999P - JIN-A02, a fourth-generation, highly effective tyrosine kinase inhibitor with intracranial activity, targeting EGFR C797S mutations in NSCLC

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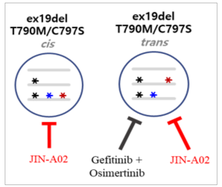
Introduction

- Even though epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have improved treatment outcomes for EGFR mutant, resistance inevitably emerges with disease progression and often with CNS metastasis.
- C797S mutation is one of the most common on-target resistance mutation after the use of 3rd generation TKIs such as Osimertinib.
- Importantly, the allelic context in which C797S is acquired has potential implications for treatment. When C797S positive cells are in cis with the T790M mutation, there are no available treatment.[1)]
- JIN-A02 is a new 4th generation investigational EGFR-TKI, which is highly selective and potent against C797S double and triple mutations.[2)]
- JIN-A02 has a strong inhibitory activity against both cis and trans allele of C797S with high brain penetration.
- Here we describe the preclinical data which indicates that JIN-A02 is a highly effective EGFR-TKI targeting C797S mutations and is potent to treat CNS metastasis.



Method

- Cellular activities of JIN-A02 were evaluated on phosphorylation-EGFR expression with AlphaLISA assay in EGFR mutant cell lines and cell viability assay in Ba/F3 cell lines overexpressing human EGFR mutants and patient-derived cell (PDC) lines harboring EGFR mutations.
- Antitumor activities of JIN-A02 were evaluated in cell derived xenograft (CDX) and patients-derived xenografts (PDX).
- The in vivo anti-tumor activity of JIN-A02 was evaluated in an intracranial tumor models which were generated through implanting H1975-luc into brains of female BALB/c nude mice. MRI analysis was performed to monitor the tumor growth.

Results

JIN-A02, highly selective and potent inhibitor

- In AlphaLISA assay, JIN-A02 showed high potency in EGFR mutants.

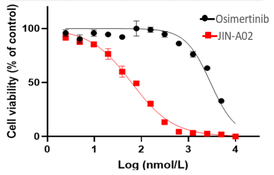
AlphaLISA assay IC_{50} (nM)

Compound	Engineered BaF3					NSCLC cell line		
	WT	DC	LC	DTC	LTC	A431 WT	PC-9	NCI-H1975 LTC
Osimertinib	109	>3000	>18000	>3000	No Activity	42	6.7	No Activity
JIN-A02	857	111	355	4.7	219	1282	9.1	12.8

WT: Wildtype, DC: ex19del/ C797S, LC: L858R/ C797S, DT: ex19del/T790M, LT: L858R/T790M, DTC: ex19del/T790M/C797S, LTC: L858R/T790M/C797S, DTQ: ex19del/T790M/L718Q, LTQ: L858R/T790M/L718Q

Cellular activity in trans/cis isomers of JIN-A02

- JIN-A02 strongly inhibited cellular activity in trans model (IC_{50}=89.7 nM, PDO) (data on file) and in cis model (IC_{50}=61.5 nM, PDC) of EGFR ex19del/T790M/C797S, with superiority over the 3rd generation TKI Osimertinib (IC_{50} >2,000 nM for both isomers).



In vitro cell viability assay

- In vitro cell viability assay, JIN-A02 exhibited a potent inhibitory effect of EGFR mutants, especially mutant harboring C797S mutations while sparing EGFR wild type (WT).

Cell viability assay IC_{50} (nM) in Engineered Ba/F3

Compound	WT	ex19del	L858R	DT	LT	DC	DTC	LTC	DTQ	LTQ
Osimertinib	11.9	3.5	3.6	3.3	4.3	868.5	>2,000	>1,000	>1,000	>800
JIN-A02	>1,000	3.2	9.1	12.3	5.3	0.02	81.7	49.2	102.0	62.1

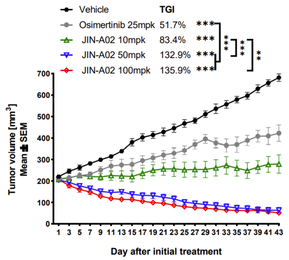
Cell viability assay IC_{50} (nM) in NSCLC cell lines

Compound	A549	PC-9 ex19del	HCC-4006 ex19del	PC-9GR DT	NCI-H1975 LT	YUO-057 (trans) DTC	YU-1097 (cis) DTC
Osimertinib	-	1.63	7.71	24.29	36.88	>10,000	>2,000
JIN-A02	742.40	13.48	14.41	62.05	72.29	89.65	61.50

In vivo anti-tumor activity of JIN-A02

In vivo PDX model (ex19del/T790M/C797S)

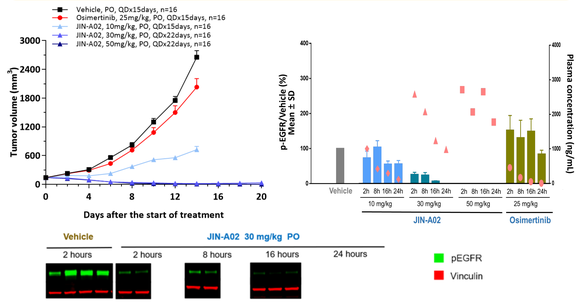
- In PDX mouse model (YU-1097, EGFR ex19del/T790M/C797S), JIN-A02 50 and 100 mg/kg significantly suppressed tumor growth.
- In the PDX mouse model (YHIM-1094, EGFRex19del/T790M/C797S) (data on file), JIN-A02 delayed tumor growth at a dose of 30 mg/kg.



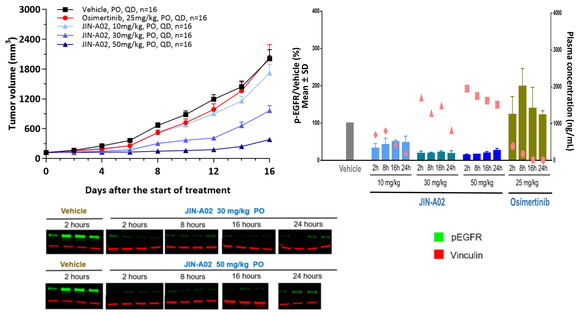
Significant inhibition of EGFR autophosphorylation of JIN-A02 in a time- and dose-dependent manner

- Oral, once daily administration of JIN-A02 resulted in significant tumor regression.
- After repeated once a day, oral administration of JIN-A02, JIN-A02 inhibited pEGFR in BaF3 ex19del/C797S, L858R/C797S, and L858R/T790M/C797S CDX models.

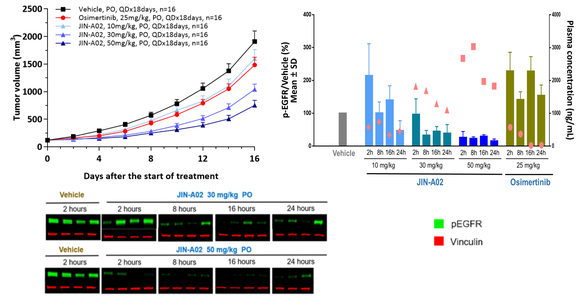
In vivo CDX (BaF3-ex19del/C797S)



In vivo CDX (BaF3-L858R/C797S)

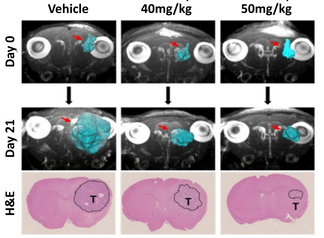


In vivo CDX (BaF3-L858R/T790M/C797S)

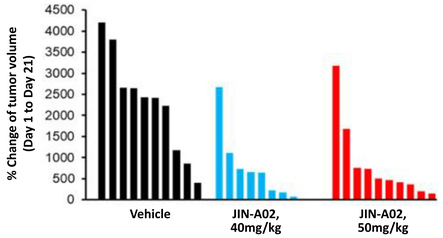


Intracranial anti-tumor activity

- In the brain metastases model, antitumor activity of JIN-A02 was observed with intracranial implanted NCI-H1975 tumors.



- JIN-A02 showed a tendency to delay tumor growth in a dose-dependent manner compared to the control group (Vehicle) on Day 21.



Conclusion

- JIN-A02 is a highly potent 4th generation EGFR-TKI against double and triple C797S resistance mutations, including both cis and trans isomers
- JIN-A02 is selective away from EGFR WT and showed BBB penetration with strong intracranial anti-tumor effects.
- JIN-A02 is scheduled to start the First-in-human clinical trial (NCT05394831) this year based on these convincing results.

References

1) A Leonetti et al. British Journal of Cancer (2019) 121:725–737
2) Cho BC et al. IASLC 2022 WCLC

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Disclosures

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