Preliminary results of safety and antitumor activity from a first-in-human Phase 1 study of AWT020, a bifunctional anti-PD-1/IL-2 fusion protein, in patients with advanced tumors

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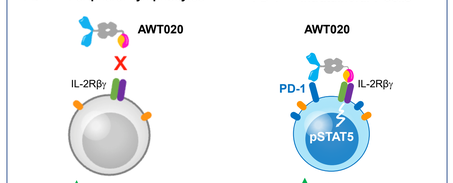
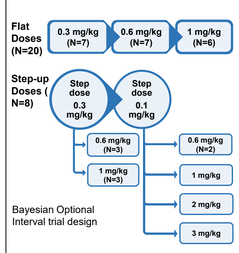
BACKGROUND

Immune checkpoint inhibitors have transformed treatment landscape across multiple cancer types, however, resistance to anti-PD-(L)1 therapies remains a significant unmet medical need. AWT020 is a bifunctional fusion protein comprised of an anti-PD-1 antibody and a potency optimized IL-2. In preclinical studies, the mouse surrogate of AWT020 demonstrated superior antitumor activity compared to anti-mPD-1 alone or in combination with IL-2, in both anti-PD-1 sensitive and resistant models. These findings suggest AWT020 monotherapy has the potential to surpass standard anti-PD-1 therapies and provide a valuable treatment option for patients resistant to anti-PD-1 therapies.

PD-1-dependent Delivery of IL-2 Activation to PD-1^{High} Intratumoral T cells



Study Design



For reporting rates of events, an N of 28 is used due to one patient being included in two dose groups

Criteria for Participants

INCLUSION CRITERIA

- ✓ Age ≥18 years old
- ✓ Adequate organ function
- ✓ ECOG PS 0-1
- ✓ Life expectancy ≥3 months
- ✓ Advanced/metastatic cancer without standard treatment options

EXCLUSION CRITERIA

- ⊗ Newly diagnosed brain metastases
- ⊗ Prior organ or HSC transplant
- ⊗ Active autoimmune disease

Objectives and Endpoints

PRIMARY OBJECTIVES

- Safety
- MTD/RP2D
- Dosing interval

SECONDARY OBJECTIVES

- PK
- PD
- Immunogenicity
- Biomarkers
- Anti-tumor response

PRIMARY ENDPOINTS

- TEAE, TRAE, and clinically significant changes in vital signs, physical examination, and clinical lab results
- DLT (incidence, percentage of patients, and posterior probability)

SECONDARY ENDPOINTS

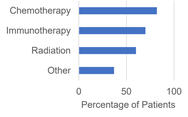
- PK parameters
- PD biomarkers
- ADA (percentage of subjects, time of emergence, and titer)
- ORR, DCR, DOR, TTR, PFS, and OS

Baseline Demographics

Demographics

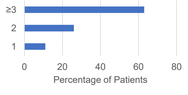
Age (years), median (range): 58 (20-79)
Race (%): White (78), Asian (19), Others (4)

Prior Therapy



Prior anti-PD-(L)1 Status

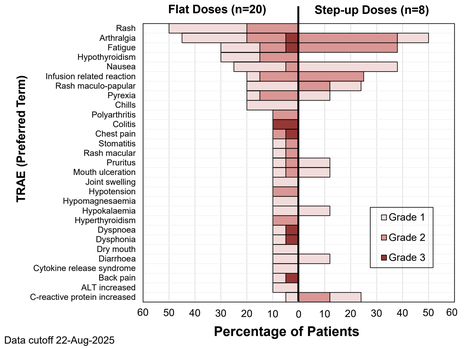
Prior Lines of Treatment



Distribution of Tumor Types

Three of Each	• TNBC
Two of Each	• Cholangiocarcinoma • Clear cell RCC • Colon adenocarcinoma • Mesothelioma • Non clear cell RCC • Thymic Carcinoma
One of Each	• Adenoid Cystic Carcinoma • Cervical SCC • Lung Adenocarcinoma • Melanoma • Neuroendocrine NSCLC • Neuroendocrine Renal Carcinoma • Prostate Adenocarcinoma • Small bowel adenocarcinoma • Small Cell Neuroendocrine Carcinoma • Thymoma • Urothelial Carcinoma • Uterine sarcoma

Safety Profile



Data cutoff 22-Aug-2025

TRAE Preferred Term (n, %)	Flat Doses (n=20)	Step-up Doses (n=8)
Drug related Grade 3 or 4 AEs	**11 (55)**	**1 (13)**
Colitis	2 (10)	0
Amylase increased	1 (5)	0
Anaphylactic reaction	0	1 (13)
Arthralgia/Back pain/Chest pain/Cold sweat/ Dysphonia/Dyspnoea*	1 (5)	0
Diabetes mellitus	1 (5)	0
Fatigue	1 (5)	0
Haemoperitoneum	1 (5)	0
Hepatitis	1 (5)	0
Infusion related hypersensitivity reaction#	1 (5)	0
Pain in extremity	1 (5)	0
Rheumatoid arthritis	1 (5)	0
Thrombocytopenia	1 (5)	0

* Reactions are related to one infusion from the same participant
# Grade 4, all others were Grade 3

Safety Summary

- Data include all 28 patients receiving ≥1 dose of AWT020
  - Flat-dose cohorts at 0.3, 0.6 and 1 mg/kg IV Q2W
  - Step-up dose cohorts at 0.3→0.6 mg/kg, 0.3→1 mg/kg, and 0.1→0.6 mg/kg IV Q2W
- Frequency of treatment related adverse events (TRAEs) occurring in ≥2 patients in either flat-dose (n=20) or step-up dose (n=8) cohorts

Key Findings

- Majority of TRAEs were mild to moderate (Grade 1–2).
- No evidence of vascular leak syndrome or ≥Grade 2 CRS.
- Arthralgia (46%), rash (36%), fatigue (32%), and nausea (29%) were the most common AEs related to therapy.

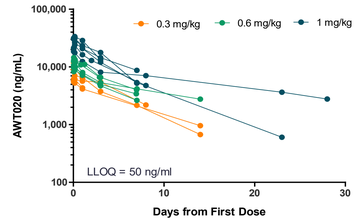
Impact of Step-up Dosing on Safety

- Improved tolerability during early treatment cycles, most notably with limited occurrence and reduced severity of any type of rash.
- Reduced incidence of Grade 3 and 4 treatment related AEs.
- Attenuation of irAE, AESI and drug related SAE incidence.

Dose escalation in the step-up dose cohorts is ongoing.

Preliminary PK

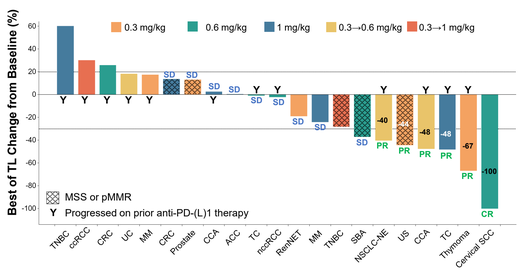
PK Profile After First Dose

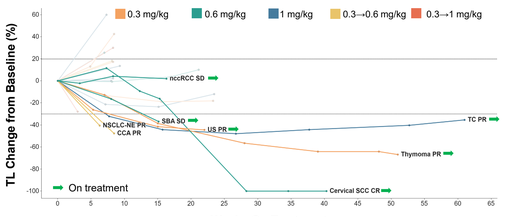


- Following a single one-hour infusion of AWT020, mean exposure parameters (Cmax and $AUC_{0\text{-}INF}$) increased in an approximate dose-proportional manner between 0.3 mg/kg and 1 mg/kg.
- Half-life of AWT020 ranged from 5.4 to 6.4 days.

Early Signals of Strong Clinical Response to AWT020 Monotherapy

Activity Demonstrated in Patients Resistant to Anti-PD-(L)1 and in Mismatch Repair-Proficient Hard-to-Treat Tumor





Data cutoff 22-Aug-2025

	All	Progressed on Prior anti-PD-(L)1
Response Evaluable*	21	12
CR	1	0
PR	5	4
SD	9	3
ORR (%)	**29**	**33**
DCR (%)	**71**	**58**

* Received ≥1 RECIST v1.1 evaluation post treatment

Key Findings

- Objective responses observed across diverse tumor types, including neuroendocrine NSCLC, cholangiocarcinoma, uterine sarcoma, cervical squamous cell carcinoma, thymoma, and thymic carcinoma.
- Overall ORR 29% and DCR 71%, with comparable activity in patients previously progressed on anti-PD-(L)1 therapy (ORR 33% and DCR 58%).
- Complete resolution of target lesions in cervical SCC achieved 7 months after starting treatment.
- Durable responses demonstrated lasting up to 16 months.

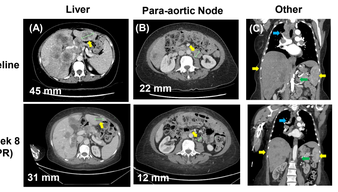
ACC=adenoid cystic carcinoma; CCA=cholangiocarcinoma; ccRCC=clear cell renal cell carcinoma; CRC=colorectal cancer; MM=mesothelioma; nccRCC=non clear cell RCC; NSCLC-NE=neuroendocrine non-small cell lung cancer; RenNET=neuroendocrine renal carcinoma; SBA=small bowel adenocarcinoma; SCC=squamous cell carcinoma; TC=thymic carcinoma; TNBC=triple-negative breast cancer; UC=urothelial carcinoma; US=uterine sarcoma

Case 1: Durable PR in Thymic Cancer with Secondary Anti-PD-1 Resistance

Subject
57-year-old white female with Stage IV metastatic thymic carcinoma

Prior Lines
- 1L Carboplatin and Paclitaxel (BoR: SD)
- 2L Claudin 18.2 ADC (ATG-022, BoR: PD)
- 3L Pembrolizumab (BoR: SD >6 months)

Response to AWT020 at 1 mg/kg
- Five target lesions located at the right lung, left pleura, right hilar node, left para-aortic node, and liver segment 3, with a baseline sum of diameter (SoD) of 127 mm.
- Lesions reduced by 33% at Week 8. CT images demonstrate reduction in liver (A) and para-aortic (B) target lesions. Additional findings (C) include reduced hepatosplenomegaly (yellow arrows) and improvement in mediastinal (blue arrows) and para-aortic (green arrows) lymphadenopathy.
- Dose modified to 0.6 mg/kg (Week 31) then 0.8 mg/kg (Week 55).
- Response further improved to 48%, maintained for 16+ months with ongoing AWT020 treatment.



Case 2: Complete Response in Cervical Cancer Naïve to Anti-PD-(L)1

Subject
68-year-old female with Stage IV cervical squamous cell carcinoma

Prior Lines
- 1L chemoradiotherapy with weekly cisplatin and 54 Gy (BoR: PR)
- 2L chemotherapy with paclitaxel/carboplatin for 6 cycles (BoR: PR)
- 3L palliative chemoradiotherapy with weekly cisplatin

- **Response to AWT020 at 0.6 mg/kg**
- Two target lesions located in the abdomen and the pelvis, with a baseline SoD of 78 mm.
- Initial 12% increase in lesion size at Week 8 but then decreased by 9% below baseline by Week 13.
- Continued decrease until all target lesions completely resolved (-100% decease) by Week 29, with confirmed PR by Week 35.
- By Week 41, all non-target lesions also became undetectable, demonstrating a complete response.
- Complete response continues with ongoing AWT020 treatment for 11+ months.

Week	Change of SoD from Baseline	Non-TL	Overall Response
8	12%	Present	iUPD
13	↓9%	Present	SD
16	**↓16%**	Present	SD
29	**↓100%**	Present	**PR**
35	**↓100%**	Present	**cPR**
41	**↓100%**	**Absent**	**CR**

Case 3: Confirmed PR in Uterine Sarcoma Proficient for Mismatch Repair

Subject
52-year-old Asian female with Stage IV uterine sarcoma

Prior Lines
- 1L clinical trial agent (BoR: PD)

- **Response to AWT020 at 0.3 mg/kg**
- Two target lesions in the right suprarenal region and the anterior satellite, with a baseline SoD of 99 mm.
- Week 8 first restaging showed disease stabilization with a 26% reduction and improved to 41% by Week 16 with a confirmed PR by Week 23 (-44%).
- AWT020 treatment is ongoing for more than 6 months.

Week	Change of SoD from Baseline	Non-TL	Overall Response
6	**↓26%**	NR	SD
16	**↓41%**	NR	**PR**
23	**↓44%**	NR	**cPR**

NR = not reported

CONCLUSIONS

In this first-in-human study, AWT020 demonstrates promising antitumor activity, including in patients with secondary resistance to anti-PD-(L)1 therapies and in patients with tumors which typically are unresponsive to immune monotherapy. There have been 1 complete response and 5 partial responses to treatment with maintenance of response in ongoing patients lasting from 4 to 16 months. The complete response in a patient with cervical cancer showed 100% resolution of target lesions by Week 29. Preliminary effect in patients with thymic epithelial tumors (TET) including thymic carcinoma and thymoma warranted the US FDA granting AWT020 Orphan Drug Designation for the patient population.

In addition to the positive preliminary antitumor activity of AWT020, the safety profile is manageable with significant improvement in the adverse event profile with the implementation of step-up dosing. Dose escalation is ongoing to establish MTD/RP2D with step-up dosing for the further evaluation of AWT020 in TET and other tumor types that have already demonstrated early signals of activity, as well as exploration of additional indications including NSCLC.