Abstract #3089: A Phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors

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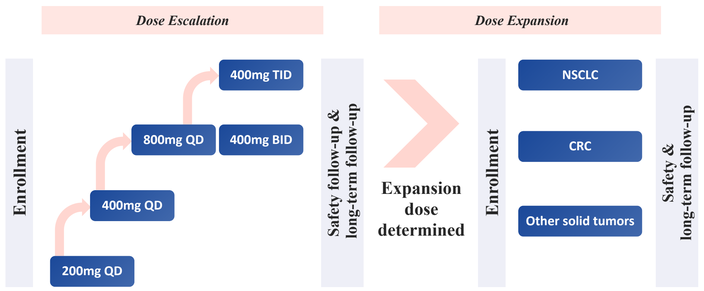
BACKGROUND

- KRAS^{G12C} mutations act as oncogenic drivers. In China, these mutations occur in approximately 4.3% of lung cancer, 2.5% of colorectal cancer (CRC), and 2.3% of biliary cancer. [1]
- JAB-21822 (Jacobio, China) is a novel, highly selective, orally bioavailable, covalent KRAS^{G12C} inhibitor
- Preclinical data have demonstrated that JAB-21822:
  - Has potent *in vitro* and *in vivo* antitumor activity
  - Has better oral bioavailability resulted in higher drug exposure compared with two leading KRAS^{G12C} inhibitors in US
  - Exhibits favorable safety profile with no risk of QT prolongation
- We present the data of the phase I portion of study (NCT05009329)

METHODS

- Key eligibility criteria
  - Advanced or metastatic solid tumor with preferable KRAS^{G12C} mutation
  - Adequate organ functions
  - Patients with advanced solid tumors who are refractory or intolerable to standard of care (SOC), or are not willing to receive SOC therapy
  - No more than 3 lines of prior therapy (specifically NSCLC expansion cohort)
  - Measurable disease according to RECIST v 1.1
  - No active brain or spinal metastases
  - ECOG 0 or 1

Figure 1. JAB-21822 Study Design*



*First-in-human, open-label; accelerated titration and 3+3 design

- Study Objectives:
  - Assess safety and tolerability of JAB-21822
  - Determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
  - Characterize pharmacokinetic (PK) profile of JAB-21822 after single and multiple doses
  - Evaluate preliminary antitumor activity
- The trial is being conducted in multiple centers in China
- The date of data cutoff is April 1, 2022

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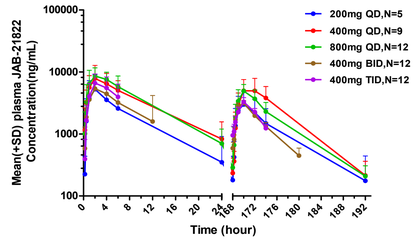
RESULTS

Table 1. Baseline Characteristics

Baseline Characteristics	All Patients (N=72)
Age, years	
median (range)	62.5 (38-85)
Sex, No. (%)	
Female	22 (30.6%)
Male	50 (69.4%)
ECOG PS, No. (%)	
0	8 (11.1%)
1	64 (88.9%)
Prior lines of systemic therapy, No. (%)	
0	5 (6.9%)
1	30 (41.7%)
2	17 (23.6%)
3	13 (18.1%)
≥4	7 (9.7%)
Brain metastases, No. (%)	
Yes	12 (16.7%)
No	59 (81.9%)
Missing	1 (1.4%)
Tumor types, No. (%)	
NSCLC	52 (72.2%)
Prior anti-PD-1/L1 therapy	
Yes	35 (67.3%)
No	17 (32.7%)
CRC	17 (23.6%)
PDAC	3 (4.2%)

Figure 2. JAB-21822 Pharmacokinetic Profile



PK Results

- JAB-21822 was well absorbed, with median time to reach peak plasma concentration of 2 hours
- Mean half-life was 4.99-5.54 hours

As of April 1, 2022, a total of 72 patients have received at least one dose of JAB-21822.
Two NSCLC patients in the 200 mg QD cohort did not have KRAS^{G12C} mutation.
Most patients are heavily treated with 51% having received ≥ 2 prior lines of therapy.

Table 2. Safety Summary: Treatment related adverse events (TRAE) with frequency > 5% in patients

	Total N=72	200 mg QD (N=5)		400 mg QD (N=18)		800 mg QD (N=22)		400 mg BID (N=12)		400 mg TID (N=15)	
AE	Any Grade	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Blood bilirubin increased	29 (40.3%)	2 (40.0%)	0	3 (16.7%)	0	5 (22.7%)	1 (4.5%)	8 (66.7%)	0	9 (60.0%)	1 (6.7%)
Anemia	21 (29.2%)	1 (20.0%)	0	4 (22.2%)	0	5 (22.7%)	0	6 (50.0%)	0	5 (33.3%)	0
Alanine aminotransferase* increased	11 (15.3%)	0	0	3 (16.7%)	0	2 (9.1%)	0	2 (16.7%)	2 (16.7%)	1 (6.7%)	1 (6.7%)
Aspartate aminotransferase* increased	11 (15.3%)	0	0	3 (16.7%)	0	1 (4.5%)	0	3 (25.0%)	2 (16.7%)	1 (6.7%)	1 (6.7%)
Proteinuria	8 (11.1%)	0	0	1 (5.6%)	0	1 (4.5%)	0	4 (33.3%)	0	2 (13.3%)	0
White blood cell count decreased	7 (9.7%)	0	0	1 (5.6%)	0	1 (4.5%)	0	3 (25.0%)	0	1 (6.7%)	1 (6.7%)
Neutrophil count decreased	5 (6.9%)	0	0	1 (5.6%)	0	1 (4.5%)	0	0	2 (16.7%)	0	1 (6.7%)
Rash	5 (6.9%)	0	0	0	0	2 (9.1%)	0	1 (8.3%)	0	2 (13.3%)	0
Vomiting	5 (6.9%)	0	0	3 (16.7%)	0	1 (4.5%)	0	0	0	1 (6.7%)	0
Diarrhea	4 (5.6%)	0	0	0	0	2 (9.1%)	0	2 (16.7%)	0	0	0
Hyponatremia	4 (5.6%)	0	0	1 (5.6%)	0	1 (4.5%)	0	2 (16.7%)	0	0	0

- Most common AE (frequency ≥ 10%) amongst all cohorts: Blood bilirubin increased, anemia, alanine aminotransferase and aspartate aminotransferase increased, proteinuria
- Majority of TRAEs are grades 1-2
- Lower Grade 3-4 TRAEs in QD cohort comparing with BID or TID cohort
- No TRAEs led to discontinuation
- No Grade 5 TRAEs were observed
- 3 patients (4.2%) experienced treatment-related SAEs

Table 3: Objective Response Rate in Patients with KRAS^{G12C} solid tumors

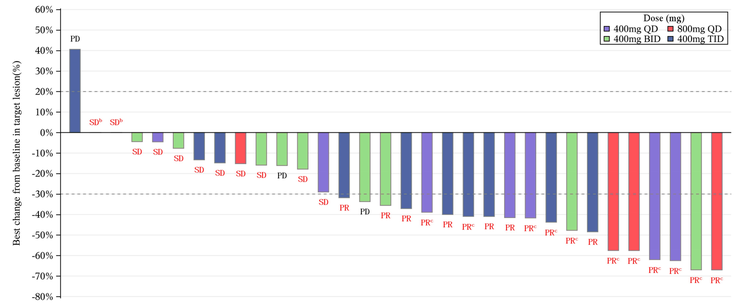
	200 MG QD (N=2)	400 MG QD (N=9)	800 MG QD (N=11)	400 MG BID (N=12)	400 MG TID (N=15)	All Patients (N=49*)
Best Overall Response No. (%)						
Complete Response (CR)	0	0	0	0	0	0
Partial Response (PR)	0	5 (55.6%)	5 (45.5%)	3 (25.0%)	7 (46.7%)	20 (40.8%)
Stable Disease (SD)	2 (100.0%)	4 (44.4%)	6 (54.5%)	7 (58.3%)	6 (40.0%)	25 (51.0%)
Progressive Disease (PD)	0	0	0	2 (16.7%)	2 (13.3%)	4 (8.2%)
Objective Response Rate (ORR)	0	5 (55.6%)	5 (45.5%)	3 (25.0%)	7 (46.7%)	20 (40.8%)
Disease Control Rate (DCR)	2 (100.0%)	9 (100%)	11 (100%)	10 (83.3%)	13 (86.7%)	45 (91.8%)

*Efficacy evaluable patient is defined as having completed at least one post-treatment assessment. At data cutoff, 19 patients have not reached 1st post-treatment tumor assessment.

- All solid tumors:
  - ORR 40.8% (20/49)
  - DCR 91.8% (45/49)
- KRAS^{G12C} mutant NSCLC: (Figure 3 and 4)

RESULTS - KRAS^{G12C} NSCLC

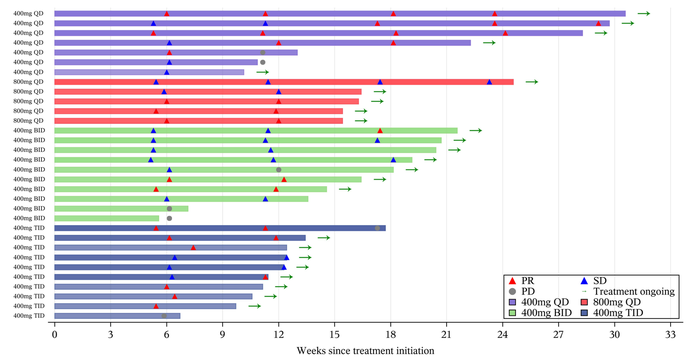
Figure 3: Patients with KRAS^{G12C} mutant NSCLC



b: one patient 800 mg QD and one patient 400 mg BID; c: confirmed PR

- **ORR 56.3% (18/32); DCR 90.6% (29/32)**
- QD COHORT (included 400mg & 800mg QD):
  - **ORR for 400 mg and 800 mg QD cohorts is 66.7% (8/12)**
  - **DCR for QD dosing 400 mg and 800 mg 100% (12/12)**

Figure 4: Treatment duration: Patients with KRAS^{G12C} mutant NSCLC



CONCLUSION

- JAB-21822 is well tolerated with no DLTs in the dose escalation phase
- In KRAS^{G12C} mutant NSCLC : Overall, ORR 56.3% (18/32), DCR 90.6% (29/32); in QD cohort, ORR 66.7% (8/12) and DCR 100% (12/12).
- Preliminary efficacy results demonstrate promising clinical activity of single-agent JAB-21822 in patients with KRAS^{G12C} mutant NSCLC
- Subject recruitment is ongoing, and trial remains open to enrollment

REFERENCES

1.Loong HH, et al. Transl Lung Cancer Res. 2020;9(5):1759-1769.