A Phase 2 Study of ADU-S100 in Combination With Pembrolizumab in Adult Patients With PD-L1+ Recurrent or Metastatic HNSCC: Preliminary Safety, Efficacy and PK/PD Results

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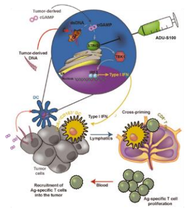
Introduction

- Whilst pembrolizumab can significantly improve overall survival compared to cetuximab plus chemotherapy for first line recurrent, unresectable or metastatic head and neck squamous cell carcinoma (HNSCC) patients who are PD-L1 positive, not all patients will respond to treatment[1]
- As the responsiveness of tumors to immunotherapy is, in part, dependent on the immunophenotype of the TME, direct injection of innate immune modulators into the tumor may promote an adaptive tumor-specific immune response[2-5]
- ADU-S100 (MIW815) is a novel synthetic cyclic dinucleotide that activates the stimulator of interferon genes (STING) pathway (see Figure 1)

Figure 1. Therapeutic Mechanism of STING (Stimulator of Interferon Genes) Activation



- The STING pathway senses intracellular nucleic acids to trigger production of type I IFNs, including IFN-β
- STING activation impacts both the innate and adaptive immune response by inducing APC activation and recruitment, and priming of tumor-specific CD8+ T cells
- In the natural setting of tumor immune surveillance, tumor-derived DNA or cyclic-dinucleotides (CDNs) initiate production of IFN-β by tumor resident DCs through STING
- In the therapeutic setting, type I IFN can be induced in the tumor microenvironment (TME) with a STING agonist

Adapted from: Corrales and Gajewski. Clin Can Res 2015 and Marcus *et al.* Immunity 2018

- Direct activation of STING via intratumoral injection of ADU-S100 (MIW815) has been shown to activate tumor-resident APCs, and enhance priming of tumor antigen specific CD8+ T cells[6]
- Preclinical models, including a model of HNSCC, indicate that survival and local tumor shrinkage were significantly enhanced when ADU-S100 (MIW815) is administered with an αPD-1 antibody, suggesting that PD-1 blockade may act synergistically with concomitant STING activation[7,8]
- Phase 1 clinical studies have shown durable responses when ADU-S100 is combined with a PD-1 inhibitor

Study Design and Patient Population

- ADU-CL-20 is an open-label, multicenter Phase 2 clinical trial designed to evaluate the efficacy and safety of ADU-S100 (MIW815) combined with pembrolizumab in the first-line setting. Trial Registration: NCT03937141
- Up to 34 adults with PD-L1 positive recurrent or metastatic HNSCC will be enrolled
- Study utilizes a Simon's 2 Stage design. The clinical trial schematic can be found in Figure 2A
- Enrollment for this trial is currently on going. As of the data cutoff date of 04 September 2020, 11 patients have been enrolled into the study. The clinical trial profile can be found in Figure 2B

Figure 2A. ADU-CL-20 Clinical Trial Schematic

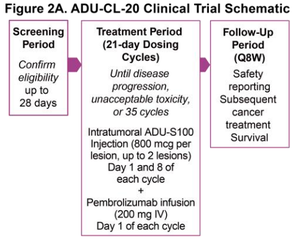
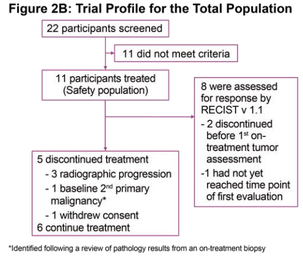


Figure 2B: Trial Profile for the Total Population



*Identified following a review of pathology results from an on-treatment biopsy

Key Inclusion Criteria

- Histological or cytological confirmation of recurrent or metastatic HNSCC
- Measurable disease as defined by RECIST v1.1
- PD-L1 positive, defined as combined positive score (CPS) ≥1 using the Dako PD-L1 22C3 pharmDx companion diagnostic assay

Key Exclusion Criteria

- Diagnosis of recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology; or salivary gland or non-squamous histologies (e.g. mucosal melanoma)
- Disease amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
- Prior systemic anti-cancer therapy (use of chemotherapeutic agents, targeted small molecules, immunotherapy, or monoclonal antibodies) for the treatment of recurrent or metastatic HNSCC

Endpoints

Primary Endpoint

- Objective response rate (ORR) per RECIST v1.1

Key Secondary Endpoints

- Safety and tolerability
- OS, PFS, duration of response, and duration of disease control
- PK characteristics of ADU-S100

Key Exploratory Endpoints

- Changes from baseline in selected protein and genomic expression parameters from blood and tissue samples

Results

Data Cut Off 04 September 2020

All results shown are preliminary and based on best available data due to COVID-19 restrictions.

Patient Characteristics

- Baseline characteristics for 11 patients included in the analysis are shown in Table 1

Safety

- As of 04 September 2020, there were no deaths, treatment discontinuations or dose reductions due to AEs
- 10 (90.0%) had AEs, with 8 (72.7%) experiencing treatment related AEs according to investigator assessment
- One SAE of Grade 4 bradycardia unrelated to both study medications was reported after data cutoff date
- Treatment-related SAEs: Gr 3 cytokine release syndrome (n=1), Gr 3 localized edema (n=1), Gr 3 hypophysitis (n=1) and Gr 3 laryngeal edema (n=1)
- Grade 3 treatment emergent treatment related AEs include localized oedema (n=1), dysphagia (n=1), hypophysitis (n=1), arthralgia (n=1), back pain (n=1), laryngeal oedema (n=1), and cytokine release syndrome (n=1)
- Treatment related AEs observed in ≥ 2 patients are shown in Table 2
- There were no clinically significant changes observed in ECGs and no abnormal laboratory findings

Table 1. Demographics

	(N=11)
Age (years)	
Median (Min, Max)	64 (51, 81)
Sex	
Male	7 (63.6%)
Female	4 (36.4%)
Race	
Asian	1 (9.1%)
Black or African American	1 (9.1%)
White	9 (81.8%)
Baseline ECOG Performance Status	
Grade 0	1 (9.1%)
Grade 1	10 (90.9%)
Site of Primary Tumor (HNSCC)	
Larynx	2 (18.2%)
Oral Cavity	5 (45.5%)
Oropharynx	3 (27.3%)
Hypopharynx	1 (9.1%)
Combined Positive Score (CPS)	
1 to <20	5 (45.5%)
≥20	6 (54.5%)
HPV Status of Tumor (p16 Stain)	
Positive	3 (27.3%)
Negative	1 (9.1%)
Not Done	7 (63.6%)
Prior Radiotherapy	
Yes	9 (81.8%)
No	2 (18.2%)
Prior Cancer Related Surgery	
Yes	10 (90.9%)
No	1 (9.1%)

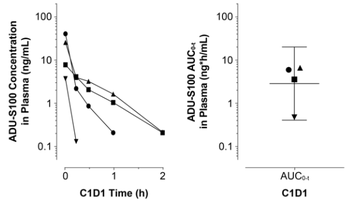
Results (cont'd)

Table 2. Treatment Emergent, Treatment Related AEs Reported in 2 or More Patients (N=11)

Preferred Term	ADU-S100 + Pembrolizumab (N=11)
Fatigue	5 (45.5%)
Localised Oedema	3 (27.3%)
Pyrexia	3 (27.3%)
Diarrhoea	3 (27.3%)
Nausea	3 (27.3%)
Anaemia	3 (27.3%)
Chills	2 (18.2%)
Injection Site Pain	2 (18.2%)
Hypothyroidism	2 (18.2%)
Tumour Pain	2 (18.2%)

Figure 3. Pharmacokinetic Profile of ADU-S100

Absorption kinetics and area under the curve



Pharmacokinetics (PK)

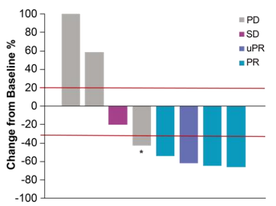
- Rapid absorption and disappearance of ADU-S100 from plasma with half-life ranging from 3 to 27 min
- PK profile of ADU-S100 in 1st line metastatic HNSCC consistent with observations during Phase 1 dose escalation (NCT02675439; SITC 2018 [P10763])

Efficacy

- At the time of this data cut-off (04 September 2020), 8 patients were evaluated for response by RECIST v1.1. Waterfall plot of best overall response (BOR) by RECIST v 1.1 can be found in Figure 4A
  - 4 partial responses (PRs, 3 confirmed), 1 stable disease (SD) and 3 progressive disease (PDs) were observed
- Target tumor response for lesions injected with ADU-S100 vs. those lesions that were not injected were also evaluated (see Figure 4B)
  - All injected target lesions of responders decreased in size by 47-67%
  - Only 4 patients had measurable non-injected lesions. These lesions either decreased in size (n=1), remained stable (n=2) or increased in size (n=1)
- Preliminary median duration of response is 128 days and median duration of disease control is 158 days, with 6 patients continuing to receive treatment (see Figure 5). One responder continues to respond after ≥12 months of treatment
- Based on these results, enrollment into Stage 2 of the Simon's 2 stage design has been initiated

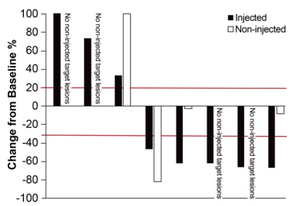
Figure 4. Waterfall Plots of Best Overall Response in Response Evaluable Subjects

A. Best Overall Response by RECIST v1.1



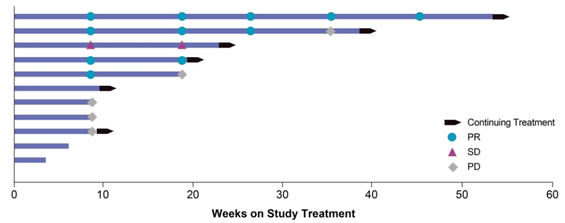
*PD due to appearance of new lesion

B. Best Response for Target Injected vs Non-Injected Lesions (Sum of Lesions)



Note: Injected lesion measurements take into account any new lesions that are injected and are measurable

Figure 5. Swimmer's Plot of Treatment Duration for Each Patient



Per protocol, patients may continue treatment beyond initial progression and evaluated for response by iRECIST (results not shown)

Pharmacodynamics

- As shown in Figure 6, systemic IFNβ levels peaked after 6 hours post-ADU-S100 treatment
- Analysis of tumor biopsy samples collected 24 hours after first treatment found increased expression of interferon stimulated genes relative to pre-dose levels (Figure 7)
- These results are consistent with STING activation of an innate immune response

Figure 6. Circulating IFNβ Increased 6 Hours After ADU-S100 Administration

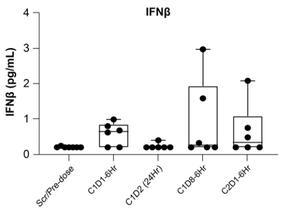
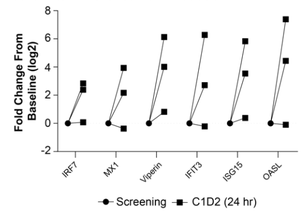


Figure 7. Interferon Stimulated Genes are Induced Within the Tumor 24 Hours After ADU-S100 Administration



SUMMARY

- These early results provide preliminary evidence that ADU-S100 plus pembrolizumab is well tolerated
- PK shows rapid absorption kinetics. This profile is consistent with that observed for the 800 mcg dose in the Phase 1b dose escalation trial, MIW815x2101
- Early evidence of efficacy is observed. Enrollment into Stage 2 of the Simon's 2 stage design has now been initiated
- Pharmacodynamic data indicate early activation of Interferon Stimulated Genes in the injected tumor and increased levels of plasma IFNβ following ADU-S100 administration

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