innovaTV 207: NEW COMBINATION DOSING COHORTS IN THE OPEN LABEL PHASE 2 STUDY OF TISOTUMAB VEDOTIN IN SOLID TUMORS (TRIAL IN PROGRESS)

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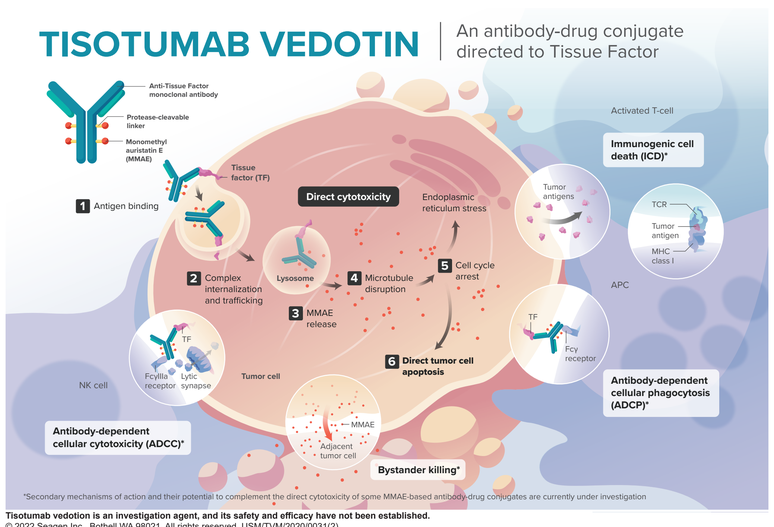
TISSUE FACTOR TARGET

- In tumor cells, TF has been shown to promote tumor growth, angiogenesis, and metastasis.[1,2]
- TF is prevalent in several solid tumors, including cervical cancer, HNSCC, and NSCLC. In these tumors where TF is present, levels are elevated relative to normal tissue.[3,4]
- In clinical trials, responses to tisotumab vedotin (TV) were observed regardless of TF expression level; hence, TF expression was not an inclusion criterion for participation.

TISOTUMAB VEDOTIN

- TV is an investigational TF-directed ADC composed of a fully human monoclonal antibody (IgG1k) specific for TF, the microtubule-disrupting agent MMAE, and a protease-cleavable linker that covalently links MMAE to the antibody.[5,6,7]
- TV has anti-tumor activity on multiple tumor types and kills cells by direct cytotoxicity, bystander cytotoxicity, ADCC, ADCP, and in a manner consistent with ICD.[8]
- TV monotherapy was granted an accelerated approval by the US FDA for adult patients with r/m CC, with disease progression on or after chemotherapy, based on tumor response rate and durability of response.
- TV is being investigated in other tumor types including HNSCC and sqNSCLC.

Figure 1. Tisotumab Vedotin Proposed Mechanisms of Action



Tisotumab vedotion is an investigation agent, and its safety and efficacy have not been established.

OPPORTUNITY TO OPTIMIZE TREATMENT IN PREVIOUSLY UNTREATED PATIENTS WITH r/m HNSCC OR sqNSCLC

- Pembrolizumab + platinum + 5-FU is the preferred treatment for 1L r/m HNSCC in the US (for all patients) and in the EU (for patients with PD-L1 positive tumors); pembrolizumab monotherapy is an alternative for patients with PD-L1 positive tumors.
- Likewise, pembrolizumab+carboplatin+paclitaxel/nab-paclitaxel is the recommended 1L SOC for patients with advanced/metastatic NSCLC; pembrolizumab monotherapy is an option for patients with TPS ≥1 and is more often used for patients with TPS ≥50%
- There is an opportunity to optimize the chemotherapy backbone used in combinations with CPIs in first line for both r/m HNSCC and sqNSCLC and consequently may improve response rates in this setting.
- Results from Part A of this study show encouraging antitumor activity with 2.0 mg/kg Q3W TV in r/m and heavily pretreated HNSCC[9] and sqNSCLC patients with a confirmed ORR of 16% and 23%, respectively.
- To this effect, Part D of this study will explore dosing of TV in combination with pembrolizumab, with or without a platinum agent, in treatment-naïve patients with advanced and/or metastatic HNSCC or sqNSCLC.
- Cell death induced by MMAE agents has been hypothesized to be immunogenic.[10] This overall immune activation via TV-induced ICD may complement CPIs to stimulate antitumor immune response. This is further supported by clinical results from TV in combination with bevacizumab, pembrolizumab, or carboplatin that show encouraging and durable antitumor activity.[11]

Abbreviations

5-FU, 5-fluorouracil; 1L, first-line; ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; AE, adverse events; APC, antigen-presenting cell; AUC, area under the curve; CC, cervical cancer; CI, confidence interval; CNS, central nervous system; CPI, checkpoint inhibitor; CPS, combined positive score; CR, complete(s); DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinomas; HRQOL, health-related quality of life; ICD, immunogenic cell death; IHC, immunohistochemistry; MHC, major histocompatibility complex; MMAE, monomethyl auristatin E; NK, natural killer cells; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response(s); PRO, patient reported outcomes; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks; r/m, recurrent/metastatic; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard-of-care; sq, squamous; TCR, T-cell receptor; TF, tissue factor; TPS, Tumor Proportion Score; TTR, time to response; TV, tisotumab vedotin

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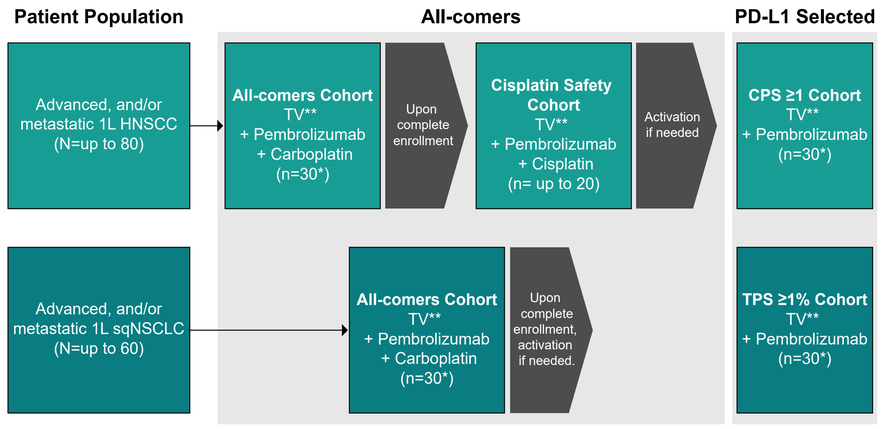
innovaTV 207 STUDY DESIGN: PART D

PHASE 2 • OPEN-LABEL • MULTICENTER • NON-RANDOMIZED

Part D of innovaTV 207 (NCT03485209) will enroll previously untreated patients with r/m HNSCC or sqNSCLC to receive either TV+pembrolizumab or TV+pembrolizumab+platinum agent.



* Futility analysis after 15 patients have been treated and had at least 1 post-baseline response assessment
** TV at dose of 2.0 mg/kg on Day 1 of each 21-day cycle (every 3 weeks [Q3W] schedule). Open to other TV dosing regimen(s) based on future data from TV-01 Part C.
Pembrolizumab will be administered at dose of 200 mg, carboplatin at dose of AUC 5, and cisplatin at dose of 100 mg/m^2 per study design

- Up to 140 treatment-naive patients with r/m HNSCC or sqNSCLC will be enrolled.
- First, the All-Comers cohorts for HNSCC and sqNSCLC will each enroll up to 30 patients, regardless of PD-L1 expression, for Q3W dosing with 2.0 mg/kg TV+pembrolizumab+carboplatin.
- Up to 20 patients with HNSCC will then be enrolled into a Cisplatin Safety Cohort for dosing with 2.0 mg/kg TV+pembrolizumab+cisplatin.
- Enrollment into All-Comers Cohort for each tumor type will also be followed by enrollment of up to 30 patients with HNSCC (CPS ≥1) and 30 pts with sqNSCLC (TPS ≥1%) into PD-L1 Selected cohorts for dosing with TV+pembrolizumab.
- Response will be assessed every 6 weeks for the first 6 months, every 12 weeks for the next 6 months, and then every 6 months after that.

CLINICAL SAFETY AND EFFICACY OF TV MONOTHERAPY

- As monotherapy, TV has a manageable safety profile, with most AEs being mild to moderate.[12]
  - Consistent safety profiles were demonstrated across all trials in the US, EU, and Japan, evaluating TV monotherapy in r/m CC patients (innovaTV 201, 204, and 206).
  - The safety profile of TV in the pivotal trial, innovaTV 204, was manageable and no new safety signals were identified.[12]
- In patients with previously treated r/mCC, TV demonstrated clinically meaningful and durable responses across histology, TF expression and prior treatment subgroups[12]
- Preliminary evidence of activity in multiple other tumor types was noted in the innovaTV 201 study[13] and Part A of the current study, innovaTV 207.[9]

CLINICAL SAFETY AND EFFICACY OF TV IN COMBINATION WITH OTHER AGENTS

- In the dose-escalation phase of the innovaTV 205 study, there were no dose-limiting toxicities based on review by the safety data monitoring committee and the maximum tolerated dose was not reached.
  - TV plus either bevacizumab, pembrolizumab, or carboplatin was adequately tolerable and demonstrated an acceptable safety profile.[14,15]
- No overlapping safety signals were observed when TV was used in combination with other agents.
- Encouraging and durable anti-tumor activity in patients with r/m CC from combination dosing cohorts in the innovaTV 205 trial[11]
  - TV and carbo in 1L setting (N=33): Confirmed ORR of 55% (95% CI: 36, 72)
  - TV and pembro in 1L setting (N=33): Confirmed ORR of 41% (95% CI: 24, 59)
  - TV and pembro in 2L/3L setting (N=35): Confirmed ORR of 38% (95% CI: 22, 56)

OBJECTIVES

Primary Objective
Evaluate antitumor activity of TV+pembrolizumab or TV+pembrolizumab +carboplatin, as measured by investigator-determined confirmed ORR per RECIST v1.1

Secondary Objectives
- Evaluate preliminary antitumor activity of TV+pembrolizumab or TV+pembrolizumab +platinum agent as measured by confirmed and unconfirmed ORR
- Evaluate the safety and tolerability of TV+pembrolizumab or TV+pembrolizumab+carboplatin
- Evaluate preliminary safety and tolerability of TV+pembrolizumab+cisplatin
- Assess PK and immunogenicity of TV
- Evaluate stability and control of disease; DCR
- Evaluate DOR
- Evaluate TTR
- Assess PFS
- Assess OS

Additional Objectives
- Assess TF expression-response relationship
- Assess biomarkers of biological activity and resistance and predictive biomarkers of response
- Evaluate PROs and HRQOL

References

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11. Lorusso et al, ASCO Annual Meeting, 2022
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ELIGIBILITY: KEY INCLUSION CRITERIA

HNSCC	sqNSCLC
Patients with r/m HNSCC must have had no previous systemic therapy for metastatic disease (exception is systemic therapy given as part of multimodal treatment for locally advanced disease completed >6 months prior).	Patients with r/m NSCLC must have histologically or cytologically documented squamous cell NSCLC and must not have had any previous systemic therapy for metastatic disease or radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study drug.
Must have a CPS ≥1 to be eligible for the cohorts testing TV+pembrolizumab alone.	Must have a TPS ≥1% for to be enrolled to cohorts testing TV+pembrolizumab alone.
PD-L1 biomarker expression as determined by a PD-L1 IHC assay must be available.	
Measurable disease per RECIST v1.1 as assessed by investigator.	
ECOG Performance Status score of 0 or 1.	

ELIGIBILITY: KEY EXCLUSION CRITERIA

- Known allergies, hypersensitivity, intolerance, or contra-indications to pembrolizumab
- Has known allergies, hypersensitivity, intolerance, or contra-indications to any part of the specific trial treatment regimen or to platinum-containing compound selected for the subject
- Coagulation defects with increased risk of bleeding; active bleeding conditions
- Ocular surface disease at the time of enrollment (Note: cataract is not considered active ocular surface disease)
- Inflammatory lung disease, including moderate and severe asthma. Patients with chronic obstructive pulmonary disease are allowed if not requiring systemic steroids and long-term oxygen
- Uncontrolled tumor-related pain
- Peripheral neuropathy ≥ Grade 2
- History of another malignancy within 3 years of the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy
- Known active CNS lesions or brain metastasis
- Patients who are breastfeeding, pregnant, or planning to become pregnant from the time of informed consent until 6 months after the final study dose is administered
- Chronic treatment with acetylsalicylic acid in combination with other anticoagulant therapy

STUDY SITES

- 39 sites across 7 countries (as of 21Apr2022): US, Canada, Italy, France, UK, Germany, and Spain
- Part D added: Nov 2021

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