developmental therapeutics

**451PD**

**PHASE I STUDY OF THE PI3Kα INHIBITOR BYL719, AS A SINGLE AGENT IN PATIENTS WITH ADVANCED SOLID TUMORS (AST)**


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**Abstract**

**Aim:** BYL719 is a selective oral inhibitor of the Class I PI3K α-isofrom. PI3Kα is encoded by PIK3CA, a frequently altered gene in human cancers. This was a Ph I, dose-escalation and -expansion, first-in-human study of BYL719 in pts with PIK3CA-altered AST, or PIK3CA-altered or wild-type (wt) ER+ breast cancer (BC) (NCT01219699).

**Methods:** Adult pts with advanced PIK3CA-altered (mutation or amplification) AST received oral BYL719 QD or BID (28-day cycles). Pts with PIK3CA wt ER+ BC were also enrolled into the dose expansion. A Bayesian logistic regression model with overdose control guided dose escalation. Primary objective was to determine MTD and/or RP2D of single-agent BYL719. Safety (CTCAE v4.0), tolerability, PK, preliminary efficacy (RECIST) were also assessed.

**Results:** As of Mar 10, 2014, 132 pts received BYL719 QD (30–450 mg) or BID (120, 150, 200 mg). Median exposure was 11.9 (0.4–98) wks. DLTs were reported in: 4 pts (hyperglycemia x2, nausea x2) at 450 mg QD, 4 pts (hyperglycemia x4) at 200 mg BID, and 1 pt (hyperglycemia and hypophosphatemia) at 150 mg BID. BYL719 QD MTD is 400 mg (and was used for dose expansion); here, BYL719 BID MTD is declared as 150 mg. Most common (≥20%) suspected study drug-related all-Grade AEs at the MTDs were: BYL719 150 mg BID (n = 15) – hyperglycemia, nausea (both 53%), diarrhea, decreased appetite, fatigue, stomatitis (all 33%); and BYL719 400 mg QD (n = 63 including dose expansion) – hyperglycemia (51%), nausea (48%), diarrhea (41%), decreased appetite (38%), fatigue (32%), vomiting (30%), rash (20%). Overall, 15 of 131 evaluable pts had partial responses (PRs; incl. 2 [out of 24 pts] with PIK3CA-altered ER+ BC); 7 PRs were confirmed: 2 at 270 mg QD, 1 at 350 mg QD, 2 at 400 mg QD, 2 at 150 mg BID. Disease control rates (CR, PR, or SD) at MTDs were: BYL719 400 mg QD – 53%; and BYL719 150 mg BID – 67%. Median PFS at ≥270 mg in ER+ HER2– BC (n = 21) was 166 days. In pts with PIK3CA wt ER+ BC (n = 5) duration of exposure range was 7–61 days; no PRs were observed in wt pts.

**Conclusions:** BYL719 is the first α isoform-specific PI3K inhibitor to show single-agent responses in tumors with activating mutations. The safety profile was favorable with mostly on-target effects (i.e. hyperglycemia). Data comparing PIK3CA-altered and wt ER+ /HER2– BC pts will be presented.

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