2023 ASCO ANNUAL MEETING

A Phase I Study of KL590586 (A400/EP0031)

A next-generation selective RET inhibitor in patients with RET-altered solid tumors

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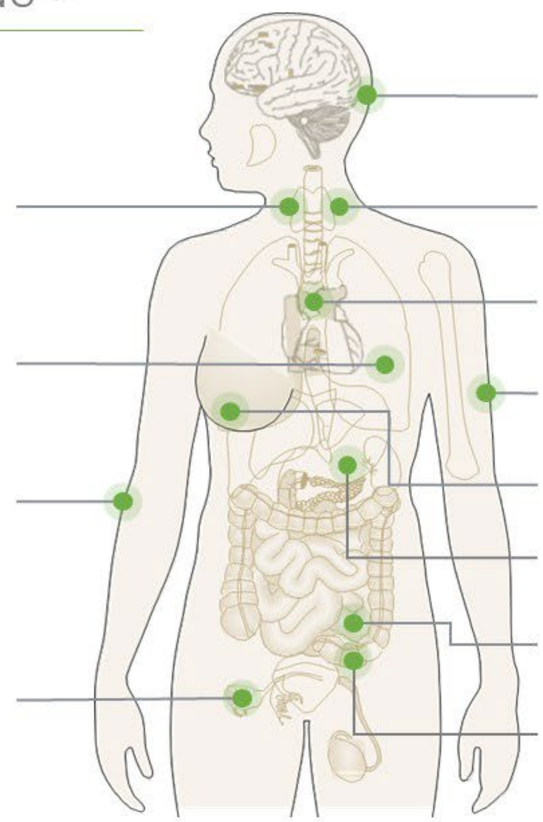
Strong Rationale

for developing next gen selective RET inhibitors

RET, A DRIVER OF MULTIPLE, DIVERSE TUMOR TYPES

RET FUSIONS[1,2]

RET MUTATIONS[1]



UNMET NEED IN RET-ALTERED TUMORS

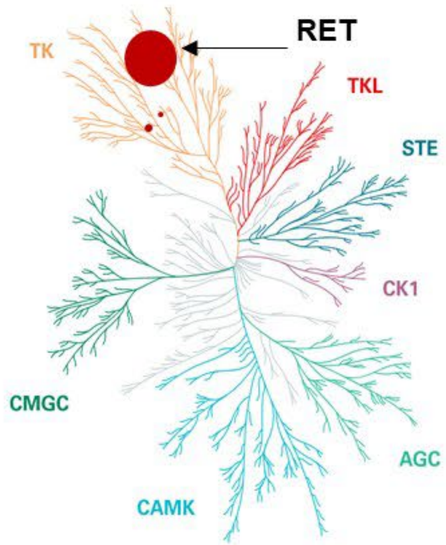
- **Multikinase inhibitors:** poor efficacy and off-target toxicity leading to frequent dose reduction/interruption[3,4]
- **1st gen selective RET inhibitors (SRIs):** tolerability/safety concerns and emergence of G810 solvent front (SF), and other resistance mutations[5,6]
- **Next gen SRIs** with ability to overcome resistance, and improve efficacy and tolerability/safety, are required

1. Kato S et al. Clin cancer Res. 2017,23(8):1988-1997. 2. Ballerini P et al. Leukemia. 2012,26(11):2384-2389.
3. Ancker OV et al. Int. J. Mol. Sci. 2017,18(3),625. 4. Drilon A et al. Nat Rev Clin Oncol 2018,15(3):151-167.
5. Solomon BJ et al. J Thorac Oncol. 2020;15(4):541-549. 6. Rosen EY et al. Nat Commun. 2022;13(1):1450.

KL590586 (A400/EP0031)

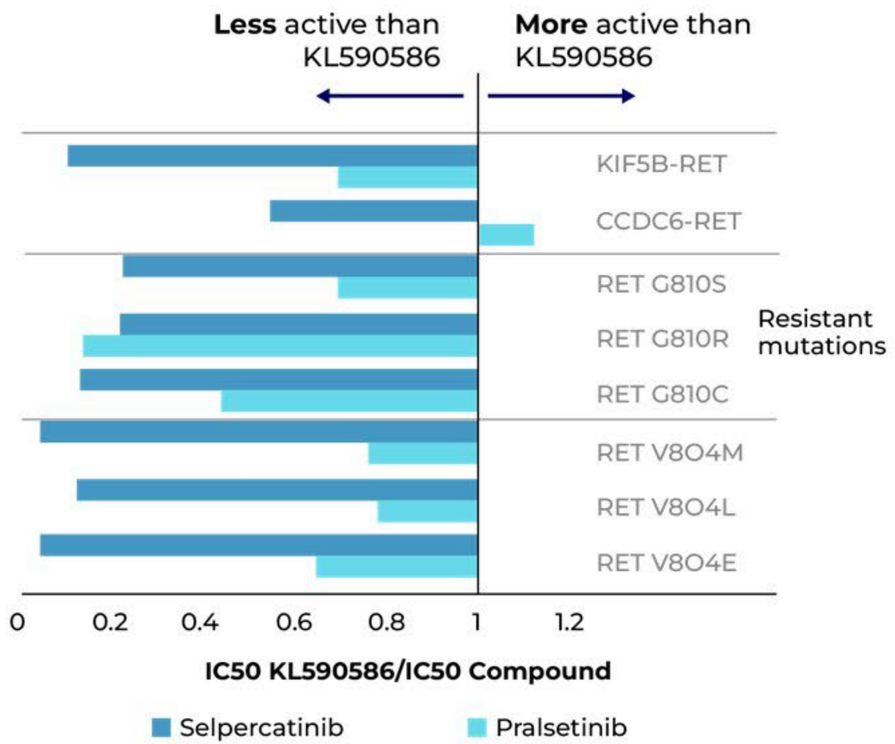
has a promising preclinical profile (1)

01 HIGHLY SELECTIVE FOR RET COMPARED WITH VEGFR AND OTHER KINASES



- **93-fold** more selective for RET than VEGFR2
- **10-fold** more selective for RET than JAK1
- **22-fold** more selective for RET than JAK2

02 GREATER POTENCY THAN 1ST GEN SRIs AGAINST COMMON AND RESISTANT MUTATIONS



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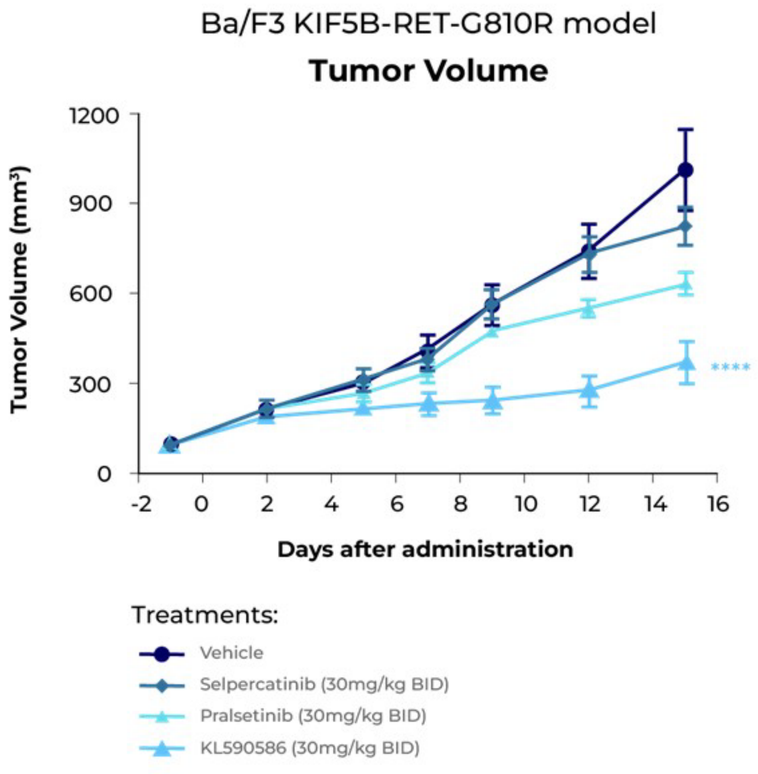
KL590586 (A400/EP0031)

has a promising preclinical profile (2)

03 GREATER ACTIVITY VS. 1ST GEN SRIs IN G810R PATIENT XENOGRAFT MODEL

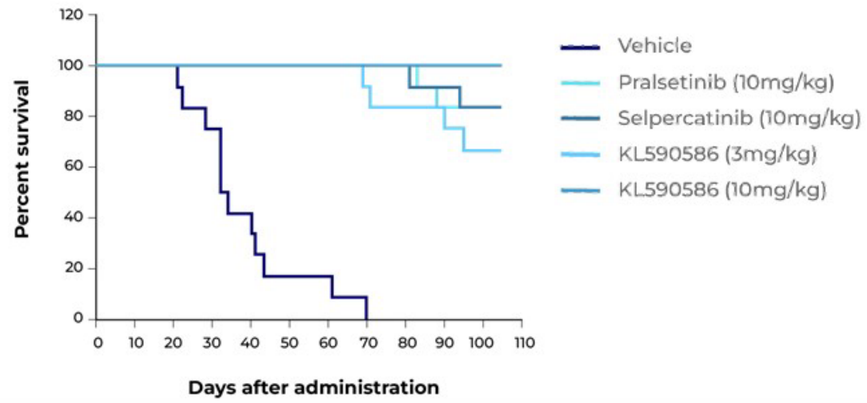


04 IMPROVED EXPOSURE & SURVIVAL VS. 1ST GEN SRIs IN INTRACRANIAL TUMOR XENOGRAFT MODEL

Increased Brain Exposure in Balbc Model (Balb/c-PK (10mg/kg-PO))

Agent		KL590586		Pralsetinib		Selpercatinib	
Parameter		Plasma	Brain/Plasma	Plasma	Brain/Plasma	Plasma	Brain/Plasma
C_{max}	ng/ml	13900	2.97%	9143	1.14%	6837	2.32%
AUC_{0-t}	h*ng/ml	179523	2.47%	31015	1.47%	33129	1.70%

Increased Survival Rate in Intracranial Tumor Xenograft Following KL590586 Treatment



KL400-I/II-01

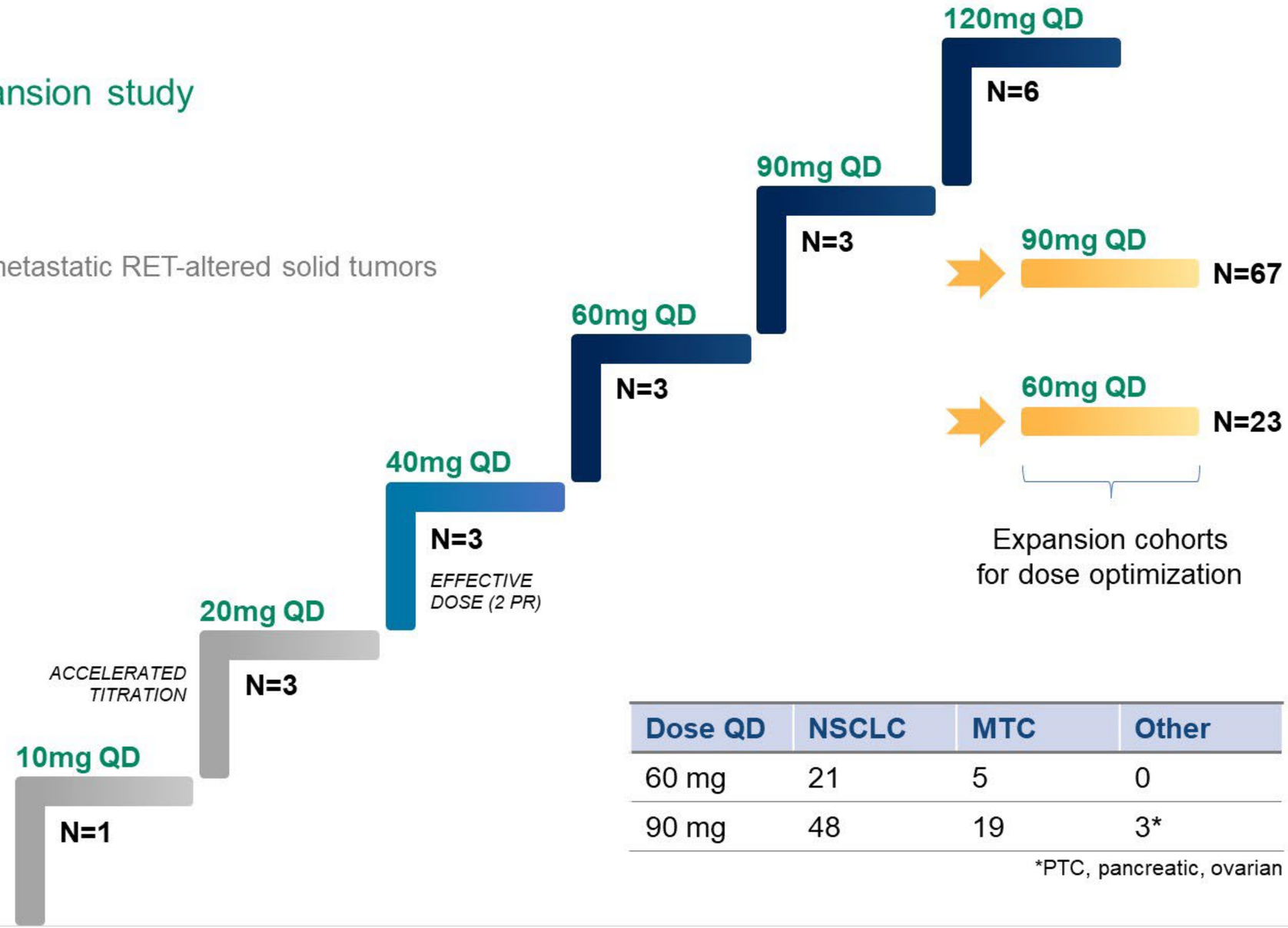
phase I dose-escalation and expansion study

ELIGIBILITY

- Patients (pts) with locally advanced or metastatic RET-altered solid tumors
- Age ≥18 years
- ECOG 0–1
- Expected survival time ≥ 3 months

KEY ENDPOINTS

- Determine MTD/or RP2D
- Safety, PK
- ORR, DCR, DoR as per RECIST 1.1



Dose QD	NSCLC	MTC	Other
60 mg	21	5	0
90 mg	48	19	3*

*PTC, pancreatic, ovarian

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KL590586 (A400/EP0031)

safety profile

All doses (10-120mg) and patients, N=109		
TRAEs (≥25% overall)	**Any grade, n (%)**	**Grade 3*,n (%)**
Overall	103 (94.5)	26 (23.9)
AST	56 (51.4)	2 (1.8)
ALT	53 (48.6)	2 (1.8)
Constipation	34 (31.2)	0
Creatinine	33 (30.3)	1 (0.9)
Headache	33 (30.3)	1 (0.9)
Anemia	31 (28.4)	3 (2.8)
Bilirubin	31 (28.4)	1 (0.9)
Dose interruptions	40 (36.7)	
Dose reductions	7 (6.4)	
Dose discontinuations	3 (2.8)	

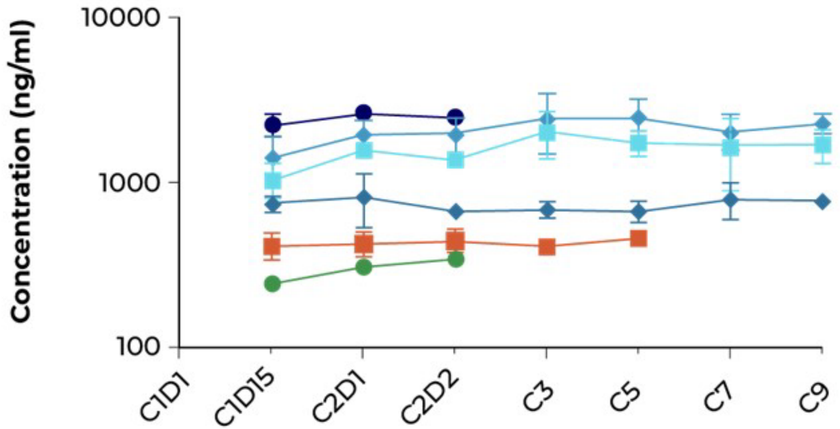
- No DLTs were observed
- 103 (94.5%) patients had a TRAE - most were grade 1-2
- Low frequency of hyponatremia (any grade 7.3%, ≥3 grade 0.9%); and hypertension (any grade 4.6%), lymphopenia (any grade 4.6%), and prolonged QTc (any grade 2.8%) all with no grade ≥3
- The only grade 3 TRAE with frequency ≥ 2% was anemia

- Median time to 1st dose interruption = 1.9 mo
  - Average duration = 1.8 weeks
- Low frequency of dose reductions/discontinuations

KL590586 (A400/EP0031)

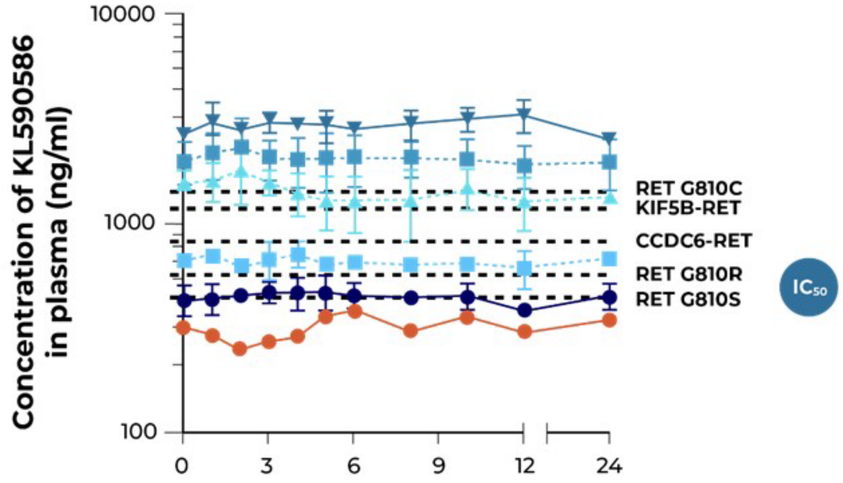
pharmacokinetics

01 MEAN PLASMA CONCENTRATIONS BY DOSE



- Single dose on C1D1 and then QD from C1D6 onwards
- Dose dependent linearity
- Steady state reached by C1D28

02 PATIENT PLASMA EXPOSURES AT DOSES ≥60mg EXCEEDED THE IC_{50} TARGETS

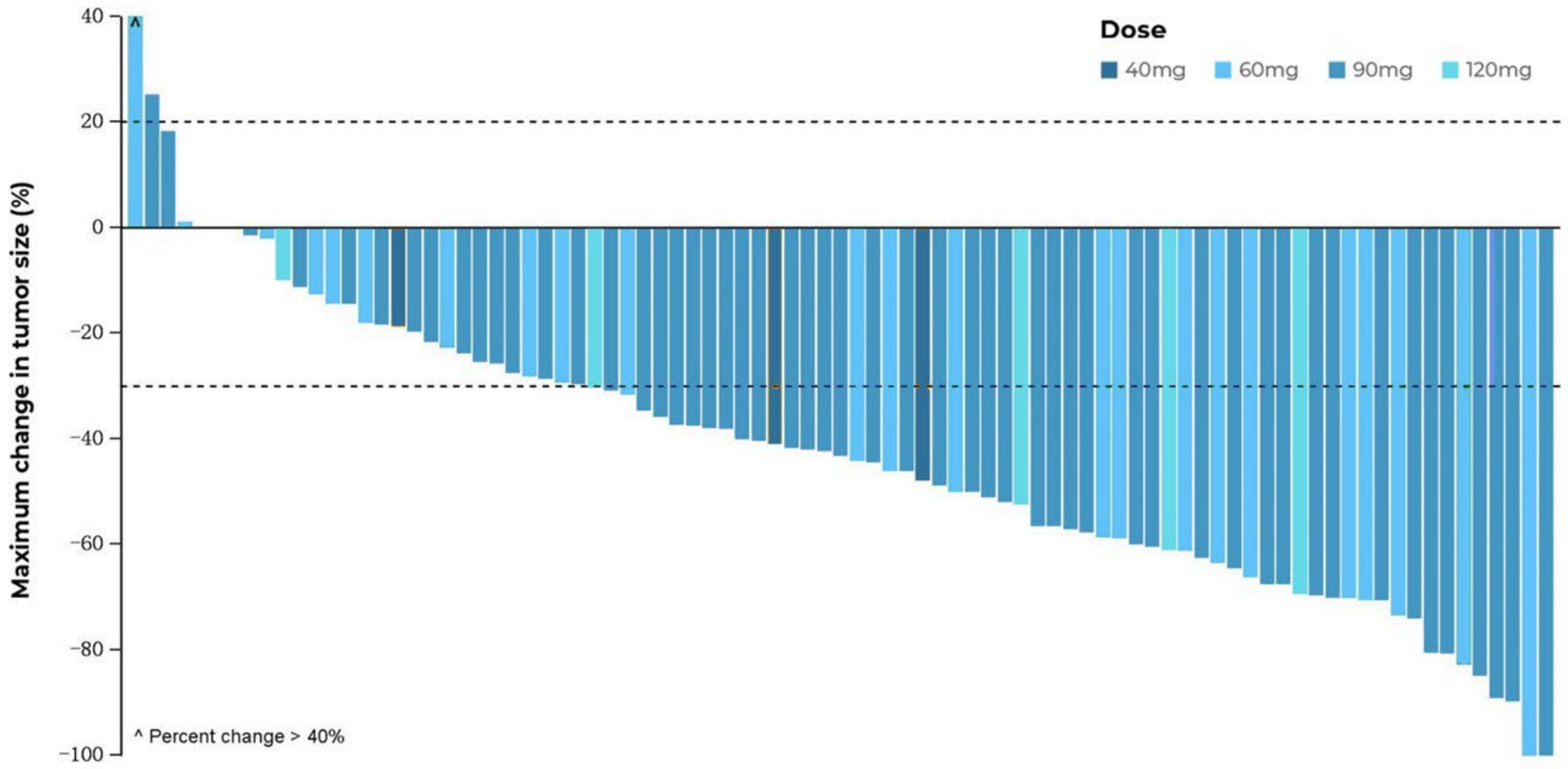


Dashed horizontal lines show the IC_{50} for each indicated RET fusion or mutation

Clinical activity of KL590586 (A400/EP0031)

in RET-altered cancers

CHANGE IN TUMOR SIZE FOR PATIENTS ADMINISTERED KL590586 40-120MG QD



- Across all tumor types and doses (40-120 mg QD) confirmed ORR was 60% (54/90), DCR was 94% (85/90)
- For the 90mg dose, ORR was 63% (35/56) and DCR was 95% (53/56)

Data cut-off date: 20 Apr 2023.

Baseline characteristics

for patients with NSCLC

Characteristic	Treatment Naïve (n=26)	Prior Treatment (N=33)
Median age (range), years	59 (31-80)	59 (36-67)
Female / Male, n (%)	15 (57.7)/11 (42.3)	19 (57.6)/14 (42.4)
ECOG 0 / 1, n (%)	6 (23.1)/20 (76.9)	3 (9.1)/30 (90.9)
Smoking history, n (%)		
Never	18 (69.2)	23 (69.7)
Distant metastasis, n (%)		
Bone	10 (38.5)	15 (45.5)
Brain	4 (15.4)	8 (24.2)
Liver	4 (15.4)	6 (18.2)
RET fusion partner, n (%)		
KIF5B	13 (50.0)	21 (63.6)
CCDC6	7 (26.9)	4 (12.1)
Other#	2 (7.7)	1 (3.0)
Unknown	4 (15.4)	7 (21.2)
Prior therapies*, median (range)	/	2 (1-9)
Platinum-based therapy, n (%)	/	31 (93.9)
Immunotherapy, n (%)	/	10 (30.3)
MKI/TKI, n (%)	/	5 (15.2)

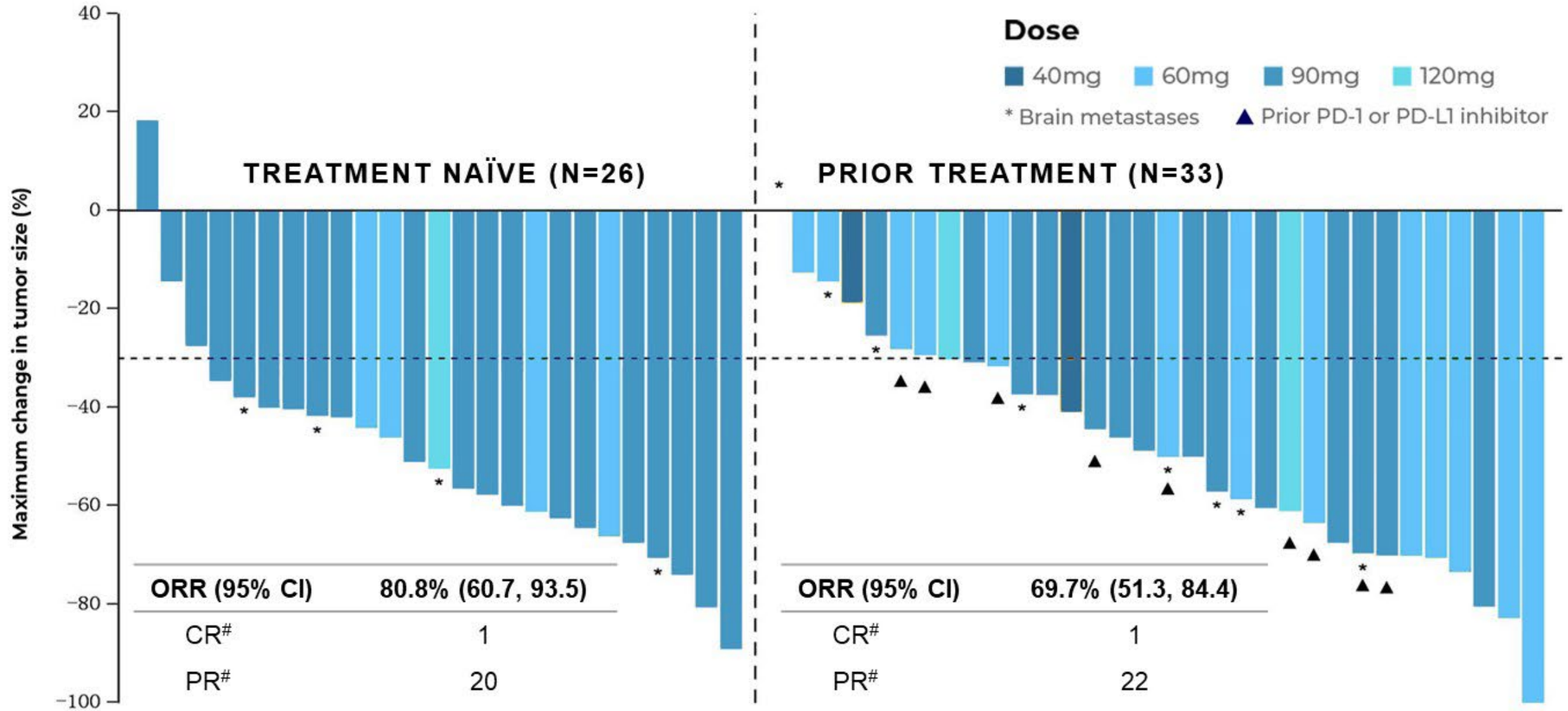
Includes NCOA4, RELCH, ERC1; * Except for prior selective RET inhibitors treatment

KL590586 (A400/EP0031) active

regardless of RET fusion or prior checkpoint inhibitor

CHANGE IN TUMOR SIZE FOR PATIENTS WITH NSCLC ADMINISTERED KL590586 40-120MG QD

 # All responses are confirmed on two consecutive assessments as per RECIST 1.1.



ORR (95% CI)	80.8% (60.7, 93.5)
CR#	1
PR#	20
SD	4
DCR (95% CI)	96.2% (80.4, 99.9)

ORR (95% CI)	69.7% (51.3, 84.4)
CR#	1
PR#	22
SD	9
DCR (95% CI)	97.0% (84.2, 99.9)

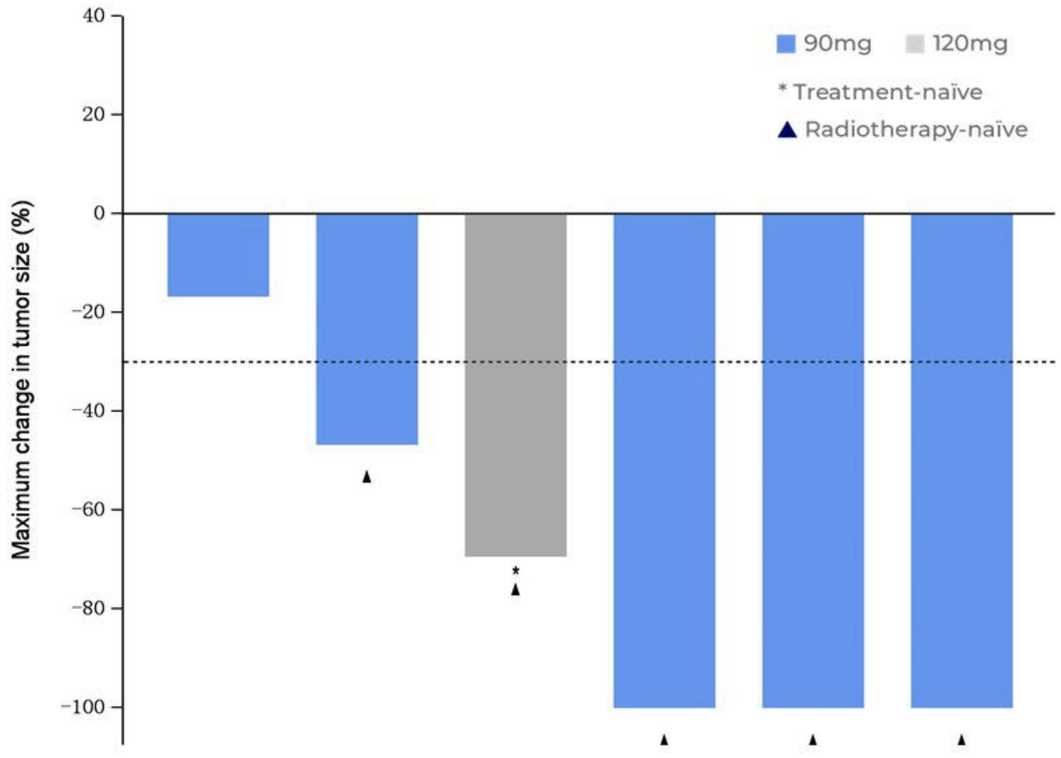
Data cut-off date: 20 Apr 2023.

KL590586 (A400/EP0031) is active

against intracranial metastases

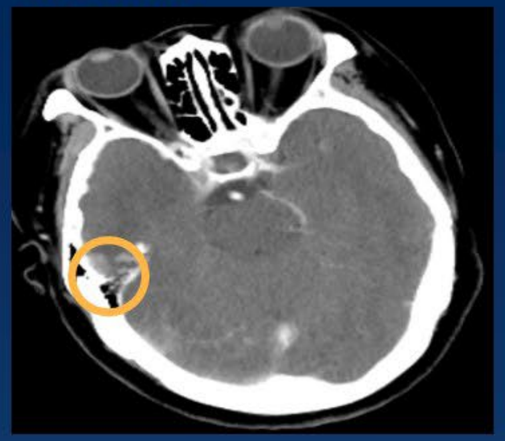
INTRACRANIAL RESPONSE IN NSCLC

- 5/6 patients with intracranial target lesions at baseline had intracranial responses
- 100% shrinkage observed in 3 patients

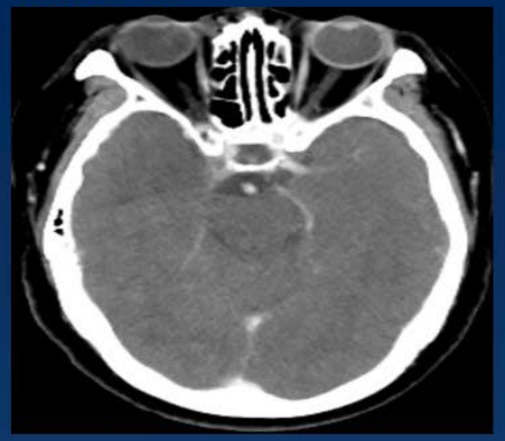


Data cut-off date: 20 Apr 2023.

BASELINE



WEEK 16



FEMALE, 60 YEARS, WITH NSCLC, 4 PRIOR TREATMENT REGIMENS

- Progressed after sintilimab (PD-1), with brain, bone and pleural metastases
- KL590586, 90mg QD
- Deep PR (70% shrinkage of target lesions)
- 100% shrinkage of brain lesions
- Response continues after 7 months

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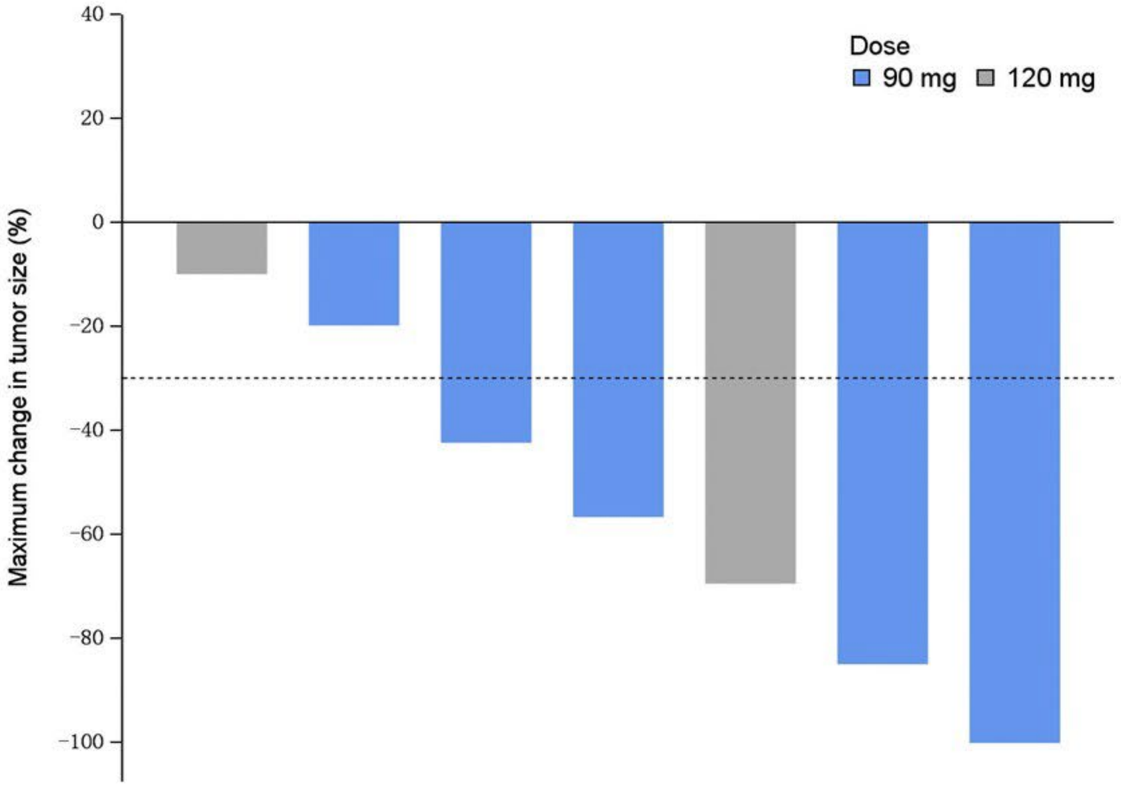
KL590586 (A400/EP0031) is active

in patients pretreated with 1st gen SRI

TARGET LESION RESPONSE IN NSCLC PATIENTS WITH PRIOR 1ST GEN SRI TREATMENT



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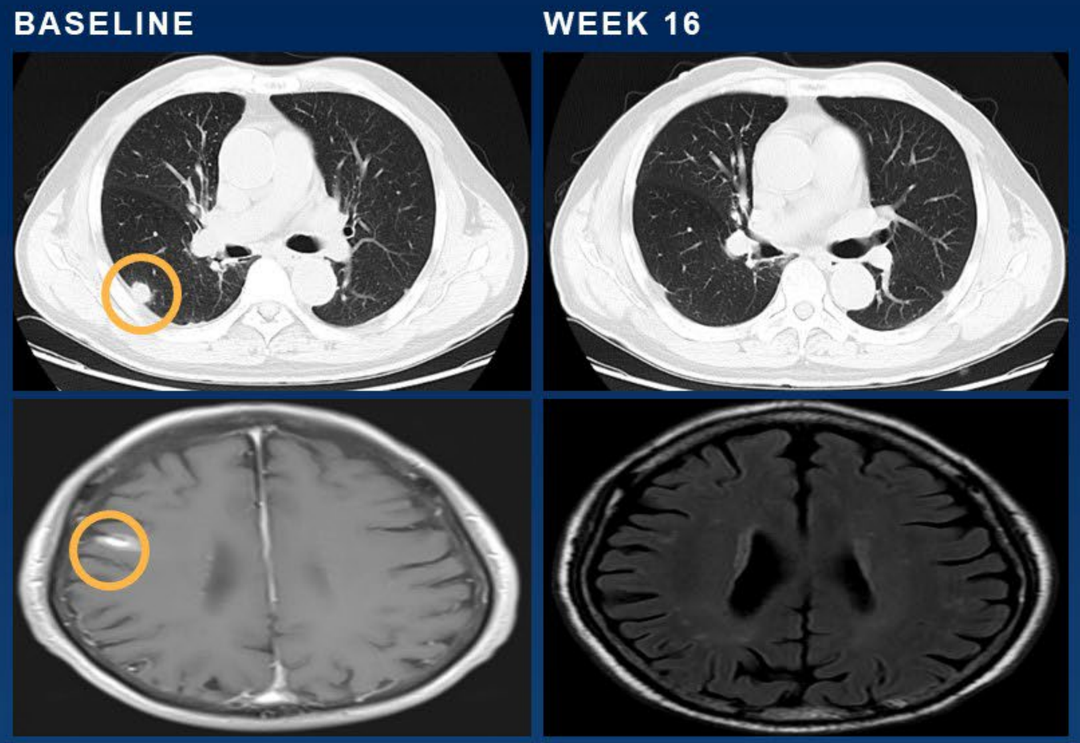
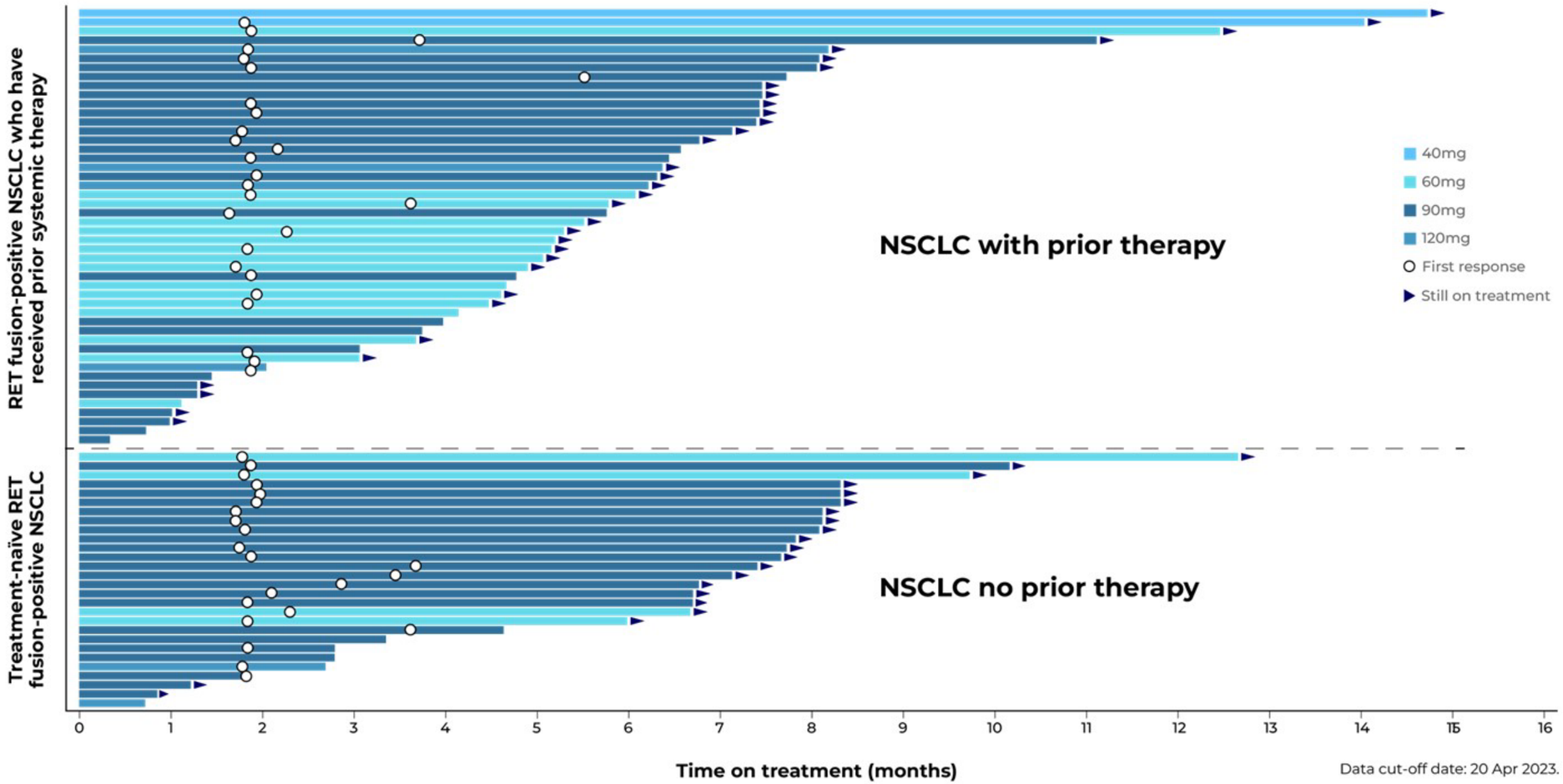


MALE, 63 YEARS, WITH NSCLC

- Progressive disease after pralsetinib (treated >2 years), with brain, bone, pleural metastases and pleural effusion
- KL590586, 90mg QD
- PR
- 47% shrinkage of brain met at week 16
- Ongoing response 8+ mo

KL590586 (A400/EP0031) induces rapid and durable responses

in RET fusion+ NSCLC



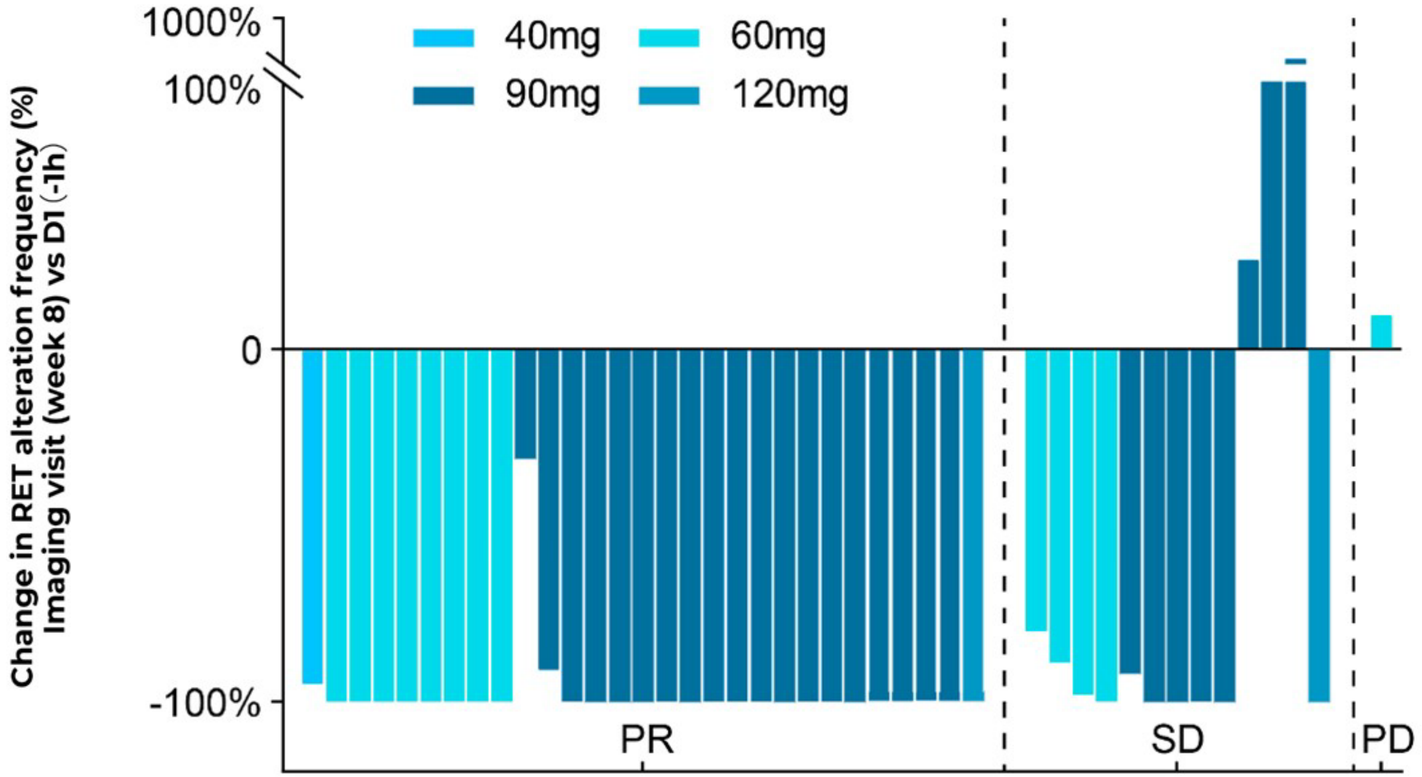
- Responses durable regardless of tumor type, RET fusion type, dose, prior treatment, or presence of brain mets
- 71% (54/76) of patients remained on treatment, with the longest >14.5 mo.
- Median duration of response not yet reached

Data cut-off date: 20 Apr 2023.

Robust clearance

of RET Variants ctDNA with KL590586 (A400/EP0031)

RET FUSION+ NSCLC, KL590586 40-120MG QD



- 26/29 (90%) PR and 6/13 (46%) SD pts with detectable RET fusion ctDNA at baseline had complete clearance within the first imaging visit (Week 8)
- Robust clearance of RET variants ctDNA with KL590586 treatment across a range of doses

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Conclusions

- Emerging clinical profile of KL590586 (A400/EP0031) consistent with selective drug design
  - Encouraging, manageable tolerability and safety profile
  - Activity across RET-altered tumors and RET fusion types
  - Robust activity in treatment-naïve and pretreated NSCLC including patients with prior immunotherapy or brain metastases
  - Clinical activity in patients pre-treated with 1st gen SRIs
- Expansion cohorts of KL590586 (A400/EP0031) in other solid tumors (including prior SRI patients) are open and enrolling
- Pivotal studies planned in RET fusion-positive NSCLC
- Parallel Phase 1 study ongoing in US and Europe (EP0031, Ellipses Pharma, NCT05443126)

Acknowledgements

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- KL400-Ⅰ/Ⅱ-01 Investigators and research coordinators
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  - Second Affiliated Hospital of Nanchang University, Nanchang, China
  - Shanxi Cancer Hospital, Taiyuan, China
  - The Fourth Hospital of Hebei Medical University, Shijiazhuang, China
  - The First Affiliated Hospital/School of Clinical Medicine Guangdong Pharmaceutical University, Guangzhou, China
  - Hunan Cancer Hospital, Changsha, China
  - General Hospital of Eastern Theater Command, Nanjing, China
  - The First Affiliated Hospital of Xiamen University, Xiamen, China
  - The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
  - Zhejiang Cancer Hospital, Hangzhou, China
  - Tangdu Hospital, The Fourth Military Medical University, Xi'an, China
  - Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
  - Affiliated Hospital of Guizhou Medical University, and Guizhou Cancer Hospital, Guiyang, China
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