductal breast (79%), ovarian (>90%), endometrial (>90%), and melanoma (>90%). (See AACR POSTER #3942 for more details)

SORT1⁺ TECHNOLOGY™ PLATFORM

- **SORT1⁺ Technology™** is an innovative oncology platform consisting of novel peptides which target the SORT1 receptor.
- Targeting sortilin receptors with these peptide-drug conjugates (PDC's) leads to receptor-mediated internalization (endocytosis) of well-established anti-cancer agents (e.g., docetaxel, doxorubicin, curcumin) that are attached to the novel proprietary peptide.
- Once inside the cancer cells, active drug is released from the peptide and exerts its cytotoxic effect directly on the cancer cell.



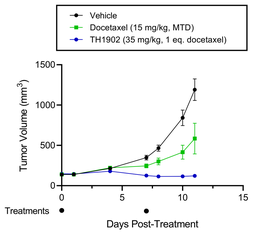
IMMUNE MODULATORS LANDSCAPE

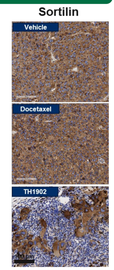
- Immune checkpoint blocker therapy has shown survival benefits for some patients with cancer.
- Many individuals remain refractory or acquire resistance to treatment, motivating the exploration of complementary immunotherapies.
- Melanomas are considered as one of the most immunogenic tumors where immune checkpoint inhibitors (CPIs) are among the standard of care.
- Combination approaches with CPIs and chemotherapy or radiation therapy are potential avenues to improve patient response.
- Modulating the immunologically cold nature of the tumor towards a more receptive/responsive tumor microenvironment could become more amenable to CPI therapy.

Results

BETTER TH1902 EFFICACY AND TUMOR IMMUNITY ACTIVATION

TH1902 Efficacy in a SORT1+ Syngeneic Melanoma Model

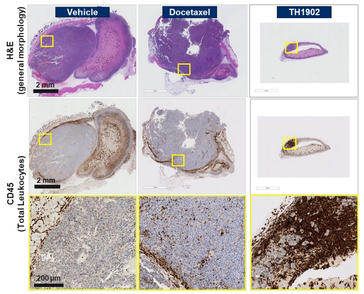


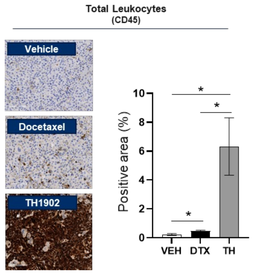


B16-F10 Syngeneic Xenograft Melanoma Model Characteristics:

- This model is known as a non-immunogenic (or 'cold') tumor.
- Given its immuno-suppressive phenotype, this model elicits limited response to single agent immune modulators such as anti-PD-L1, anti-PD-1, and anti-CTLA4 antibodies.
- B16-F10 model highly expresses Sortilin receptor whereas PD-L1 receptor is moderately expressed.

TH1902-Induced Immunogenic Switch From 'Cold' to 'Hot' Tumor





- In contrast to docetaxel, **TH1902 induces a net increase in immune cell infiltration** (CD45+ leukocytes) within the tumor core.
- *Quantification method:* all IHC stainings were quantified by positive staining per tumor surface area. Outer edge, necrotic center, and invasive margins were discarded and not quantified.

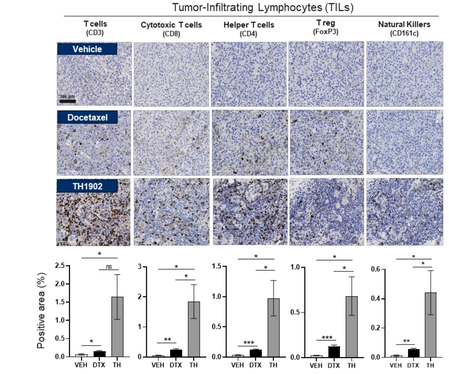
* *p<0.05.*

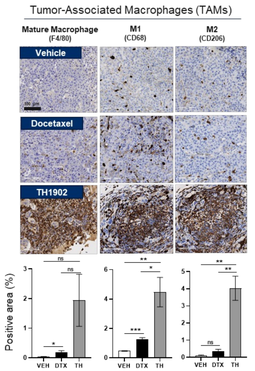
Vehicle (VEH), docetaxel (DTX), TH1902 (TH).

Results (cont'd)

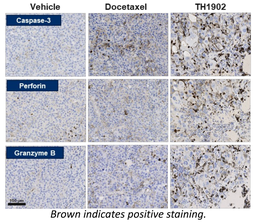
TH1902 INDUCED TUMOR INFILTRATION OF IMMUNE CELLS

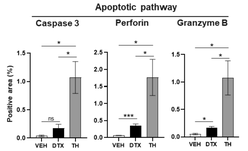
Characterization of Tumor-Infiltrating Immune Cells





- **Marked increase of TILs and TAMs** immune cell populations in TH1902-treated tumors.
- TH1902-treated tumors are highly infiltrated with immune cell population **associated to therapeutic response** such as cytotoxic T cells (CD8+), NK cells (CD161c+), and M1 macrophages (CD68+).
- **Higher cytotoxic phenotype** for TH1902-treated tumors (elevated perforin and granzyme B levels) associated to cytotoxic NK and lymphocyte T cells.
- **Stronger activation of the apoptotic pathway** by TH1902 compared to docetaxel (caspase-3).





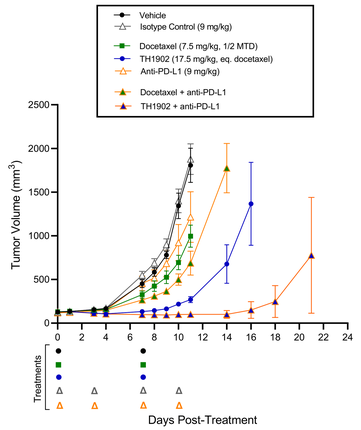
* *p<0.05, ** p<0.01, *** p<0.001, ns: not significant.*

Brown indicates positive staining.

Results (cont'd)

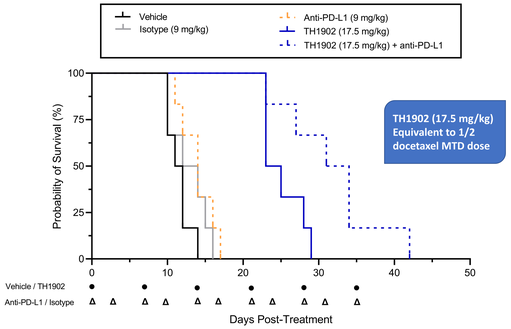
TH1902 PRODUCES STRONG INHIBITION OF TUMOR GROWTH (B16-F10 S.C. Xenografts) AND ENHANCES ANTI-PD-L1 ANTICANCER ACTIVITY IN A COLD TUMOR MODEL

Increased Tumor Growth Inhibition



- **Better efficacy** of TH1902 alone compared to:
  1) Docetaxel
  2) Anti-PD-L1 Ab
  3) Docetaxel + anti-PD-L1 combination
- **Co-administration of TH1902 increased anti-PD-L1 efficacy as well as mice survival.**

Increased Survival



Groups	Doses[a] (mg/kg)	Median Survival Time (Days)	Increase in Life Span[b] (Days)	P-values[c] (vs Vehicle)
Vehicle	0	11.5	0	-
Isotype Control Ab	9	13	1.5	ns (0.1908)
Anti-PD-L1 Ab	9	14	2.5	ns (0.0521)
TH1902	17.5	24	12.5	0.0006
TH1902 + anti-PD-L1	9 + 17.5	32.5	21	0.0006

*

**P<0.05; ns, not significant.*

[a]Weekly administration via IV bolus for TH1902 whereas anti-PD-L1 and Isotype control Abs were administered bi-weekly via IP administration.

[b,c]Increase of life span and significance compared to Vehicle group. Significance was assessed pairwise by using log-rank (Mantel-Cox) test.

Conclusions

- SORT1⁺ Technology™ is an innovative, flexible platform consisting of novel peptides that target SORT1 which is preferentially expressed in cancer cells.
- The proprietary peptide, TH19P01, can be conjugated to well characterized anticancer agents, such as docetaxel for which efficacy and safety in preclinical models have been reported.
- TH1902 induces a net increase in immune cell infiltration (TILs and TAMs) leading to a higher cytotoxic phenotype by activating the apoptotic pathway in the B16-F10 syngeneic cold tumor model.
- Superior TH1902 anticancer activity over docetaxel involves, in part, the modulation of infiltrating immune cells within the tumor microenvironment.
- Results show that immune cell infiltration may be involved in the tumor regression induced by TH1902.
- Combination of TH1902 with checkpoint inhibitors (anti-PD-L1 Ab) further reveals that this may lead to better clinical outcomes in future immunotherapy translational approaches.

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