AACR abstract # 3717

Sudocetaxel Zendusortide (TH1902) triggers the cGAS/STING pathway and potentiates anti-PD-L1 immune-mediated tumor cell killing

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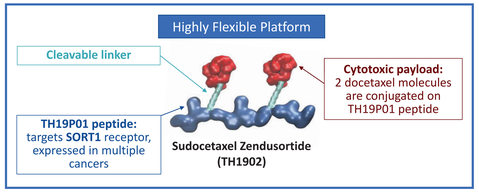
Introduction

SORTILIN RECEPTOR (SORT1) IN CANCER

- Sortilin receptor (SORT1) is highly expressed in many cancers compared to healthy tissues, which makes it an attractive target for cancer drug development.
- SORT1 Is a transmembrane scavenger receptor involved in import-export of its ligands into the cell via the endosomal/lysosomal pathway (cellular shuttle system).
- SORT1 plays multiple roles in cancer: it is associated with progression, invasion, and aggressive disease [1,2].
- SORT1 is highly expressed in various tumor types such as triple-negative breast (TNBC; ~60%), invasive ductal breast (~75%), ovarian (>90%), and endometrial (>90%) cancers, as well as melanoma (>90%) [3,4].

SORT1⁺ TECHNOLOGY™ PLATFORM

- **SORT1⁺ Technology™** is an innovative oncology platform consisting of novel peptide-drug conjugates (PDCs) that target SORT1 in cancer cells.
- Targeting SORT1 with these PDCs leads to receptor-mediated internalization (endocytosis) of anti-cancer agents.
- Sudocetaxel Zendosortide (TH1902) is currently under investigation in a phase 1 clinical trial (NCT04706962).
- Once inside the cancer cells, active drug is released from the peptide and exerts its cytotoxic effect.
- The platform enables versatile and flexible conjugation strategies with different payloads and linkers.



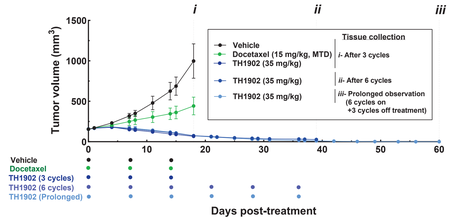
CANCER IMMUNITY AND cGAS/STING PATHWAY

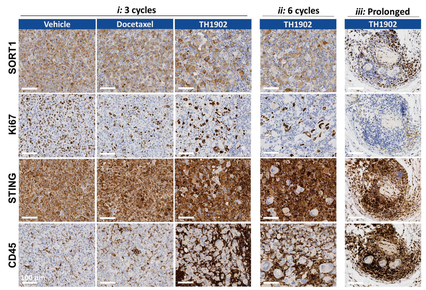
- Immune checkpoint inhibitor (CPI) therapy has shown survival benefits for some patients with cancer.
- The STING pathway is a component of the innate immune system that functions to detect the presence of cytosolic DNA.
- Activation of the STING pathway triggers the expression of inflammatory genes that can lead to senescence or to the activation of defense mechanisms (immune cell recruitment and infiltration).
- Combination approaches with CPIs and chemotherapy or radiation therapy are potential avenues to improve patient response.
- Modulating the tumor immune microenvironment (iTME) may make it more receptive and responsive to CPI therapy.

Results

TH1902 induction of the cGAS/STING pathway and tumor-infiltrating leukocytes in two TNBC models

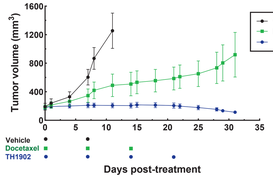
TNBC (MDA-MB-231) xenograft model



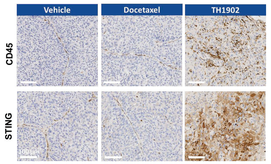


- **TH1902 induced complete and sustained tumor regressions.**
- TH1902-treated tumors maintained SORT1 expression levels, whereas the Ki67 proliferation marker was significantly decreased in cancer cells.
- The **increase in STING expression correlated with the increase of leukocytes (CD45⁺) infiltration** in TH1902-treated tumors.

TNBC patient-derived xenograft (PDX) model



- PDX tumor (TNBC, stage:II/grade3).
- **TH1902 induced tumor regressions.**

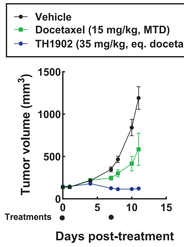


- **Increased tumor-infiltrating leukocytes (CD45⁺) and STING expression in TH1902-treated tumors.**

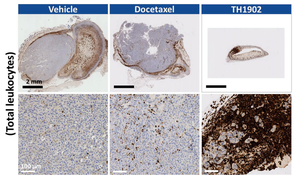
Results (cont'd)

TH1902 induction of tumor-infiltrating leukocytes

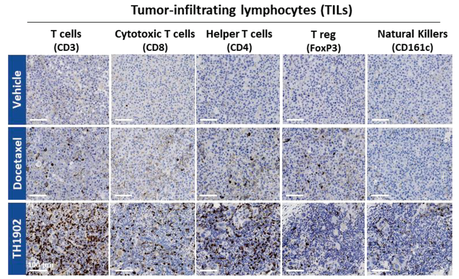
B16-F10 melanoma syngeneic model

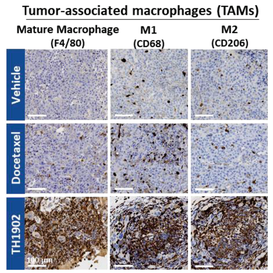


- **The B16-F10 model is known as a non-immunogenic ('cold') tumor.**
- This model elicits limited response to single-agent immune modulators such as anti-PD-L1, anti-PD-1, and anti-CTLA4 mAbs.
- **Tumor regression was found in TH1902-treated animals.**

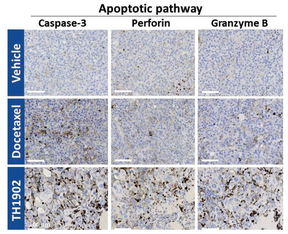


- **TH1902 induces a net increase in immune cell infiltration** (CD45⁺ leukocytes) within the tumor core.





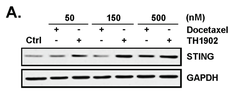
- **There was a marked increase of TILs and TAMs** immune cell populations in TH1902-treated tumors.
- TH1902-treated tumors **are highly infiltrated with immune cells** such as cytotoxic T cells (CD8+), NK cells (CD161c+), and M1 macrophages (CD68+).

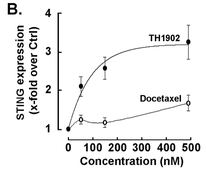


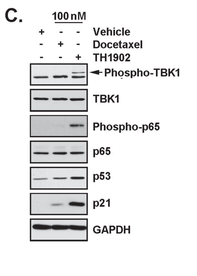
- **Higher cytotoxic phenotype** for TH1902-treated tumors (elevated perforin and granzyme B levels) was associated with cytotoxic NK and lymphocyte T cells.
- **TH1902 induced a stronger activation of the apoptotic pathway** compared to docetaxel (caspase-3).

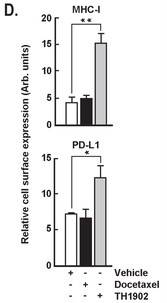
TH1902 induction of cGAS/STING pathway

cGAS/STING pathway activation by TH1902 in B16-F10 cancer cells



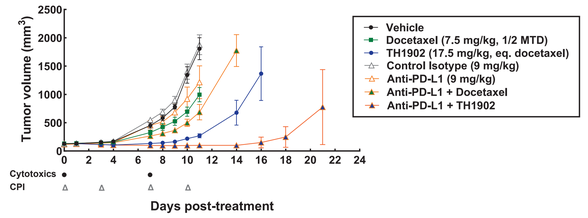






- **TH1902 significantly induced several downstream effectors of the cGAS/STING pathway.**
- **TH1902 increased MHC-I and PD-L1 cancer cell surface expression**, which potentially leads to increased recognition and cytotoxicity by infiltrating CD8⁺ T cells and provides a molecular rationale for combining TH1902 and anti-PD-L1 CPI therapies.

TH1902/anti-PD-L1 combination potentiates anti-cancer response



- A half-dose of TH1902 as a single agent **induced stronger tumor growth inhibition** compared to docetaxel, anti-PD-L1 or the docetaxel/anti-PD-L1 combination.
- TH1902 efficacy is **significantly increased when combined with anti-PD-L1** therapy.

Conclusions

- Immune cell infiltration appears to correlate with tumor regression induced by TH1902 in preclinical animal models.
- TH1902 induces the expression of interferon-stimulated genes (ISGs), potentially through the activation of the cGAS/STING pathway, which promotes the activation of the innate immune response.
- In addition to a net increase in immune cell infiltration (TILs and TAMs), TH1902 led to a higher cytotoxic phenotype by activating the apoptotic pathway in the B16-F10 syngeneic 'cold tumor' model.
- TH1902 exerts its antitumor activity, in part, through modulation of the iTME and the combination of TH1902 with checkpoint inhibitors (e.g., anti-PD-L1) may lead to improved clinical outcomes.

[1] Ghaemimanesh F, et al., J Cell Physiol. 2021;236(9):6271-6281. [2] Roselli S, et al., Oncotarget. 2015;6(12):10473-10486. [3] Roy G, et al., Eur J Cancer., 2022;174S1-S117:328. [4] Roy G, et al., Cancer Res., 2024; 83(Supp7):3942.

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