A novel immunostimulatory TLR7/8 agonist is curative as a monotherapy in Lewis Lung Carcinoma and synergizes with anti-PD-1 in B16F10 and MC38 tumor models

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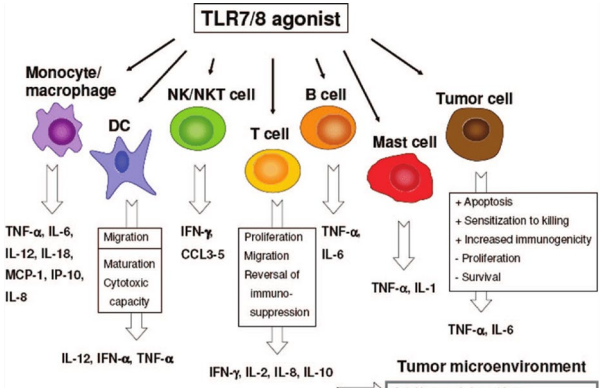
Abstract

Immunotherapy has been used as a treatment for cancer since 1891 with the use of Coley's toxin as a means to induce a strong immune response to a bacterial infection with the hopes of also curing a patient's cancer. Over the past 130 years, the field of immunotherapy has come a long way through discovery and use of immunostimulatory proteins, such as IL-2 and interferon, and now to the use of immune checkpoint inhibitors, namely anti-PD-1 and anti-CTLA4. Despite these advances, response rates remain stubbornly low – 20-22% even in tumor types with some of the highest rates of response to checkpoint inhibitors such as melanoma and renal cell carcinoma. New immunotherapies that stimulate the immune system in different ways and can synergize with and expand the population of patients who respond to existing immunotherapies are urgently needed. Inimmune has developed and evaluated a novel TLR7/8 agonist as an immunotherapy for cancer. The lead formulation of our novel TLR7/8 agonist was able to eliminate Lewis Lung Carcinoma (LLC) flank tumors in 80% of mice after just two treatments. Moreover, as a monotherapy our novel TLR7/8 slowed the growth of MC38 and B16F10 tumors and synergized when combined with anti-PD-1 therapy, leading to a 100% rejection rate in MC38 flank tumors and a 75-100% rejection rate in B16F10 tumors depending on the route of administration and dose schedule. Mechanistically, the combination of our TLR7/8 agonist plus anti-PD-1 lead to increases in monocytes, B cells, and CD8 T cell populations in the TME of B16F10 flank tumors when compared to treatment with TLR7/8 agonist or anti-PD-1 alone. As we advance our novel synthetic TLR7/8 agonist to Phase I clinical trials, these data suggest potential efficacy as a monotherapy or in combination with checkpoint inhibitors in patients with solid tumors.

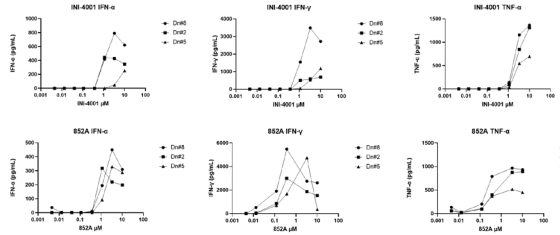
Background



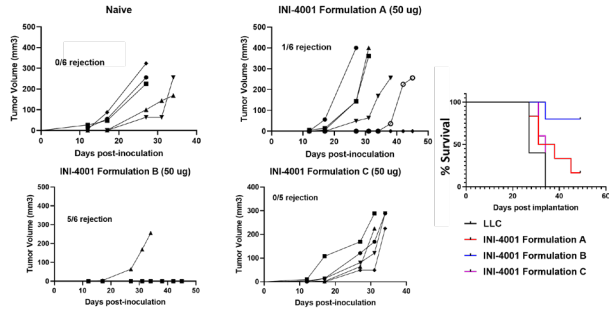
- **Toll-like receptors (TLRs) play an important role in adaptive and innate immunity.**
- **Activation of TLR 7/8 prompts acute inflammation and induction of proinflammatory cytokines, driving an anti-tumor response.**

Adapted from "The Use of TLR7 and TLR8 Ligands for the Enhancement of Cancer Immunotherapy," by E. Smits, P. Ponsaerts, Z. N. Berneman, and V. F. Van Tendeloo, 2008, *Oncologist, 13*, p. 859-875.

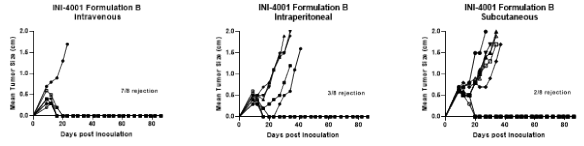
INI-4001 stimulates TLR7 and TLR8 driven cytokine production in human PBMCs



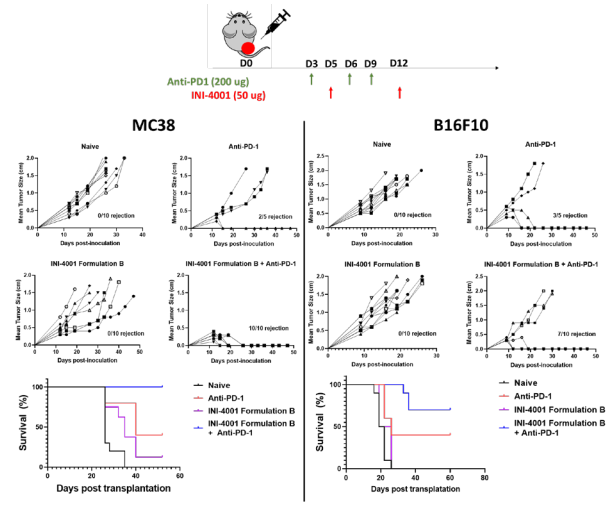
Optimized formulation of INI-4001 is efficacious as monotherapy in LLC



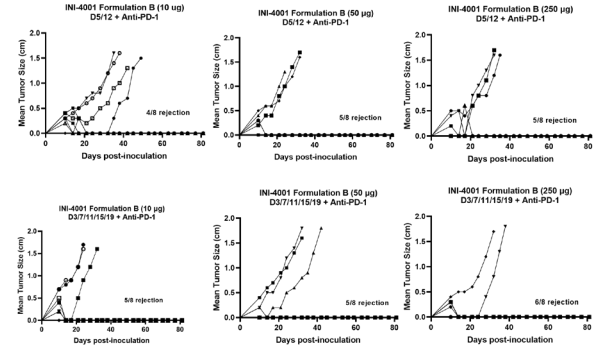
IV delivery of INI-4001 is the most effective systemic treatment route



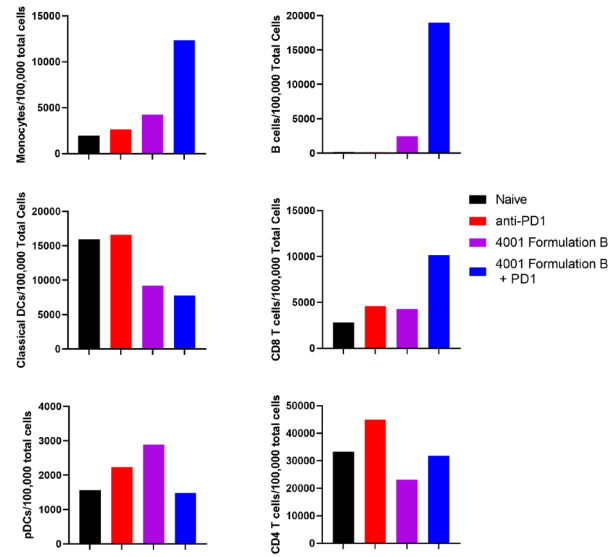
INI-4001 synergizes with anti-PD-1 in B16F10 and MC38 murine models



Treating with INI-4001 more frequently at lower doses increases efficacy in B16F10



INI-4001 plus anti-PD-1 induces monocyte, B cell, and CD8 T cell trafficking to the TME of B16F10 flank tumors



Conclusions & Future Directions

- **INI-4001 is efficacious as a monotherapy in a highly tumorigenic Lewis Lung Carcinoma (LLC) model**
- **INI-4001 shows synergy with anti-PD-1 in both MC38 and B16F10 murine tumor models**
- **INI-4001 is highly effective when dosed IV and maintains efficacy even at low doses, allowing for a greater therapeutic window**
- **INI-4001 in our lead formulation will enter Phase I clinical trials mid-2023**