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Abstract CT052: A highly selective, brain-penetrant and overcoming G2032R resistance ROS1 inhibitor JYP0322 in NSCLC patients with ROS1 fusion FREE

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Abstract

Background:

JYP0322 is a potent, brain-penetrant and highly selective ROS1 inhibitor, demonstrating over 100-fold selectivity for ROS1 compared to TRKA and sub-nanomolar potency against the ROS1 G2032R resistance mutation. JYP0322 is designed to simultaneously address the key clinical challenges including ROS1 resistance mutations, tumor brain metastases while avoiding the off-target neurotoxicity associated with TRK inhibition.

Method:

The Phase I study (NCT06128148) was designed to evaluate safety, pharmacokinetics (PK), and preliminary clinical efficacy in patients with locally advanced or metastatic ROS1+NSCLC, including both ROS1 TKI pre-treated patients as well as TKI naïve patients. Response was assessed by investigators according to RECIST V1.1.

Results:

As of December 10, 2024, dose escalation study was conducted across 7 dose levels: 50mg qd, 100mg qd, 200mg qd, 100mg bid, 150mg bid, 200mg bid, 150mg tid and dose expansion stage is ongoing at doses of 100mg bid, 150mg bid and 150mg tid. A total of 73 NSCLC patients were enrolled. No dose-limiting toxicities were observed. The most frequently reported treatment related adverse events (TRAE) were low grade including weight gains (32.9%), hyperglyceridemia (31.5%), hypercholesteremia (26%), and AST elevation (21.9%). Grade 3-5 TRAE occurred in 12.3% patients. Only low grade neurotoxicities (6.8%) occurred. Among 58

efficacy evaluable patients, objective response rates (ORRs) were 85.7% (12/14) for ROS1 TKI naive, 54.5% (12/22) for patients previously received ≥2L systemic therapy and ≥1 prior ROS1 TKIs including 19 patients pre-treated with 2 to 4 ROS1 TKIs (Table). In ROS1 G2032R mutant cancers, ORR was 71.4% (5/7) with 3 patients pre-treated with Lorlatinib. In patients with measurable brain metastasis at baseline, intracranial ORR was 33.3% (2/6) and intracranial DCR was 83.3%. JYP0322 showed significantly brain penetration ability with the brain to plasma ration 1.20. Enrollment in the dose expansion stage is ongoing.

Conclusions:

JYP0322 had a favorable safety profile with a low incidence of neurotoxicities. It showed highly promising anti-tumor effects in patients with ROS1+NSCLC including both TKI-naïve and TKI pre-treated patients, as well as those with TKI-heavily treated, brain metastases, or harboring ROS1 G2032R mutation.

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Tumor response in patients with ROS1+ advanced NSCLC				
	G2032R mutations		**Previous treatment lines≥2L and RC**	
Evaluable subjects (All dose level)	**All (n=7)**	**Lorlatinib pretreated (n=3)**	**All (n=22)**	**CNS metastasis (n=**
ORR	71.4%	66.7%	54.5%	38.5%
DCR	100%	100%	81.8%	69.2%

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