Glecirasib (JAB-21822, KRAS G12C inhibitor) Monotherapy and in Combination with Cetuximab in Patients with Advanced Colorectal Cancer

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BACKGROUND

- KRAS^{G12C} mutations act as oncogenic drivers. In China, these mutations occur in approximately 2.5% of colorectal cancer (CRC) cases. [1]
- Glecirasib (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 the US
  - Exhibits favorable safety profile with no risk of QT prolongation
  - Combination with cetuximab can increase tumor regression and delay tumor growth
- We present the data of JAB-21822 monotherapy (NCT05009329) and in combination with cetuximab (NCT05194995) for advanced CRC patients.

METHODS

- Key eligibility criteria
  - Advanced CRC patients with KRAS^{G12C} mutation
  - Adequate organ function
  - Measurable disease according to RECIST v1.1
  - No active brain or spinal metastases
  - ECOG 0 or 1
  - Monotherapy trial: Refractory or intolerable to standard of care (SOC)
  - Combination trial:
    - Systemic regimens should include fluoropyrimidine, irinotecan and/or oxaliplatin
    - MSI-H disease must have been treated with checkpoint inhibitors unless contraindicated
- Monotherapy study design presented at 2022 ASCO poster session

Figure 1. JAB-21822 + Cetuximab in Advanced CRC Study Design

- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoint: Safety, PK, DOR, PFS, OS
- The date of data cutoff is May 29, 2023.

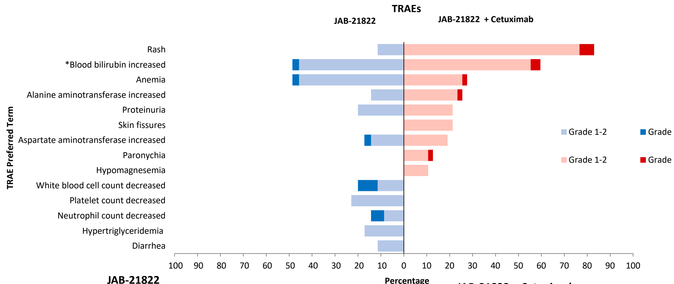
RESULTS

Table 1. Baseline Characteristics

Characteristics	21822 Monotherapy[a] (n= 35)	21822 plus Cetuximab[b] (n=47)
Age, years		
median (range)	55 (32-74)	58 (28-78)
Sex, No. (%)		
Female	12 (34.3%)	25 (53.2%)
Male	23 (65.7%)	22 (46.8%)
ECOG PS, No. (%)		
0	8 (22.9%)	21 (44.7%)
1	27 (77.1%)	26 (55.3%)
Prior systemic therapy, n (%)		
Median (range)	3 (1 – 8)	2 (1 - 4)
1	7 (20%)	12 (25.5%)
2	8 (22.9%)	16 (34%)
3	6 (17.1%)	15 (31.9%)
≥4	14 (40%)	4 (8.5%)

[a]JAB-21822 monotherapy dose of 800 mg PO QD
[b]JAB-21822 dosed 800 mg PO QD; Cetuximab 400 mg/m^2 IV and subsequent dosing 250 mg/m^2 QW or 500 mg/m^2 Q2W.
Most patients are heavily treated with ~80% (monotherapy) and ~74% (combination) having received ≥ 2 prior lines of systemic therapy.

Figure 2. Treatment-Related Adverse Events (TRAE) with frequency > 10% in patients



JAB-21822

- Majority of TRAEs are grades 1-2
- No Grade 4 or 5 TRAE observed
- No TRAEs led to discontinuation of JAB-21822
- 2 patients (5.7%) experienced treatment-related SAEs
- * Includes merged PT of blood bilirubin, unconjugated and conjugated increased

JAB-21822 + Cetuximab

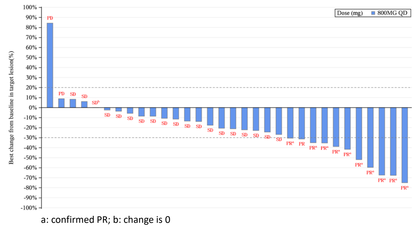
- Majority of TRAEs are grades 1-2
- No Grade 5 TRAEs were observed
- TRAEs led to discontinuation in 4.3% of patients (2/47)
- 4 patients (8.5%) experienced treatment-related SAEs

Table 2. Objective Response Rate per RECIST 1.1

Best Overall Response, n (%)	21822 Monotherapy (n=33)	21822 plus Cetuximab (N=43)
Complete Response (CR)	0	0
Partial Response (PR)	11 (33.3%)[a]	27 (62.8%)[b]
Stable Disease (SD)	19 (57.6%)	13 (30.2%)
Progressive Disease (PD)	3 (9.1%)	3 (7%)
Objective Response Rate (ORR)	11 (33.3%)	27 (62.8%)
Disease Control Rate (DCR)	30 (90.9%)	40 (93%)

*Efficacy evaluable patient is defined as having completed at least one post-treatment assessment.
[a]10 (30.3%) patients with confirmed PR
[b]20 (46.5%) patients with confirmed PR

Figure 3: Tumor Response of JAB-21822



a: confirmed PR; b: change is 0

Figure 5: mPFS of JAB-21822

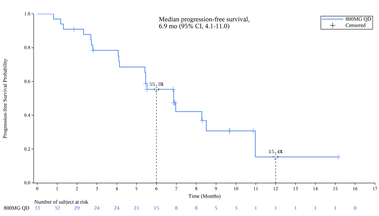
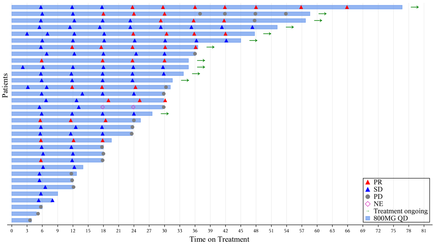
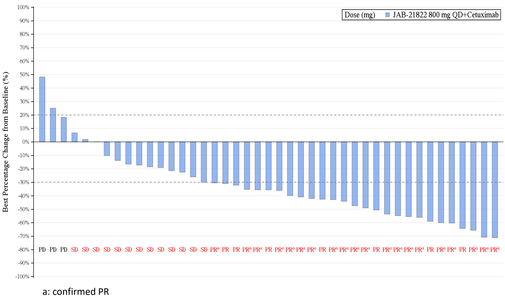


Figure 4: Treatment Duration of JAB-21822



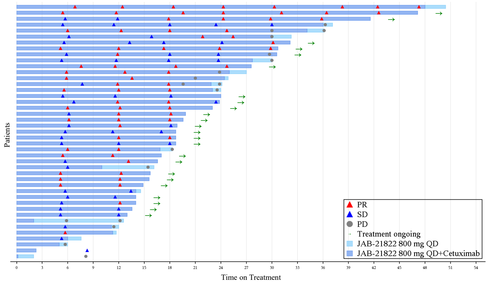
RESULTS

Figure 6: Tumor Response of JAB-21822 plus Cetuximab



a: confirmed PR

Figure 7: Treatment Duration JAB-21822 plus Cetuximab



CONCLUSION

- JAB-21822 yielded ORR 33.3% (11/33), DCR 90.9% (30/33) and mPFS of 6.9 months.
- JAB-21822 + cetuximab resulted in ORR 62.8% (27/43) and DCR 93% (40/43)
- DOR and mPFS not reached for combination study
- Efficacy results demonstrate promising clinical activity in both JAB-21822 monotherapy and JAB-21822 plus cetuximab in patients with KRAS^{G12C} mutant advanced CRC

REFERENCES

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

ACKNOWLEDGEMENTS

- We thank the patients participating in the studies.
- We thank all the investigators at each study site.
- We thank staff involved in JAB-21822-1002 and JAB-21822-1007 studies.
- Contact: oncogene@163.com
- COI: In relation to this presentation, Andrea Wang-Gillam is an employee of Jacobio Pharmaceuticals, Inc., and J. Li declares no conflicts of interest.