Phase 1 First in Human Study of Programmed Cell Death Receptor-1 (PD-1) Inhibitor Monoclonal Antibody (mAb) JTX-4014 in Adult Subjects with Advanced Refractory Solid Tumor Malignancies

ABSTRACT# P439

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Background

JTX-4014 is a fully human mAb consisting of 2 identical hinge-stabilized immunoglobulin gamma 4 (IgG4, S228P) heavy and two identical kappa (Igκ) light chains, that specifically binds to PD-1 and is designed to augment antitumor T-cell activity by blocking the interaction of PD-1 with its ligands PD-L1 and PD-L2.

The desired mechanism of action of JTX-4014 is to block the interaction of PD-1 with its ligands, PD-L1 and PD-L2, and enhance T-cell function and thus augment antitumor activity. Therefore, an IgG4 isotype that lacks Fc-effector functionality was selected as the preferred Ig backbone for JTX-4014. In addition, JTX-4014 demonstrates lack of off-target reactivity in pre-clinical studies, as well as cross-reactivity to both cynomolgus monkey and mouse PD-1.

JTX-4014 is being developed as an agent to be used either as a monotherapy or in combination with other therapies for the treatment of cancer in which inhibition of PD-1 may be of benefit. The Phase 1 trial objectives were to evaluate the safety and tolerability of the drug along with its maximum tolerated dose (MTD) and recommended Phase 2 dose.

Objectives

Primary Objectives

- Evaluate the safety and tolerability of JTX-4014.
- Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D).

Secondary Objectives

- Evaluate the pharmacokinetics (PK) of JTX-4014.
- Evaluate anti-drug antibodies (ADA) against JTX-4014.

Exploratory Objectives

- Evaluate the efficacy of JTX-4014 according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (investigator assessed).

Key Inclusion/Exclusion

- Age ≥18 yrs
- Histologically or cytologically confirmed extracranial solid tumor that is recurrent, metastatic or refractory to at least one prior line of therapy with no further standard treatment options
- No concurrent anticancer treatment
- No prior anti-PD-1 or anti-PD-L1 therapy
- No requirement for selection based on PD-L1 expression
- No history of immune-mediated conditions
- No symptomatic or uncontrolled brain metastases
- Adequate renal, hepatic, and bone marrow function
- ECOG 0 or 1
- Women not pregnant or lactating

Trial Design

- Standard 3+3 design with dose escalation after review of at least 3 subjects in each cohort
- Screening period: up to 28 days
- Dosing: once every 21 days or 42 days
- DLT period: first 21 day cycle
- Data cutoff: September 23, 2019
- Dosing Groups:

Cohort 1	Cohort 2	Cohort 3a	Cohort 3b	Cohort 3c	Cohort 4
80mg IV q3w	240mg IV q3w	800mg IV q3w	800mg IV q6w	400mg IV q3w	1200mg IV q3w

RESULTS

Table 1: Subject Demographics

	Total (N=18)
Sex, n (%)	
Male	10 (55.6)
Female	8 (44.4)
Age (yrs)	
Mean (SD)	66.3 (11.24)
Race, n (%)	
White	13 (72.2)
Hispanic or Latino	4 (22.2)
Asian	1 (5.56)
Dose Administered (cycles)	
Median (min, max)	3.5 (1, 15)
Prior Therapies	
Median (min, max)	4.5 (1, 16)

Figure 1: Subject Tumor Types

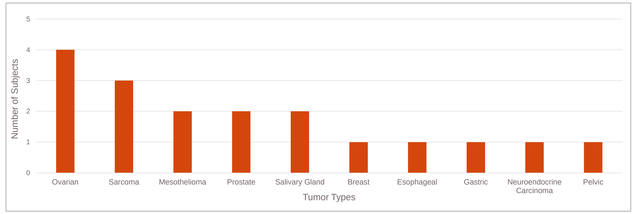


Table 2: Subject Disposition

	Cohort 1 80mg q3w n=3 (%)	Cohort 2 240mg q3w n=3 (%)	Cohort 3a 800mg q3w n=3 (%)	Cohort 3b 800mg q6w n=3 (%)	Cohort 3c 400mg q3w n=3 (%)	Cohort 4 1200mg q3w n=3 (%)	Total N=18 (%)
Subjects Remaining on Study Treatment	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	0	6 (33.3)
Subjects Discontinued from Study Treatment	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	3 (100.0)	12 (66.7)
Adverse Event/Serious Adverse Event	1 (33.3)	0	1 (33.3)	0	0	1 (33.3)	3 (16.7)
Investigator Decision	0	2 (66.7)	0	1 (33.3)	1 (33.3)	1 (33.3)	5 (27.8)
Progressive Disease	1 (33.3)	0	1 (33.3)	1 (33.3)	0	1 (33.3)	4 (22.2)

Table 3: Cycle 1 Pharmacokinetics of JTX-4014

	Cohort 1 80mg q3w (n=3)	Cohort 2 240mg q3w (n=3)	Cohort 3a 800mg q3w (n=3)	Cohort 3b 800mg q6w (n=3)	Cohort 3c 400mg q3w (n=3)	Cohort 4 1200mg q3w (n=3)
Half Life, Day (CV%)	11.78 (25.19%)	9.27 (2.96%)	10.77 (16.37%)	13.68 (31.36%)	12.30 (38.06%)	7.46 (19.76%)
Cmax, μg/L (CV%)	20,699.54 (23.55%)	77,780.08 (35.97%)	267,554.95 (27.03%)	288,568.15 (27.10%)	139,810.55 (12.91%)	408,263.84 (8.37%)
Tmax, Day (CV%)	0.04 (4.09%)	0.05 (10.24%)	0.04 (1.67%)	0.04 (6.70%)	0.04 (6.31%)	0.04 (2.82%)
AUCinf, day·μg/L (CV%)	238,720.07 (5.73%)	632,803.87 (61.54%)	2,692,313.23 (12.99%)	2,622,020.30 (18.99%)	1,519,889.64 (22.01%)	2,728,254.47 (32.79%)
Cl, L/day (CV%)	0.335 (5.731%)	0.379 (61.539%)	0.297 (12.989%)	0.305 (18.989%)	0.263 (22.015%)	0.440 (32.791%)
Vss, L (CV%)	5.699 (25.680%)	4.975 (61.729%)	4.536 (24.943%)	5.331 (24.401%)	4.708 (25.282%)	4.944 (10.190%)

Systemic exposure of JTX-4014 increased proportionally with dose. The geometric mean for terminal half-life ranged from 7 to 14 days. No anti-drug antibodies were detected as of the data cut-off.

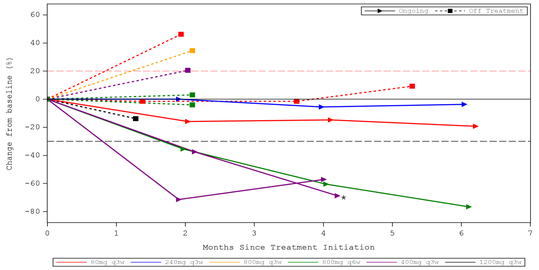
Safety Results:

- No deaths or Dose Limiting Toxicities (DLTs)
- Only related SAE was pneumonitis, which occurred after the second dose at 1200mg Q3W

Table 4: Related Treatment Emergent Adverse Events

Adverse Event	Total Adverse Events N=18 (%)	Grade 3/4 Adverse Events N=18 (%)
Subjects with at least one related TEAE	11 (61.1)	2 (11.1)
Alanine aminotransferase increased	1 (5.6)	-
Anemia	1 (5.6)	-
Arthralgia	1 (5.6)	-
Aspartate aminotransferase increased	1 (5.6)	-
Atrial fibrillation	1 (5.6)	-
Blood alkaline phosphatase increased	1 (5.6)	1 (5.6)
Blood creatine phosphokinase increased	1 (5.6)	-
Chills	1 (5.6)	-
Colitis microscopic	1 (5.6)	-
Decreased appetite	1 (5.6)	-
Dizziness	1 (5.6)	-
Dysgeusia	1 (5.6)	-
Fatigue	6 (33.3)	-
Headache	1 (5.6)	-
Hypothyroidism	1 (5.6)	-
Myalgia	1 (5.6)	-
Pneumonitis	1 (5.6)	1 (5.6)
Pruritus	1 (5.6)	-
Pyrexia	1 (5.6)	-
Rash maculo-papular	1 (5.6)	-

Figure 2: Spider Plot of Percent Change from Baseline in Sum of Diameters

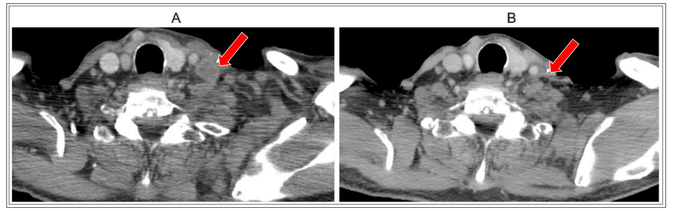


* Lymph node 80% reduction to 5mm, qualifies as CR by RECIST criteria.

Table 5: Efficacy Data

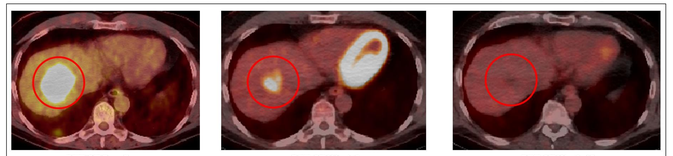
	Cohort 1 80mg q3w n=3 (%)	Cohort 2 240mg q3w n=3 (%)	Cohort 3a 800mg q3w n=3 (%)	Cohort 3b 800mg q6w n=3 (%)	Cohort 3c 400mg q3w n=3 (%)	Cohort 4 1200mg q3w n=3 (%)	Total N=18 (%)
Overall Response Rate, n (%)	0	0	0	1 (33.3)	2 (66.7)	0	**3 (16.7)**
Complete Response (CR)	0	0	0	0	1 (33.3)	0	**1 (5.6)**
Partial Response (PR)	0	0	0	1 (33.3)	1 (33.3)	0	**2 (11.1)**
Stable Disease (SD)	2 (66.7)	2 (66.7)	0	1 (33.3)	0	0	**5 (27.8)**
Progressive Disease (PD)	1 (33.3)	0	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	**6 (33.3)**
Not Evaluable (NE)	0	0	0	0	0	0	**0**
Early Termination	0	1 (33.3)	1 (33.3)	0	0	2 (66.7)	**4 (22.2)**

Figure 3: Mucoepidermoid Carcinoma of the Parotid Subject – Complete Response, 400mg Q3W



80 yo white male, diagnosed in mid-2017 with surgery in 2017 and 2018. Radiation therapy in mid-2018; prior therapy: carboplatin/cetuximab/dexamethasone. PR noted at week 9, CR noted at week 18. A) Baseline; B) Post Cycle 6 – No pathologic adenopathy

Figure 4: Carcinoma Ex-Pleomorphic Adenoma Subject – Partial Response, 800mg Q6W



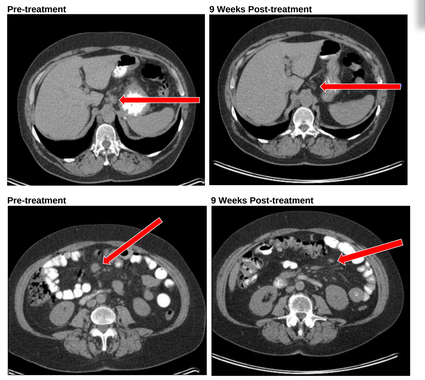
PET-CT Baseline
5.5 cm
SUV 23.8

PET-CT Week 9
3.7 cm
SUV 6.8

PET-CT Week 18
2.6 cm
Near resolution of abnormal FDG uptake

63 yo white male, diagnosed in early 2017 with surgery in the same month following diagnosis. Radiation therapy in 2017; prior therapy: trastuzumab/perjecta, Lupron/casodex, carboplatin/paclitaxel. PD-L1 expression - 100% by IHC. PR noted at week 9, confirmed at week 18 and week 27.

Figure 5: Ovarian Subject – Partial Response, 400mg Q3W



68 yo white female, diagnosed in 2013 with surgery in the month following diagnosis. Prior therapy: carboplatin/taxol, carboplatin/gemcitabine, Avastin, doxil/Imogene. PD-L1 expression - 5% by IHC. PR noted at week 9, confirmed at week 18.
Note: the bottom two scans represent a mesenteric lymph node that is in a different position relative to fixed structures on serial scans.

Conclusion

- JTX-4014 is an active PD-1 inhibitor and was found to be safe and well-tolerated in this Phase 1 study. There were no deaths or DLTs reported in the study. The only related SAE was pneumonitis, which occurred after the second dose at 1200 mg Q3W.
- Antitumor activity was observed in the difficult to treat population enrolled. JTX-4014 efficacy data:
  - 1 Complete Response (PR at 9 weeks [confirmed at 18 week], CR at 18 weeks)
  - 2 Partial Response (confirmed)
  - 5 Stable Disease
  - Overall Response Rate – 3/18 (16.7%)
  - Disease Control Rate – 8/18 (44.4%)
- JTX-4014 has a typical IgG4 profile with linear PK.
- Recommended Phase 2 dose is either 500mg Q3W or 1000mg Q6W.
- Phase 2 JTX-4014 studies are planned.

SCAN ME

NCT03790488