A modular, open-label, phase I/II study to evaluate the safety, tolerability, pharmacokinetics and efficacy of EP0031, a next generation selective RET inhibitor, in patients with advanced RET-altered malignancies

B043

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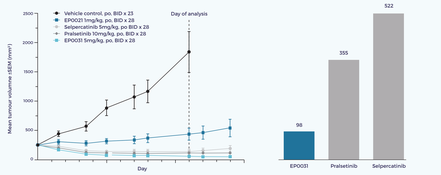
BACKGROUND

EP0031 (A400/KL590586), a next generation selective RET inhibitor (SRI), is being developed in parallel in Phase 1/2 studies in China (NCT05265091, Kelun Biotech) and in the West (NCT05443126, Ellipses Pharma).

EP0031 is highly selective for RET compared to VEGFR and other kinases and has greater potency than 1st generation SRIs against common RET mutations and RET resistance mutations. Improved brain exposure and survival compared with 1st generation SRIs has been demonstrated in intracranial xenograft models[1].

A higher PR rate was observed for EP0031 compared with 1st generation SRIs in an SRI-naive NSCLC PDX model (CTG2540) (Figure 1).

Figure 1. Comparison of efficacy versus 1st generation SRIs in an SRI-naive KIF5B-RET fusion +ve NSCLC PDX model



Impact on tumor growth

EP0031 5mg/kg:	8/8 PRs*
Selpercatinib 5mg/kg:	2/8 PRs*
Pralsetinib 10mg/kg:	1/8 PRs*

*CTG2540 is a PDX derived from a NSCLC patient with KIF5B-RET fusion who was naive to treatment with SRIs. Tumor fragments were implanted in athymic nude mice. Animals were dosed BID for 28 days. Inhibition of tumor growth was determined by calculating the percent TGI (100% x (1-(final MTV - initial MTV of a treated group) / (final MTV – initial MTV of the control group))). Treatment started on Day 0. Tumor volumes of treatment groups were compared to that of the control group. Partial responder (PR) = TV ≤ 30% of TV at Day 0 for 2 consecutive measurements; Complete responder (CR) = No measurable tumor for 2 consecutive measurements. For EP0031 (5mg/kg) treated group *p<0.0001 vs vehicle.*

Abbreviations: TGI - tumor growth inhibition, MTV - mean tumor volume, BID - twice daily

IC_{50} comparison

Tumor cells + fragments from CTG2540 PDX were seeded in a 384-well plate in PDX media on Day 0. Test agents and controls were administered via PDX media on study day 0. Luminescence readings were collected from each model on study day 6. IC50 values were calculated based on cell viability using a Cell Titer Glo plate-based luminescence assay.

Data was recently reported from the ongoing Phase I/II study in China that included 109 patients with solid tumors harboring RET aberrations[1]

- ORR 81% and 70% (treatment naïve and prior treatment, respectively) with durable responses, in SRI-naïve RET fusion +ve advanced NSCLC (Figure 2)
- Significant activity was seen in patients with RET fusion +ve advanced NSCLC that previously received a 1st generation SRI (Figure 3)

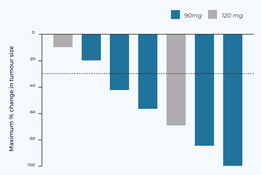
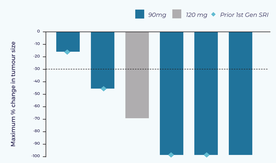


Figure 3. Response in Chinese patients with RET fusion +ve advanced NSCLC, previously treated with 1st generation SRI

- Intracranial responses observed, including patients that received prior 1st generation SRI (Figure 4)

Figure 4. Intracranial response in Chinese patients with advanced RET fusion +ve NSCLC[1]

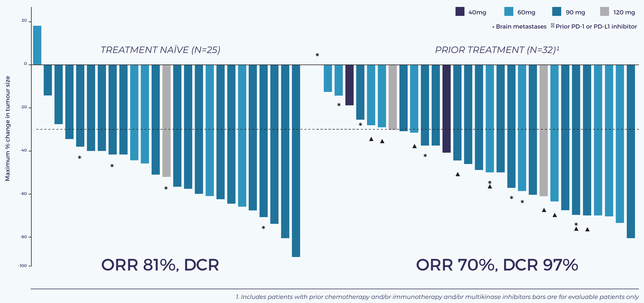


1. Brain mets at baseline were target lesions

- Safety and tolerability profile encouraging. Most AEs Grade 1 or 2 (>25%, all: Grade 3): AST (51.4, 1.8), ALT (48.6, 1.8), constipation (31.2, 0), creatinine (30.3, 0.9), headache (30.3, 0.9), anemia (28.4, 2.8), bilirubin (28.4, 0.9). Low frequency of dose reductions or discontinuations
- 90mg QD selected as RP2D in China

Here we report on progress with the ongoing study in Western patients (EP0031-101). This study has the aim of rapidly confirming the safety and efficacy profile observed in the Chinese population before expansion in patient populations naïve to, or with prior exposure to a 1st generation SRI.

Figure 2: Tumor response in Chinese patients with 1st generation SRI-naïve RET fusion +ve advanced NSCLC at doses of 40-120 EP0031 mg QD



1. Includes patients with prior chemotherapy and/or immunotherapy and/or multikinase inhibitors bars are for evaluable patients only

Acknowledgements

We are grateful to patients and their loved ones for their key contribution, and the participating sites for their hard work.

References

1. Zhou et al. JCO 2023, 41:16, suppl. Abstr. 3007.

STUDY DESIGN

Dose finding

Dose escalation is based on a rolling 6 design, followed by expansion at potential RP2Ds for dose optimization

Eligibility

- Patients with locally advanced or metastatic RET-altered solid tumors
- Age ≥18 years
- ECOG 0–1

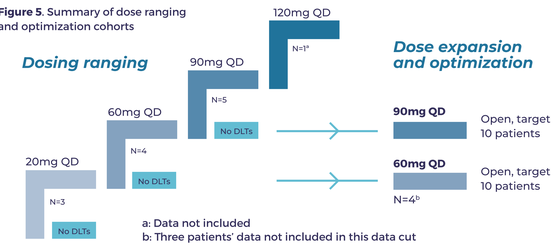
Key endpoints

- Safety and tolerability
- Determine MTD/or RP2D
- PK, PD
- ORR, BOR, DOR, change in tumor size, PFS, OS

Other evaluations

Tumor biopsy and ctDNA to determine RET gene fusions, mutations and correlation with efficacy (data not available currently)

Figure 5. Summary of dose ranging and optimization cohorts



a: Data not included
b: Three patients' data not included in this data cut

RESULTS

Summary of patient characteristics

As of 30th September 2023, a total of 17 patients, 6 medullary thyroid cancer (MTC), 8 NSCLC, and 3 patients with other tumor types have been enrolled across dose cohorts of 20mg (N=3), 60mg (N=8), 90mg (N=5) and 120 mg (N=1).

As of 4th August 2023, 13 patients were evaluable for safety (6 male, 7 female; most patients ECOG 1; median age 54 years (32-75): 6 NSCLC, 5 MTC, 1 neuroendocrine CRC, 1 pancreatic.).

As of 13th September 2023, 10 patients were evaluable for efficacy (4 NSCLC, 5 MTC, 1 neuroendocrine CRC).

Safety and tolerability

An encouraging preliminary safety and tolerability profile was observed (Table 1):

- No dose-limiting toxicities or treatment-related deaths occurred
- Grade 3 TEAEs included hypertension (2 patients, 20mg), gamma-glutamyl transferase increase (1 patient, 60mg), neutropenia (1 patient, 20mg), pneumonia (1 patient, 60mg), diarrhea due to C. difficile (1 patient, 60mg), hyponatremia (1 patient, 60mg)
- EP0031 dosing was interrupted in 3 patients (due to TRAE in 1 patient at 20mg and TEAE in 2 patients at 60mg). No other dose reductions, discontinuations or withdrawals due to toxicity were seen across all dosing cohorts

Table 1. Summary of safety findings by dose

Category	20mg (N=3)	60mg (N=5)	90mg (N=5)	Total (N=13)
Any TEAE	3	4	3	10
Any DLT	0	0	0	0
Any TEAE Grade >= 3	3	3	0	6
Any TRAE Grade >= 3	3	0	0	3
Any TEAE leading to dose reduction	0	0	0	0
Any TRAE leading to dose reduction	0	0	0	0
Any TEAE leading to temporary interruption	1	2	0	3
Any TRAE leading to temporary interruption	1	0	0	1

TEAE = treatment emergent adverse event. TRAE = treatment related adverse event

Pharmacokinetics

The pharmacokinetic (PK) profile was compatible with once-daily dosing

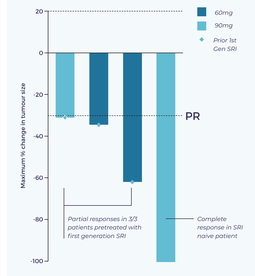
- Using population PK parameter estimates, the predicted free exposure of EP0031 for multiple doses of 20-90 mg QD for a 70 kg patient were simulated. A free fraction of 0.017 and a linear increase in exposure were assumed
- In plasma, it is estimated that free drug concentrations will exceed the IC90 for relevant RET kinase targets at steady state (Figure 7)
- Preliminary PK data in Western patients is consistent with the Chinese patient population (data not shown)

Efficacy

EP0031 resulted in stabilization of disease or marked tumor shrinkage and response across doses of 20-90mg:

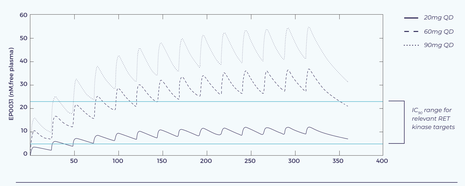
- PRs observed in 3/3 patients with RET fusion +ve advanced NSCLC previously treated with 1st generation SRI (Figures 6 and 9).
- CR observed in 1/1 patient with RET fusion +ve NSCLC naïve to 1st generation SRI (Figures 6 and 8)
- Robust suppression of calcitonin observed in two 1st generation SRI naïve patients with advanced MTC with initial stabilization of disease. Dosing initiated at 20 mg then escalated to 60mg in both patients. One of these patients went on to achieve a PR
- 3 patients with advanced MTC that had received prior 1st generation SRI had progressive disease, but two continued receiving treatment due to clinical benefit
- Progressive disease was best response in a patient with RET +ve neuroendocrine colorectal cancer

Figure 6. Preliminary response data in patients with RET fusion +ve advanced NSCLC[1]



1 Evaluable patients as of 13 September 2023, 2 other NSCLC patients were not evaluable

Figure 7. Simulation of pharmacokinetics by dose cohort

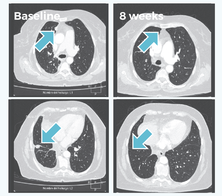


Simulations of 20mg, 60mg and 90mg QD using population PK parameters. Plasma free concentrations vs IC90 for key wild type and mutant RET kinases

Figure 8. Complete response in 75 year-old female with SRI-naïve KIF5B-RET fusion +ve advanced NSCLC

Patient history

- Right lower lobectomy
- Adjuvant platinum based chemotherapy for 2 cycles (carboplatin/pemetrexed) – best response of SD
- Patient treated with EP0031, 90mg QD
- CR at Cycle 3: 100% overall reduction
- Non-target lesions in lymph nodes (<10mm at Cycle 3, Day 1)
- Patient continues to receive treatment



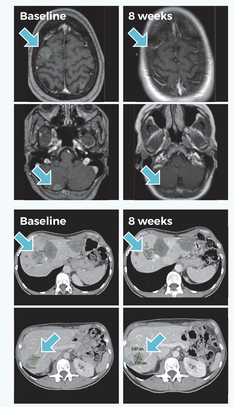


Figure 9. Partial response in the brain for a 41 year-old female with KIF5B-RET fusion +ve advanced NSCLC who previously received pralsetinib

Patient history

- Total of 4 prior treatment regimens
- Progressive disease after receiving pralsetinib for 17 months
- Patient treated with EP0031, 60mg QD
- PR at cycle 3: 34% overall reduction
- Brain metastases reduced by 67%
- Patient continues to receive treatment

SUMMARY & CONCLUSION

- Preliminary data from this study in Western patients indicates EP0031 has an encouraging safety and tolerability profile with evidence of efficacy in patients naïve to or previously treated with 1st generation SRIs
- Findings are consistent with data from the parallel Phase I/II study in China (NCT05265091; Kelun Biotech) that has shown promising safety and tolerability with[1]:
  - High response rate and durable activity in a large cohort of patients with NSCLC naïve to 1st generation SRIs
  - Significant activity in patients previously treated with 1st generation SRI
  - Intracranial responses in patients naïve to, or previously treated with 1st generation SRI
- This study is ongoing in centers in US and Spain, opening in UK and France, and rapidly expanding to additional sites and countries
- Once RP2D is identified, additional cohorts are planned in first generation SRI naïve and pre-treated patients with NSCLC, MTC and other solid tumors with RET aberrations. Registration cohorts in SRI naïve NSCLC are now recruiting in the study in China
- Preclinical and clinical data from the overall program indicates that EP0031 has promise as a next generation SRI. Continued evaluation in patients that have tumors with RET aberrations naïve to or previously treated with 1st generation SRI is merited

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