1392P Dose-determination results from a phase Ib/II study of ceritinib (CER) + ribociclib (RIB) in ALK-positive (ALK+) non-small cell lung cancer (NSCLC)

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Background: Preclinical data suggest cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) may improve ALK inhibitor (ALKi) efficacy in ALK+ NSCLC. A Phase Ib/II study (NCT02292550) is assessing CER (ALKi) + RIB (CDK4/6i) in patients (pts) with ALK+ NSCLC; here we report data from the Phase Ib dose-escalation.

Methods: Pts with Stage IIIB/IV ALK+ NSCLC (≥1 prior therapy for advanced NSCLC; no prior CDK4/6i) received escalating doses of CER (starting dose 300 mg once daily [QD]; continuous [cont]) + RIB (starting dose 100 mg QD; 3 weeks [wks] on/1 wk off) under fed conditions. Primary objective: maximum tolerated dose/recommended Phase II dose (RP2D); secondary objectives: safety, pharmacokinetics, and efficacy.

Results: As of Jan 8, 2018, 27 pts were enrolled into 5 dose cohorts (Table); 8 were ALKi naive, 14 had prior crizotinib; 5 had prior 3rd-generation (gen) ALKi. Treatment was ongoing in n = 4; the most common reason for discontinuation was disease progression (n/n; 10/27). One dose-limiting toxicity occurred (CER 450 mg + RIB 100 mg; Grade [G] 2 increased blood creatinine for ≥7 consecutive days); RP2D was CER 300 mg QD (cont) + RIB 200 mg QD (3 wks on/1 wk off). At steady state, CER and RIB exposure (AUC_{0-24h}) each increased by ~1.5–2 fold compared with CER and RIB single-agent exposures under fasting conditions, with considerable variability in the setting of limited pt numbers. G3/4 treatment-related adverse events occurred in 15 pts; the most common (≥10% of pts) were decreased neutrophil count, increased ALT, and

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	CER 300 mg + RIB 100 mg	CER 450 mg + RIB 100 mg	CER 300 mg + RIB 200 mg	CER 450 mg + RIB 200 mg	CER 450 mg + RIB 300 mg	All
Enrolled (n)	4	7	4	7	5	27
Prior antineoplastic therapy, n (%)						
ALKi naive	3 (75.0)	2 (28.6)	1 (25.0)	1 (14.3)	1 (20.0)	8 (29.6)
Prior crizotinib‡	1 (25.0)	4 (57.1)	2 (50.0)	5 (71.4)	2 (40.0)	14 (51.9)
Prior 3rd-gen ALKi§	0	1 (14.3)	1 (25.0)	1 (14.3)	2 (40.0)	5 (18.5)
Treatment ongoing, n (%)	2 (50.0)	1 (14.3)	1 (25.0)	0	0	4 (14.8)
Discontinuation due to disease progression, n (%)	2 (50.0)	1 (14.3)	1 (25.0)	3 (42.9)	3 (60.0)	10 (37.0)
Most common Grade 3/4 treatment-related adverse events (≥10% of all pts), n (%)						
All	2 (50.0)	5 (71.4)	1 (25.0)	4 (57.1)	3 (60.0)	15 (55.6)
Decreased neutrophil count	0	1 (14.3)	0	2 (28.6)	3 (60.0)	6 (22.2)
Increased ALT	0	2 (28.6)	0	2 (28.6)	0	4 (14.8)
Increased AST	0	2 (28.6)	0	2 (28.6)	0	4 (14.8)
Best overall response, n (%)						
Complete response	1 (25.0)	0	0	0	0	1 (3.7)
Partial response	1 (25.0)	4 (57.1)	2 (50.0)	3 (42.9)	2 (40.0)	12 (44.4)
Stable disease	2 (50.0)	2 (28.6)	1 (25.0)	2 (28.6)	2 (40.0)	9 (33.3)
Progressive disease	0	0	0	0	1 (20.0)	1 (3.7)
Unknown*	0	1 (14.3)	1 (25.0)	2 (28.6)	0	4 (14.8)
ORR,‖ n (%) [90% CI]	2 (50.0) [0.10–0.90]	4 (57.1) [0.22–0.87]	2 (50.0) [0.10–0.90]	3 (42.9) [0.13–0.77]	2 (40.0) [0.08–0.81]	13 (48.1) [0.31–0.65]

*These 4 pts discontinued study treatment prior to completing their first tumor evaluation;

‡Pts received prior crizotinib only;

§Pts received prior 3rd-gen ALKi only (n = 2) or prior 3rd-gen ALKi and crizotinib (n = 3); ‖ORR = complete response + partial response.

increased AST. Efficacy data are shown in the table. ORR (n/n; 90% CI) was 50% (4/8; 0.19–0.80) in ALKi-naive pts; 64% (9/14; 0.39–0.84) in pts with prior crizotinib; 0% (0/5; 0.00–0.45) in pts with prior 3rd-gen ALKi.

Conclusions: RP2D was CER 300 mg QD (cont) + RIB 200 mg QD (3 wks on/1 wk off) in pts with Stage IIIB/IV ALK+ NSCLC. CER + RIB showed a manageable safety profile and preliminary efficacy, including in pts with prior ALKi exposure.

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