

Dacomitinib (PF-00299804) is an investigational agent and has not been approved for marketing by any regulatory agency at this time.

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| <p>ABOUT DACOMITINIB</p> | <ul style="list-style-type: none"> • Dacomitinib is an oral, once-daily, pan-HER inhibitor. It is an irreversible inhibitor of HER-1 (EGFR), HER-2 and HER-4 tyrosine kinases.¹ Dacomitinib targets multiple receptors of the HER pathway, whereas currently marketed HER-1 (EGFR) inhibitors for non-small cell lung cancer (NSCLC) target only one receptor in this pathway.¹ • Clinical evaluation of dacomitinib is ongoing in a number of clinical trials in patients with advanced NSCLC across lines of therapies and a range of histologies and molecular subtypes, such as EGFR and KRAS status.^{2,3,4,5,6} • Additionally, there is an ongoing clinical trial evaluating dacomitinib in recurrent and/or metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN).⁷ |
| <p>THE ROLE OF HER AND CANCER</p> | <ul style="list-style-type: none"> • The HER family of tyrosine kinases includes receptors HER-1 (EGFR), HER-2, HER-3 and HER-4. The HER signaling pathway plays a role in the normal regulation of cell growth and proliferation, differentiation, and apoptosis.^{8,9,10} • Activation of HER receptors drives signal transduction pathways; dysregulated signaling through the HER receptors may lead to malignant transformation and tumor growth.^{8,10} • Mutations or amplification of the HER receptor family, as well as overexpression of the HER receptors and/or ligands, have been associated with late stage cancers including lung, breast, gastric, head and neck, and colorectal cancers.¹⁰ • Current drug development against the HER family in NSCLC has been focused mostly on small molecule selective and reversible tyrosine kinase inhibitors (TKIs) and chimeric monoclonal antibodies (mAbs).⁸ • Altered activity of a specific HER receptor can be functionally compensated for by another HER receptor or other signaling pathways. This crosstalk can result in compensatory tumor signaling and growth, which can lead to drug resistance.⁸ • In pre-clinical studies, dacomitinib has been shown to inhibit the signaling in both wild type and mutant HER-1 (EGFR) including forms of NSCLC that are resistant to currently marketed HER-1 (EGFR) inhibitors, such as erlotinib and gefitinib.^{1,11} |

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| <p>CLINICAL STUDIES</p> | <p>Following is a list of some of the Phase 1, 2 and 3 dacomitinib trials:</p> <p><u>NSCLC</u></p> <p>Phase 3</p> <ul style="list-style-type: none"> BR.26: A double-blind, placebo-controlled randomized trial evaluating dacomitinib in patients with advanced NSCLC with varying histologies and molecular subtypes, after at least one chemotherapy regimen and erlotinib or gefitinib (NCIC-Clinical Trial Group led trial).² – Currently recruiting ARCHER 1009: A randomized, double-blind, multicenter trial evaluating dacomitinib versus erlotinib for the treatment of patients with advanced NSCLC following at least one prior chemotherapy.¹² – Currently recruiting |
| <p>CLINICAL STUDIES (continued)</p> | <p>Phase 2</p> <ul style="list-style-type: none"> ARCHER 1042: An open-label, multi-cohort trial evaluating the effect of prophylactic intervention and an interrupted dosing schedule on the incidence of adverse events in patients treated with dacomitinib.¹³ – Currently recruiting A7471028: A randomized trial evaluating dacomitinib versus erlotinib in patients with advanced NSCLC with varying histologies and molecular subtypes, after at least one chemotherapy regimen.³ – Ongoing, recruitment complete A7471017: An open-label trial of dacomitinib in untreated advanced adenocarcinoma NSCLC, clinically or molecularly selected for EGFR mutations and HER2 mutation or amplification.⁴ <ul style="list-style-type: none"> Cohort A: Non-smokers or former light smokers; patients with EGFR mutated NSCLC, regardless of smoking status⁴ – Ongoing, recruitment complete Cohort B: Patients with HER2 mutated or amplified NSCLC⁴ – Currently recruiting A7471002: An open-label trial evaluating dacomitinib in patients with advanced adenocarcinoma and non-adenocarcinoma NSCLC with KRAS wild-type and varying EGFR molecular subtypes, after at least one chemotherapy regimen and erlotinib.⁵ – Ongoing, recruitment complete A7471003: A Phase 1/2 open-label, single-arm trial of dacomitinib in Korean patients with KRAS wild-type advanced NSCLC, after at least one chemotherapy regimen and erlotinib or gefitinib.⁶ – Ongoing, recruitment complete <p>Phase 1</p> <ul style="list-style-type: none"> A8081006: An open-label, dose escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics of the combination of crizotinib and dacomitinib in patients with advanced NSCLC.¹⁴ – Currently recruiting <p><u>Head and Neck Cancer</u></p> <p>Phase 2</p> <ul style="list-style-type: none"> A7471027: A multicenter trial of dacomitinib as a first-line treatment in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.⁷ – Complete <p>For a complete listing of dacomitinib clinical trials, please visit www.clinicaltrials.gov.</p> |

- ¹ Gonzales AJ, Hook KE, Althaus IW et al. Antitumor activity and pharmacokinetic properties of PF-00299804, a second-generation irreversible pan-erbB receptor tyrosine kinase inhibitor. *Mol Cancer Ther.* 2008;7:1880-89.
- ² ClinicalTrials.gov. PF-00299804 in Treating Patients With Stage IIIB or Stage IV Non-Small Cell Lung Cancer That Has Not Responded to Standard Therapy for Advanced or Metastatic Cancer. Available at: <http://clinicaltrials.gov/ct2/show/NCT01000025>. Accessed August 7, 2012.
- ³ ClinicalTrials.gov. Randomized Trial Of PF-00299804 Taken Orally Versus Erlotinib Taken Orally For Treatment Of Advanced Non-Small Cell Lung Cancer That Has Progressed After One Or Two Prior Chemotherapy Regimen .Available at <http://clinicaltrials.gov/ct2/show/NCT00769067>. Accessed August 7, 2012.
- ⁴ ClinicalTrials.gov PF-00299804 As A Single Oral Agent In Untreated Adenocarcinoma Of The Lung In Non-Smokers Or Former Light Smokers. Available at: <http://clinicaltrials.gov/ct2/show/NCT00818441>. Accessed August 7, 2012.
- ⁵ ClinicalTrials.gov. PF-00299804 As A Single Agent, In Patients With Advanced Non-Small Cell Lung Cancer Who Have Failed Chemotherapy And Erlotinib. Available at: <http://clinicaltrials.gov/ct2/show/NCT00548093>. Accessed August 7, 2012.
- ⁶ ClinicalTrials.gov. Trial of PF-00299804 In Patients With Advanced Refractory Lung Cancer. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00553254>. Accessed on August 7, 2012.
- ⁷ ClinicalTrials.gov. Open-Label Trial Of Oral PF-00299804 By Continuous Dosing In Patients With Recurrent Or Metastatic Head And Neck Squamous Cell Cancer. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00768664>. Accessed August 7, 2012.
- ⁸ Huang Z, Bedlik C., Shepard HM. A pan-HER approach for cancer therapy: background, current status and future development. *Expert Opin Biol Ther.* 2009;9:97-110.
- ⁹ Britten CD. Targeting ErbB receptor signaling: A pan-ErbB approach to cancer. *Mol Cancer.* 2004;3:1335-42.
- ¹⁰ Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Bio.* 2001;2:127-37.
- ¹¹ Engelman JA, Zejnullahu K, Gale C-M et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res.* 2007;67:11924-32.
- ¹² ClinicalTrials.gov. ARCHER 1009: A Phase 3 Study Of PF-00299804, a pan-HER inhibitor, vs. Erlotinib for the Treatment Of Advanced Non-Small Cell Lung Cancer. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT01360554>. Accessed August 7, 2012.
- ¹³ ClinicalTrials.gov. Adverse Event Toxicity Intervention Study to Evaluate the Effect of Prophylactic Treatment and an Interrupted Dosing Schedule on the Incidence of Adverse Events in Patients Treated with Dacomitinib. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT01465802?term=PF-00299804&rank=1>. Accessed August 7, 2012.
- ¹⁴ ClinicalTrials.gov. A Study Of Combined C- MET Inhibitor And PAN-HER Inhibitor (PF-02341066 And PF-00299804) In Patients With Non- Small Cell Lung Cancer. Available at: <http://clinicaltrials.gov/ct2/show/NCT01121575>. Accessed August 7, 2012.