**Cyclin-Dependent Kinase 4 and 6 Inhibitor: PD 0332991**

**THE ROLE OF CDK**

- Cyclin-dependent kinases (CDKs), a group of proteins and enzymes, that have been shown to play a key role in regulating cell cycle progression and to a large degree manage cellular transitions from growth phase ($G_1$ and $G_2$) into phases associated with DNA replication (S) and mitosis (M). $^{1,2}$
  - Interaction between CDKs and cyclin proteins, such as cyclin D, has been shown to be crucial in the progression of $G_1$ to S in the cell cycle. $^3$
- Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer.$^{1,3}$

**RATIONALE FOR TARGETING CDK 4/6 IN CANCER**

- CDK4 and CDK6 are two closely related kinases that enable tumor cell progression during phase $G_1$ to phase S in the cell cycle.$^2$
  - CDK 4 and 6 stimulate cell cycle progression, necessary for DNA replication and for cell division, in combination with cyclin D. $^2$
  - More than 90 percent of human tumors abandon control mechanisms for the transition of $G_1$-S phase through a variety of genetic and biochemical adaptations.$^2$
- In preclinical studies, increased levels of cyclin D and decreased levels of p16, a naturally occurring inhibitor of CDK4, have been associated with increased sensitivity to CDK 4 and 6 inhibition.$^3$
- Alterations in cell cycle regulators have been implicated in human malignancies including, breast cancer and myeloma.$^{3,4}$
- Preclinical studies suggest that inhibition of cyclin D-dependent kinase activity may prevent tumor growth.$^2$
  - Inhibition of CDK 4 and 6 has been shown to prevent the deactivation of retinoblastoma (Rb), a tumor suppressor protein, and interfere with tumor cell progression.$^4$

**ABOUT PD 0332991**

- PD 0332991 is an investigational, orally active and selective inhibitor of the CDK4 and CDK6 kinases.$^5$
- Pfizer is evaluating PD 0332991 in multiple Phase 1 and Phase 2 studies including a Phase 2 study of letrozole with or without PD 0332991 for the first-line treatment of estrogen-receptor positive, HER2-negative advanced breast cancer.$^5$
  - Results of the Phase 1 portion of the study showed that the combination of PD 0332991 and letrozole was generally well tolerated, with the recommended dose of PD 0332991 to be 125 mg once daily.$^6$
- The Phase 2 portion of the study was initiated to determine the overall safety and efficacy of PD 0332991 (125 mg) and letrozole (2.5 mg) in post-menopausal women with estrogen-receptor positive, HER2-negative advanced breast cancer.$^5$
  - Results from part 1 of the Phase 2 study presented at the 2012 IMPAKT Breast Cancer Conference show statistically significant improvement in median progression-free survival (PFS) in the PD 0332991 plus letrozole arm versus letrozole alone. The most commonly reported adverse events (AEs) were
neutropenia, leucopenia, and fatigue. These AEs were generally manageable.

- In part 2 of the study post-menopausal women with ER+, HER2-negative breast cancer were enrolled using biomarker selection (cyclin D1 (CCND1)-gene amplification and/or loss of p16).
- Both part 1 and part 2 are ongoing but no longer enrolling, and a randomized Phase 3 trial is planned.

- PD 0332991 is currently being evaluated in other tumor types including late-line metastatic breast cancer, liposarcoma, non-small cell lung cancer, liver cancer, ovarian cancer, glioblastoma, refractory solid tumors, multiple myeloma and mantle cell lymphoma.
6 ASCO Accepted Poster Presentation #3060. Phase 1 study of PD 0332991, a cyclin-D kinase (CDK) 4/6 inhibitor in combination with letrozole for first-line treatment of patients with ER-positive, HER2-negative breast cancer. Monday, June 7, 2010: 8:00am-12:00pm. D. Slamon – Presenter. 46th Annual Meeting of the American Society of Clinical Oncology (ASCO). June 4-8, 2010.