• Immune checkpoint inhibitors such as the PD-1 blocking antibody pembrolizumab have demonstrated marked improvements in duration of response and long-term survival over the standard of care (SOC) in head and neck squamous cell carcinoma (HNSCC).

• However, the significant percentage of patients who are nonresponsive to these immunotherapies (primary resistance) or experience progression of disease following an acquired immune resistance mechanism (secondary resistance) highlights the need for additional therapies for this patient population.

• As tumor responsiveness to immunotherapy may depend, in part, on the immunophenotype of the tumor microenvironment (TME)\(^1\), an exploratory approach to establish, reposition, or enhance adaptive immune surveillance conditions within the TME to allow immune modulators directly to the tumor to promote an adaptive immune response to cancer.

• Monotherapy activation of the stimulator of interferon genes (STING) pathway demonstrated tumor control. STING activation combined with a checkpoint inhibitor led to reversal of adaptive immune resistance, complete tumor inhibition, and abscopal control of distant tumors\(^2\).

• ADU (MIW185) is a novel synthetic cyclic diadenosine 5' monophosphate (cADP) molecule that activates the STING pathway within the TME leading to activation of tumor-resistant antigen-presenting cells (APCs) and priming of tumor specific CD8\(^+\) T cells.

• Direct activation of STING via intratumoral injection of ADU-1856 has been shown to overcome adaptive tolerance mechanisms through stimulation of resident leukocyte populations.

• Preclinical models indicate that survival and local tumor shrinkage were shown to overcome active tolerance mechanisms through stimulation of the STING pathway leading to activation of tumor-resident leukocyte populations resulting in establishment, or enhance active immune surveillance.

• PRECLINICAL EFFECTS OF ADU-1856

- A cyclic dinucleotide (CDN) containing two Phosphorothioate substitution increases resistance to phosphodiesterase degradation
- Nitrogen 1000 has been shown to be well tolerated. Tumor shrinkage and durable responses have been observed after treatment with ADU-1856 alone or in combination with a PD-1 inhibitor.

- ADU-1856 has enhanced potency over natural CDN ligands in human cells and mouse models.