Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/investigating-the-next-generation-of-cdk2-4-6-inhibitors-insights-from-the-2021-sabcs/12981/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Investigating the Next Generation of CDK2/4/6 Inhibitors: Insights from the 2021 SABCS

Announcer Introduction:
You're listening to *Project Oncology* on ReachMD. On this episode, sponsored by Lilly, we're going to hear from Dr. Timothy Yap, who's an Associate Professor in the Department for Investigational Cancer Therapeutics and the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas MD Anderson Cancer Center. Dr. Yap will be discussing his talk presented at the 2021 San Antonio Breast Cancer Symposium on post CDK4/6 inhibitor treated HR+ breast cancer patients. Here's Dr. Yap now.

Dr. Yap:
One of the most significant challenges to facing ER positive breast cancer patients is that there is no clear standard of care in the post-CDK4/6 inhibitor setting. So, to address this important unmet need, research has been focused intensively on the development of additional therapies that can overcome drug resistance such as that driven through CDK2 activation, and potentially provide these patients with more effective and safer treatment options. I was delighted, therefore, to present the first data from our first-in-class, first-in-human, Phase 1 trial of the CDK2/4/6 inhibitor, PF6873600, given either alone or with endocrine therapy in patients with advanced breast/ovarian cancer. The CDK2/4/6 inhibitors differentiated from the approved CDK4/6 inhibitors, such as palbociclib, with its ability to additionally target CDK2. And since CDK2 activation seems to drive palbociclib resistance in some breast cancers, this molecule has the potential to overcome such resistance. Promisingly, PF 3600 as a first-in-class, selective inhibitor of CDK2/4/6, and pre-clinical studies have demonstrated anti-tumor activity of PF3600 as a single agent, and when combined with endocrine therapy.

So, the objectives of this study were to determine the recommended dose or expansion, and to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of PF3600, either alone or combined with endocrine therapy in patients with HR-positive, HER2-negative breast cancer, triple negative breast cancer, or ovarian cancer. Patients received escalating doses of single-agent PF3600 from one milligram up to 50 milligrams, twice daily orally, on a continuous basis. The single-agent PF3600 recommended dose was also then used in combination with fulvestrant. In terms of safety, dose-limiting toxicities, or DLTs occurred in about 12 percent of DLT-evaluable patients treated with single-agent PF3600 at the highest dose levels of 35 milligrams or 50 milligrams, twice daily. The PF3600 recommended dose was 25 milligrams, b.i.d. in a single agent and combination groups, and no DLTs were observed at this recommended dose. The most frequently reported, treatment related, all-grade AEs for single agent PF3600, and PF3600 plus fulvestrant combination, were nausea and anemia. In terms of pharmacokinetics, plasma exposures of PF3600 increased with doses, up to 35 milligrams twice daily. PF35600 was absorbed rapidly and there was minimal accumulation following repeated, twice daily, dosing. Plasma pharmacokinetics of PF3600 was largely comparable between single agent and combination therapy with fulvestrant.

In terms of pharmacodynamics, inhibition of cell cycle biomarkers, 42RB and Ki-67 was observed in patients who achieved disease control after PF3600 treatment, indicating target modulation in the tumor.

We've been very encouraged by the early responses we're seeing thus far with this inhibitor, even as monotherapy, especially considering that we are treating patients who have previously progressed on CDK4/6 inhibitors, which is consistent with our hypothesis that CDK2 contributes to resistance to current standard of care treatments and that a CDK2/4/6 inhibitor can potentially mitigate such resistance. Overall, the disease control rate amongst response evaluable patients was 56 percent for single agent PF3600, and 88 percent for the combination. Promisingly, four heavily pretreated patients with HR-positive, HER2-negative breast cancer, treated with single agent PF3600, had recessed partial responses, including two confirmed and two unconfirmed partial responses in patients who had previously progressed on CDK4/6 inhibitors.

So, to summarize, in terms of key takeaways, PF3600 had an acceptable safety profile, and preliminary anti-tumor activity. It can be

© 2023 ReachMD

safely combined with endocrine therapy in heavily pre-treated patients, including those with HR-positive, HER2-negative breast cancer progressing on endocrine therapy plus CDK4/6 inhibitor and chemotherapy. The recommended dose for expansion was determined to be 25 milligrams, twice daily, as single agent PF3600, or in combination with fulvestrant.

Announcer Close:
This episode of *Project Oncology* was sponsored by Lilly. To access other episodes of this series, visit reachmd.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening!

© 2023 ReachMD