Phase 1 Study of JTX-8064, a LILRB2 (ILT4) inhibitor, as monotherapy and combination with pimivalimab (pimi), a PD-1 inhibitor (PD-1i), in patients (pts) with advanced solid tumors

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ABSTRACT

Background: JTX-8064, a highly selective and potent IgG4 inhibitor of myeloid-specific Leukocyte Immunoglobulin Like Receptor B2 (LILRB2), leads to macrophage reprogramming from an immunosuppressive to an immune activated state, resulting in T cell activation. INNATE (NCT04669899) is a phase (P) 1/2 dose escalation/expansion study of two investigational agents, JTX-8064 monotherapy (mono) and combination (combo) with pimi. P1 data defining recommended P2 Dose (RP2D) are presented.

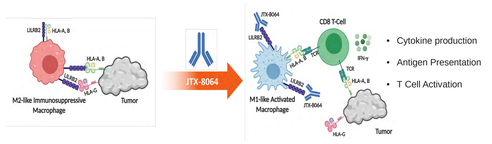
Methods: Pts with advanced solid tumors who progressed after all available therapy were treated at 7 dose levels of JTX-8064 mono IV q3w (50, 150, 300, 450, 600, 900, 1200 mg) and 2 dose levels of JTX-8064 (700, 1200 mg) + pimi 500 mg IV q3w using Bayesian design. 1º objectives: safety, tolerability, RP2D. 2 º objectives: receptor occupancy (RO), PK, immunogenicity. Objective response rate (RECIST 1.1) was exploratory.

Results: 31 pts were treated in dose escalation: 22 JTX-8064 mono, 9 JTX-8064 + pimi. No dose limiting toxicities; maximum tolerated dose not reached. Safety: Mono: Median age 67. 11 pts (50%) had treatment-related adverse events (TRAE). Most common were fatigue (n= 5), upper abdominal pain, arthralgia, flushing, nausea, and pyrexia (n= 2 each). The only Grade 3 (G3) TRAE and only serious related AE (SRAE) was tumor flare at 1200 mg. Combo: Median age 63. 6 pts (66.7%) had TRAE, most common fatigue (n=4) and pyrexia (n=2). No ≥ G3 TRAEs, no SRAEs.
PK was linear. Full RO thru 21 days was achieved at ≥ 300 mg. RP2D of 700 mg q3w was selected for JTX-8064 +/- pimi to optimize RO in tumor, with Cmin at steady state 63.4 (26.0-139.7) ug/mL. Treatment induced antibodies to JTX-8064 occurred in 1 mono and no combo pts.
P1 Efficacy: Mono: 0 PR, 7 SD with 2 durable SD (appendiceal cancer 8.3, ovarian cancer 12.2 mo). Combo: 1 PR (6.2 mo) at 700 mg in PD-1i resistant cholangiocarcinoma with resolution of both bone pain and cachexia, 3 SD with 1 durable SD (post-PD-1i NSCLC 6 mo).

Conclusions: JTX-8064 was well-tolerated as mono and in combination with pimi, with 700 mg q3w selected as the preliminary RP2D. Enrollment is ongoing in Phase 2, including cohorts in renal and ovarian cancer that have met Simon's 2-stage response criteria to expand.

MOA and Study Design

Figure 1: Mechanism of Action of JTX-8064 Potential to Reverse PD-(L)1i Resistance



- IC_{50} and EC_{50} at sub-nM concentrations
- High specificity to LILRB2
- Inhibition of LILRB2 reprograms macrophages from immunosuppressive M2 to immunostimulatory M1 state[1]
- JTX-8064 reprogrammed macrophages are more effective at stimulating T cells in co-culture[2]

1. Cohen *et al.*, Abstract 5007, AACR 2019; 2. McGrath *et al.*, Abstract 1727, AACR 2021.

Figure 2: JTX-8064-101 Study Schema

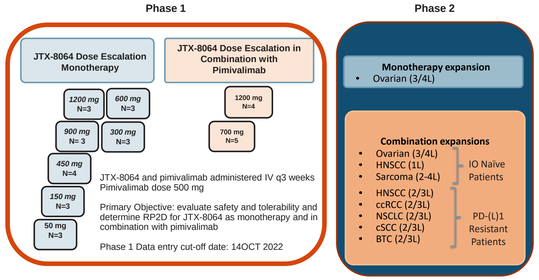


Table 1: Patient Disposition

	Mono Dose Escalation								Combo Dose Escalation		
	50 mg (N=3)	150 mg (N=3)	300 mg (N=3)	450 mg (N =4)	600 mg (N=3)	900 m (N=3)	1200 mg (N=3)	Total (N=22)	700 mg + Pimi (N=5)	1200 mg + Pimi (N=4)	Total (N=9)
Number of Patients Dosed	3	3	3	4	3	3	3	22	5	4	9
Discontinued Treatment, n (%)	3 (100.0)	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	22 (100.0)	4 (80.0)	4 (100.0)	8 (88.9)
Primary Reason for Discontinuation, n (%)											
Radiographic Disease Progression	1 (33.3)	2 (66.7)	3 (100.0)	3 (75.0)	2 (66.7)	2 (66.7)	3 (100.0)	16 (72.7)	3 (60.0)	3 (75.0)	6 (66.7)
Clinical Disease Progression	1 (33.3)	1 (33.3)	0	0	0	0	0	2 (9.1)	0	1 (25.0)	1 (11.1)
Adverse Event	0	0	0	1 (25.0)	0	0	0	1 (4.5)	1 (20.0)	0	1 (11.1)
Other*	1 (33.3)	0	0	0	1 (33.3)	1 (33.3)	0	3 (13.6)	0	0	0
End of Phase 1 Study, n (%)	3 (100.0)	2 (66.7)	3 (100.0)	4 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	20 (90.9)	3 (60.0)	4 (100.0)	7 (77.8)

*Other category includes physician decision and lack of efficacy

RESULTS

Table 2: Demographics and Baseline Characteristics

- Tumor types included colorectal, non-small cell lung, small cell lung, pancreas, breast, prostate, esophagus, liposarcoma, cholangiocarcinoma, renal cell carcinoma
- >50% of patients had ≥3 lines of prior therapy

	Mono Dose Escalation (N = 22)	Combo Dose Escalation (N = 9)	Total (N = 31)
Age, years			
Median (range)	67 (43 - 86)	63 (47- 74)	66 (43 – 86)
Sex, n (%)			
Male	8 (36.4)	4 (44.4)	12 (38.7)
Female	14 (63.6)	5 (55.6)	19 (61.3)
Ethnicity, n (%)			
Hispanic or Latino	4 (18.2)	1 (11.1)	5 (16.1)
Not Hispanic or Latino	14 (63.6)	6 (66.7)	20 (64.5)
Unknown/not reported	4 (18.2)	2 (22.2)	6 (19.4)
Race, n(%)			
White	18 (81.8)	7 (77.8)	25 (80.6)
Black or African American	2 (19.1)	0	2 (6.5)
Asian	0	2 (22.2)	2 (6.5)
Other	2 (9.1)	0	2 (6.5)
ECOG, n (%)			
0	6 (27.3)	2 (22.2)	8 (25.8)
1	16 (72.7)	7 (77.8)	23 (74.3)
Prior line of therapy			
Median (range)	2 (1 – 13)	3 (2-7)	3 (1 – 13)
n (%)			
≤ 1	6 (27.3)	0	6 (19.4)
≥ 2	5 (22.7)	3 (33.3)	8 (25.8)
≥3	10 (45.5)	6 (66.7)	16 (51.6)
Missing	1 (4.5)	0	1 (3.2)
Prior PD-1 or PD-L1 therapy, n (%)			
Yes	5 (22.7)	3 (33.3)	8 (25.8)
No	17 (77.3)	6 (66.7)	23 (74.2)

Table 3: JTX-8064 was well tolerated alone and in combination with pimivalimab

- No DLTs were observed
- <5% (N=1) of monotherapy patients experienced related Gr ≥3 Adverse Events
- 11% (N=1) of combination patients experienced related Gr ≥3 Adverse Events

a. Monotherapy: Most common monotherapy TRAEs occurring in ≥2 subjects included fatigue (N=5), and pyrexia, arthralgia, abdominal pain, flushing, nausea (each N=2)

	JTX-8064 Monotherapy Dose Escalation							
	50 mg (N = 3)	150 mg (N = 3)	300 mg (N = 3)	600 mg (N = 3)	450 mg (N = 4)	900 mg (N = 3)	1200 mg (N = 3)	Total (N = 22)
TEAEs	2 (66.7)	3 (100.0)	2 (66.7)	3 (100.0)	4 (100.0)	3 (100.0)	3 (100.0)	20 (90.9)
DLTs	0	0	0	0	0	0	0	0
Related TEAEs	2 (66.7)	2 (66.7)	1 (33.3)	0	2 (50.0)	2 (66.7)	2 (66.7)	11 (50.0)
Related TEAEs >=Grade 3	0	0	0	0	0	0	1 (33.3)	1 (4.5)
Serious TEAEs	0	0	0	1 (33.3)	1 (25.0)	1 (33.3)	3 (100.0)	6 (27.3)
Treatment related serious TEAEs	0	0	0	0	0	0	1 (33.3)**	1 (4.5)
Immune related TEAEs	0	0	1 (33.3)	0	0	0	0	1 (4.5)
Infusion related TEAEs	0	0	1 (33.3)	0	0	0	0	1 (4.5)
TEAEs leading to dose interruption	0	0	0	0	0	0	0	0
TEAEs leading to dose hold / delay	0	0	0	0	1 (25.0)	0	1 (33.3)	2 (9.1)
TEAEs leading to study drug discontinuation	0	0	0	0	1 (25.0)	0	0	1 (4.5)
TEAEs leading to death	0	0	0	0	1 (25.0)*	0	0	1 (4.5)

*TEAE leading to death was pulmonary embolism, not related to treatment **Treatment related SAE is tumor flare

b. Combination: Most common combination therapy TRAEs occurring in ≥2 subjects included fatigue (N=4) and pyrexia (N=2)

	Combo Dose Escalation		
	700 mg + Pimi (N = 5)	1200 mg + Pimi (N = 4)	Total (N = 9)
TEAEs	4 (80.0)	4 (100.0)	8 (88.9)
DLTs	0	0	0
Related TEAEs	2 (40.0)	4 (100.0)	6 (66.7)
Related TEAEs >=Grade 3	1 (20.0)	0	1 (11.1)
Serious TEAEs	2 (40.0)	3 (75.0)	5 (55.6)
Treatment related serious TEAEs	1 (20.0)#	0	1 (11.1)
Immune related TEAEs	1 (20.0)	2 (50.0)	3 (33.3)
Infusion related TEAEs	0	0	0
TEAEs leading to dose interruption	0	0	0
TEAEs leading to dose held / delay	1 (20.0)	1 (25.0)	2 (22.2)
TEAEs leading to study drug discontinuation	1 (20.0)	2 (50.0)	3 (33.3)
TEAEs leading to death	0	0	0

#Treatment related SAE is immune-related pneumonitis

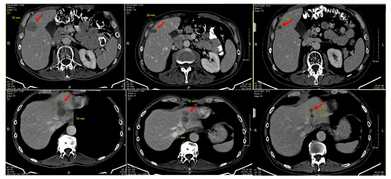
Table 4: Best Overall Response by RECIST 1.1 Investigator Assessment

- Monotherapy: 35% SD, including 2 SDs with PFS ≥ 6 months at 150 mg and 300 mg
- Combination: 1 PR and 3 SD, including 1 SD with PFS ≥ 6 months at 700 mg JTX-8064
- Duration of response for patient with PR was 6.2 months

	Mono Dose Escalation (N = 22)	Combo Dose Escalation (N = 9)
Efficacy Evaluable, n	20	9
Best Overall Response, n (%)		
CR	0	0
PR	0	1 (11.1)
SD	7 (35.0)	3 (33.3)
SD with PFS >= 6mos	2 (10.0)	1 (11.1)
PD	12 (60.0)	5 (55.6)
Not Evaluable (NE)	0	0
Not Reported/Unknown/Missing	0	0
Early Death/Termination	1 (5.0)	0
Overall Response Rate (ORR) , n (%)	0	1 (11.1)
Disease Control Rate (DCR) , n (%)	7 (35.0)	4 (44.4)

Figure 3: Patient with Cholangiocarcinoma with durable PR

- Cachectic patient with cholangiocarcinoma with liver and bone metastases and bone pain
- Prior treatments: Gem/Cis (1st line) and Nivo plus 5-FU/LV/nal-IRI (2nd line) with best response of PD to all prior therapy
- Analysis of an archival biopsy prior to the nivolumab containing regimen showed low levels of CD8 and 0% of PD-L1 CPS by IHC, indicating a tumor microenvironment less likely to respond to anti-PD-1 therapy



- Patient received JTX-8064 700 mg + pimi 500 mg q3w
- 9 weeks: PR, 12 lb weight gain and bone pain decreased
- 18 weeks: confirmed PR, ECOG 0 and returning to work
- 27 week: continued PR (-60%); ~30 lb weight gain
- 36 week: PD, new lesion. No change in target lesions. Received radiation and continued study treatment

Table 5: JTX-8064 Saturates LILRB2 on Peripheral Monocytes Starting at 300 mg

Dose (mg)	N		Arithmetic Mean (SD) Monocyte RO (%) at:	
	$N_{1.5h}$	N_{504h}	$RO_{1.5h}$	RO_{504h}
50	3	3	92.4 (1.33)	43.7 (44.64)
150	3	3	92.9 (2.71)	83.1 (5.08)
300	3	3	89.5 (4.64)	86.3 (2.50)
450	3	2	96.7 (1.76)	93.3 (4.20)
600	2	2	91.8 (2.98)	84.5 (6.58)
900	3	2	96.2 (1.09)	82.5 (6.45)
1200	2	3	96.5 (1.16)	92.1 (6.87)

- In this assay, peripheral monocyte receptor occupancy (RO) consistently plateaus at saturation levels of 85-90%.
- Saturation of peripheral monocyte RO (full LILRB2 receptor antagonism) is considered achieved when this plateau is attained and maintained for the entire 3-week dosing interval for all subjects in the cohort.

Table 6: JTX-8064 has a favorable PK Profile

- Clearance and half-life estimates stabilize at doses of 300 mg and above, indicative of TMDD saturation
- At doses ≥300 mg, JTX-8064 exhibits standard PK parameters for a mAb
- A 2-compartment population PK model for JTX-8064 (built based on monotherapy dose escalation data) also confirmed linear PK at doses ≥ 300 mg (i.e. TMDD is saturated).
- Treatment induced ADA observed in 1/29 (3.4%) patients.
- At the preliminary RP2D of 700 mg q3w, predicted median [90%CI] C_{trough} for JTX-8064 is 63.4 [26.0-139.7] µg/mL.

Cohort	Dose (mg)	N	PK Parameter				
			C_{max} (ug/mL)[1]	AUC_{inf} (Day*ug/mL)[1]	Half-Life (Day)[2]	CL (L/Day)[2]	Vz_obs (L)[2]
Mono Dose Escalation	50	3	19.9 (22.3)	103 (28.3)	4.83 (3.425)	0.497 (0.1257)	3.05 (1.244)
	150	3	60.7 (49.1)	472 (61.2)	7.39 (0.7968)	0.353 (0.1929)	3.76 (2.181)
	300	3	134 (15.8)	1312 (20.4)	9.60 (1.281)	0.232 (0.04837)	3.16 (0.2494)
	450	4	181 (21.6)	1715 (39.6)	11.6 (2.785)	0.275 (0.08884)	4.34 (0.7992)
	600	3	194 (15.3)	2050 (25.5)	13.1 (1.821)	0.299 (0.07843)	5.62 (1.309)
	900	3	415 (11.8)	3812 (28.4)	9.51 (1.322)	0.242 (0.06465)	3.24 (0.4546)
	1200	3	513 (61.2)	4930 (67.2)	9.94 (3.710)	0.278 (0.1835)	3.95 (2.836)
Combo Dose Escalation	700 + Pimi	5	253 (16.1)	2504 (19.8)	13.7 (4.926)	0.284 (0.05895)	5.47 (1.452)
	1200 + Pimi	4	364 (11.2)	3281 (24.6)	9.50 (2.564)	0.374 (0.08816)	4.92 (0.9223)

1-Geometric mean (geometric coefficient of variation[CV]) 2-Arithmetic mean (standard deviation)

Table 7: The JTX-8064 dose of 700 mg met all prespecified criteria for selection as the RP2D

RP2D Criteria	Dose
Acceptable safety and tolerability	Up to 1200 mg q3w
Saturation of TMDD	From 300 mg q3w
Saturation of monocyte RO over Cycle 1	From 300 mg q3w
Cycle 1 C_{trough} ≥ 2-fold higher than the C_{trough} at the first dose showing saturation of both TMDD and RO	700 mg q3w predicted median $C_{trough,\ 700\ mg}$ = 63.4 µg/ml ~ 2.5 median $C_{trough,\ 300\ mg}$ 27.2 µg/ml

Note: the 2-fold factor for C_{trough} was established based on a translational physiologically-based PK (PBPK) model suggesting tumor concentrations 2-3-fold lower than serum concentrations

SUMMARY

- JTX-8064, a high affinity LILRB2-specific antagonist antibody with the potential to reverse PD-(L)1i resistance, has demonstrated a good safety and tolerability profile, both as monotherapy and in combination with pimivalimab.
- The dose of 700 mg was selected as RP2D based on acceptable safety and tolerability and prespecified PK/RO criteria.
- The combination treatment showed activity (durable PR) in a patient with advanced biliary tract cancer who failed prior treatment with a PD-1 inhibitor.
- Enrollment into multiple expansion cohorts is ongoing.

ACKNOWLEDGEMENTS

We wish to thank patients, their families and caregivers, the investigators and their teams, as well as Di Li, Veenu Bala, Yasmin Hashambhoy-Ramsay, Jean-Christophe Pignon, Anne Marie Cleary, Amandine Manon, Karen Brown Allison Naumovski, Johan Baeck, Adam Beltran and Vojislav Vukovic for their contributions to this clinical study

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