Overcoming Resistance to Anti-PD-1 with [DRUG]

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Improving Local Control and Overcoming Resistance to ICI

- Resistance to ICI, which is observed in >80% of treated patients, is a challenge for immuno-oncology.[1] Combination therapies with ICI and RT could improve ICI response rates.[2,3]
- Administered intratumorally, [DRUG] is designed to enhance the energy dose deposited by ionizing radiation within tumor cells, increasing the anti-tumor efficacy of RT.
- Here we present evidence that [DRUG] activated by RT primes the immune system, producing a local and systemic anti-tumor response in both mice models and patients.[4,5]

Key Features of [DRUG]

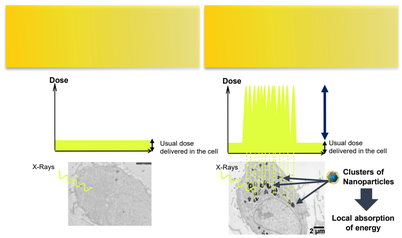
- [DRUG] is administered by a one-time ITI and activated by RT, such as SBRT/IMRT.[6]
- The physical and universal proposed MoA of [DRUG] is designed to trigger cellular destruction and prime an adaptive immune response.[4,7]
- [DRUG] is designed to increase the radiotherapy energy deposit inside tumor cells and subsequently increases tumor cell death compared to RT alone.[4,6,7]

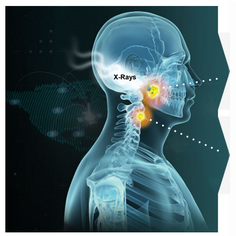
RT Alone[8,9]

[client-provided image]

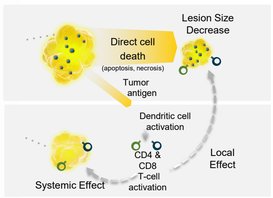
RT + [DRUG] [8,9]

[client-provided image]





Proposed Mechanism of Action[4,5,7,8,9,10]



Local and Abscopal Effects of [DRUG]

- In pre-clinical studies immunocompetent mice were injected in both flanks with CT26 murine colon carcinoma cells (2 independent experiments; 12-14 mice per group). Intratumoral injection of [DRUG] (or vehicle: 5% glucose, Glc) was performed in right flank tumors, followed by RT (3x4Gy). Tumor growth was followed, and animals sacrificed when tumors reached 800 mm^3.
- In these studies, **[DRUG]+RT produced local as well as systemic control** and induced an immune response not observed with RT alone with a significant increase in CD8+ T-cell infiltrates in both treated and untreated tumors.

Local control

[client-provided image]

+Systemic control

[client-provided image]

Impact survival

[client-provided image]

Treated

Untreated

[client-provided image]

Impact of [DRUG] in Solid Tumors

[DRUG] Activated by RT Improves Anti-tumor Efficacy in STS[6,9,11]

- In the Phase II/III randomized Act.in.Sarc trial, patients with locally advanced STS received [DRUG] + RT or RT alone followed by wide tumor resection.
- **The study met its primary endpoint** with a pCRR 2X greater than RT alone and provided a **proof of concept.**

[DRUG] Activated by RT Modulates the Tumor Immune Profile[6,9,11]

- In this proof of concept study, pre- and post-treatment tumor samples from patients were analyzed by IHC and digital pathology for immune biomarkers.
- Similarly, **increased CD8+ T-cell density (pre- vs post-treatment) was observed** in tumor tissues from patient with STS treated with [DRUG] + RT.
- Compared to RT alone, [DRUG] activated by RT increased the density of CD8+ cytotoxic T lymphocytes and decreased FOXP3+ (Treg) cell numbers in the tumors, while macrophage (CD68+) numbers remained relatively constant. These data indicated that [DRUG] activated by RT modulates the antitumor immune response.

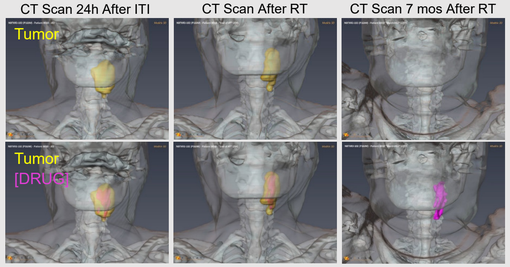
[client-provided image]

Signs of Clinical Efficacy

Increased Local Control

- A Phase I dose-escalation/dose-expansion study[12] is evaluating [DRUG] in patients with locally advanced HNSCC of the oral cavity or oropharynx, not eligible for cisplatin or cetuximab. **The primary lesion response rate was 83.9% in the evaluable population for efficacy (N=XX) in the dose-expansion cohort.**
- A Phase I dose-escalation study[13] is evaluating [DRUG] in patients with HCC or liver metastases. **The ORR in injected target lesions from patients with HCC was 66.7%.**

CT Scan 24h After ITI | CT Scan After RT | CT Scan 7 mos After RT



Overcoming anti-PD-1 Resistance in Mice

- In combination with anti-PD-1, [DRUG] + RT also **improved local and systemic control** in mice bearing anti-PD-1 resistant lung tumors and **resulted in a reduced number of spontaneous lung metastases**.
- Results were generally similar in PD-1 sensitive cell lines.

Local control

[client-provided image]

+Systemic control

[client-provided image]

Impact survival

[client-provided image]

Decreased Metastases

[client-provided image]

Note: Data represent means ± standard errors of the mean. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

First in Human Trial of [DRUG] RT in Combination with anti-PD-1

A multicenter, open-label, non-randomized, Phase I, dose-escalation with dose-expansion study[14] evaluating [DRUG] activated by RT in combination with anti-PD-1 therapy (R3/RT/PD-1) in patients with advanced cancers:

COHORT	[DRUG] Dose*	RT Dose
1- Locoregional recurrent or recurrent and metastatic HNSCC amenable to re-irradiation of the HN	33% or 44%	XX Gy / 5 x 7 Gy
2- Lung metastases from any primary cancer eligible for anti-PD-1	44% or 55%	XX Gy / 5 x 9 Gy
3- Liver metastases from any primary cancer eligible for anti-PD-1	33%, 44%, or 55%	XX Gy / 3 x 15 Gy

*injected volume calculated as a % of baseline GTV contour by MRI or CT

Primary Objective
- DLTs, MTDs, RP2Ds

Secondary Objectives
- ORR
- Safety and feasibility
- Body kinetic profile of [DRUG]

Exploratory Objectives
- Survival outcomes
- Duration of response
- Biomarkers of response

Conclusions

- Pre-clinical studies demonstrated that [DRUG] + RT induces an immune response not observed with RT alone and enhances systemic control.
- The combination of [DRUG] activated by RT with anti-PD-1 triggers an abscopal effect that translates into primary and secondary tumor volume growth delay, improved survival, and decreased number of lung metastasis in mice bearing anti-PD-1 resistant tumors.
- [DRUG] activated by RT modulated the immune profile of the tumor in patients with STS of the extremity or trunk wall resulting in 2x greater pCRR than RT alone.
- [DRUG] demonstrated efficacy in solid tumors, in a Phase II/III STS study, and two Phase I studies in HNSCC, and HCC.
- These data provided a rationale for evaluating the combination of [DRUG] activated by RT with ICI, which could increase RT-mediated local tumor control and prime the immune system for greater systemic ICI response.

Disclaimer: The scientific information discussed in this presentation related to [DRUG] is preliminary and investigative. [DRUG] is not approved by the US Food and Drug Administration; therefore, no conclusions can nor should be drawn regarding the safety or effectiveness of the investigational product.

Abbreviations: anti-PD-1, anti-programmed cell death protein 1; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; DLT, dose-limiting toxicity; HCC, hepatocellular carcinoma; HNSCC, Head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitors; IHC, immunohistochemistry; IMRT, intensity-modulated radiation therapy; iRECIST, modified RECIST for immunotherapy; ITI, intratumoral injection; MoA, mechanism of action; MTD, maximum tolerated dose; ORR, objective response rate; pCRR, pathological complete response rate; RP2D, recommended Phase II dose; RECIST, Response Evaluation Criteria In Solid Tumors; ROS, reactive oxygen species; RT, radiotherapy; SBRT, stereotactic body radiation therapy; STS, soft tissue sarcoma.

Requests for information can be made to medicalaffairs@COMPANY.com. [LOGO]

References: [1]Author et al. *Cell*. 2015;161(2), 205-14. [2]Author et al. *Nat Rev Clin Oncol*. 2018;15(8):477-94. [3]Author et al. *N Engl J Med*. 2012;366(10):925-31. [4]Authorl et al. *Radiother Oncol*. 2019;141:262-66. [5]Author et al. *Int J Radiat Oncol Biol Phys*. 2019;105(1S):E651. Abs 3513. [6]Author et al. *Lancet Oncol.* 2019;20:1148-59. [7]Author et al. *Int J Nanomedicine*. 2020;15:3843-50. [8]Author et al. *Future Oncol.* 2012;8(9):1167-81. [9]In House Data. [10]Author et al. *J Clin Oncol*. 2020;38:TPS3173-TPS. [11]https://clinicaltrials.gov/ct2/show/NCT0XXXXXXX. [12]https://clinicaltrials.gov/ct2/show/NCT0XXYXXXY.