1437P Phase I dose expansion data for M6620 (formerly VX-970), a first-in-class ATR inhibitor, combined with gemcitabine (Gem) in patients (pts) with advanced non-small cell lung cancer (NSCLC)

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Background: Ataxia telangiectasia and Rad3-related protein (ATR) is an essential DNA damage response regulator, and is required for proliferating cell survival. DNA-damaging agents often induce replicative stress leading to activation and reliance on ATR; inhibition of ATR signalling is an attractive strategy to sensitize tumors to DNA-damaging chemotherapy. M6620 is a potent, selective inhibitor of ATR with preclinical anticancer activity in combination with DNA-damaging chemotherapy. Here, we report dose expansion cohort data for a phase I trial of M6620 plus Gem in pts with advanced NSCLC (NCT02157792).

Methods: Eligible pts had measurable (RECIST 1.1) advanced NSCLC with up to 2 lines of prior therapy, with one including a platinum analog. Of 40 pts planned for enrollment, $\geq$20 had to have a TP53 mutation (TP53+), $\leq$10 ATM loss of expression (ATM–) (both alterations associated with ATR inhibitor sensitivity in preclinical studies), and $\approx$10 neither TP53+ nor ATM–; status was determined from fresh or archival tissue. Pts received Gem 1000 mg/m^2 on days 1 + 8 and M6620 210 mg/m^2 on days 2 + 9 of each 21-day cycle. Pharmacokinetics was assessed on day 2 of cycle 1. Primary endpoints were safety and overall response rate (ORR).

Results: The safety set included 33 pts who received combination therapy (median age, 62.0 years [range 36–76]; TP53+, 19; WHO PS 0/1, 9/23). 31/33 pts had a treatment-emergent adverse event (TEAE), with 19 (57.6%) having grade $\geq$3 TEAEs: fatigue (n = 6), neutropenia (4), anemia (3), thrombocytopenia (3), malaise (2), vomiting (2), ALT increase (2), AST increase (2), pneumonia (2), sepsis (2) (grade $\geq$3 TEAES occurring in $\geq$ 2 pts). Of the 24 treated pts with baseline and on-treatment assessments, 3 pts had a partial response (PR; ORR 12.5%) and 18 pts (75%) had stable disease (SD). Four pts had PR or SD $\geq$ 6 months (clinical benefit rate 16.7%). Updated efficacy and PK data will be presented from an upcoming analysis.

Conclusions: The ATR inhibitor M6620 combined with Gem showed signs of activity in advanced NSCLC; tolerability was acceptable.

Clinical trial identification: NCT02157792.

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