2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA USA

Name of Finished Product: Not applicable

Name of Active Ingredient: Ganitumab (AMG 479)

Title of Study: An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer

Investigator(s) and Study Center(s): This was an international study conducted at 58 centers. Study centers and investigators are listed in Appendix 4.

Publication(s): Kaufman PA, Ferrero JM, Bourgeois H, et al. A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of AMG 479 With Exemestane (E) or Fulvestrant (F) in Postmenopausal Women With Hormone-Receptor Positive (HR+) Metastatic (M) or Locally Advanced (LA) Breast Cancer (BC). San Antonio Breast Cancer Symposium. 2010:S1-4.

Study Period: 27 March 2008 (first subject enrolled) to 05 May 2010 (data cutoff date for primary analysis)

Development Phase: 2

Introduction and Objectives: Ganitumab is a fully human monoclonal IgG1 antibody against human insulin-like growth factor receptor type 1 (IGF-1R) developed to provide inhibitory effects on tumor growth and invasion, likely in combination with standard cancer therapy, molecularly targeted therapy, or both. Ganitumab exerts its antitumor activity by blocking ligand binding (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor-2 [IGF-2]) and inducing receptor internalization and degradation without cross-reacting with the insulin receptor.

This randomized, double-blind, placebo-controlled, phase 2 study was designed with the primary objective to estimate the treatment effect, as measured by progression-free survival (PFS), of ganitumab in combination with endocrine therapy (exemestane or fulvestrant) compared with endocrine therapy (exemestane or fulvestrant) without ganitumab in postmenopausal women with hormone-receptor(HR)-positive, locally advanced, or metastatic breast cancer.

The secondary objectives were to investigate the effect of ganitumab compared with placebo when administered in combination with exemestane or fulvestrant on the safety and tolerability, patient-reported outcomes (PROs), pharmacokinetics of ganitumab, and additional efficacy measures including clinical benefit rate, objective response rate, duration of response, time to progression, time to response, time to treatment failure, and overall survival (OS).

The primary efficacy analysis was performed when 123 PFS events (planned for at least 120 events) had been observed. The current report summarizes data for subjects through the data cutoff for the primary analysis.

Methodology: This was a randomized, double-blind, placebo-controlled, phase 2 study that evaluated the efficacy and safety of the combination of endocrine therapy (exemestane or fulvestrant) with ganitumab (12 mg/kg once every 2 weeks [Q2W]) or placebo in postmenopausal women with confirmed HR-positive, locally advanced, or metastatic breast cancer who had disease progression during or within 12 months after completing prior adjuvant endocrine therapy or during the first prior endocrine therapy for metastatic disease.

Based on investigator discretion, subjects were prescribed an endocrine therapy of either exemestane or fulvestrant to be administered throughout the study. The study planned to randomize 150 subjects in a 2:1 ratio to ganitumab in combination with endocrine therapy (exemestane or fulvestrant) or placebo in combination with endocrine therapy (exemestane or fulvestrant). At least 45 of the 150 subjects randomized were required to be prescribed to each endocrine therapy (exemestane and fulvestrant). Randomization was stratified by prescribed endocrine therapy (exemestane or fulvestrant) and by extent of the subject's disease (soft tissue disease only, bone disease [with or without soft tissue and without visceral disease], or visceral disease [with or without other sites]).

Study treatment with ganitumab or placebo and endocrine therapy (exemestane or fulvestrant) continued until disease progression, unacceptable toxicity, consent withdrawal, investigator discretion, initiation of a new anticancer treatment, or death. Subjects randomized to placebo in combination with endocrine therapy could have the opportunity to continue receiving study treatment as open-label ganitumab in combination with the endocrine therapy originally prescribed ("rollover treatment") upon disease progression.

In order to safeguard the interest of the subjects and maintain the study integrity, an unblinded data review team (DRT) that was external to the study team involved in the daily conduct of the study, but internal to Amgen was formed to review safety data and efficacy analysis results.

Number of Subjects Planned: 150 subjects

Number of Subjects Enrolled: 156 subjects

Sex: 156 women (100%)

Age: mean (standard deviation [SD]) 62.3 (10.3) years (range: 36 to 88 years)

Ethnicity (Race): 147 (94%) white; 4 (3%) black; 3 (2%) Asian; 1 (1%) Hispanic or Latino; 1 (1%) other

Diagnosis and Main Criteria for Eligibility: The main inclusion criteria for subjects in this study included postmenopausal woman ≥ 18 years of age with histologically or cytologically confirmed carcinoma of the breast with locally advanced or metastatic disease not amenable to surgery or radiation with curative intent, HR (estrogen and/or progesterone receptor)-positive disease using institutional standards for analysis of the primary tumor tissue or tissue obtained thereafter (based on medical history review), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable or nonmeasurable disease (as defined by the modified Response Evaluation Criteria in Solid Tumors [RECIST] criteria), adequate renal and hepatic function, and adequate glycemic function for subjects with known diabetes (type 1 or 2). Subjects also had to be amenable to receive endocrine therapy as per investigator discretion and had to have had disease progression while receiving prior endocrine therapy for locally advanced or metastatic breast cancer or recurrence while receiving prior endocrine therapy as adjuvant treatment or within 12 months of treatment discontinuation. A complete list of inclusion/exclusion criteria is provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, and Manufacturing Batch Number: Ganitumab was provided in single-use vials containing 3 mL of a frozen 30-mg/mL sterile solution. Ganitumab or placebo was administered via intravenous (IV) infusion Q2W as

defined in the protocol; Ganitumab was administered at a dose of 12 mg/kg. Lot numbers for ganitumab used in this study are provided in Appendix 18.

Duration of Treatment: Subjects received ganitumab or placebo in combination with endocrine therapy (exemestane or fulvestrant) until disease progression, unacceptable toxicity, consent withdrawal, investigator discretion, initiation of a new anticancer treatment, or death. Subjects randomized to placebo in combination with endocrine therapy could have the opportunity to continue receiving study treatment as rollover treatment upon disease progression. Estimated median length of individual subject treatment, not including rollover treatment, was 4 months in the placebo treatment group and was 6 months in the ganitumab treatment group.

Reference Therapy, Dose and Mode of Administration, and Manufacturing Batch Number: Placebo was provided by the sponsor in vials identical to ganitumab except containing only vehicle. The dilution method and mode of administration were identical to that of ganitumab. Lot numbers for placebo used in this study are provided in Appendix 18.

Based on investigator discretion, subjects were prescribed an endocrine therapy of either exemestane (25 mg tablets once a day [QD] by mouth [PO]) or fulvestrant (loading dose [500 mg intramuscular (IM) on day 1, then 250 mg IM on day 15] then 250 mg IM on day 29 and every 28 days thereafter) to be administered throughout the study.

Study Endpoints

Primary Endpoint: PFS, as measured by modified RECIST per local review

Secondary Endpoints:

- Clinical benefit (complete response, partial response, or stable disease for ≥ 24 weeks as measured by modified RECIST per local review), objective response rate (complete and partial response as measured by modified RECIST per local review), duration of response, time to progression, time to response, time to treatment failure, and OS
- Incidence of adverse events, abnormal laboratory values, and antiganitumab antibody formation
- Pharmacokinetics parameters of ganitumab
- Breast cancer related symptoms, health-related quality of life (HRQOL), and skin toxicity burden

Exploratory Endpoints: [redacted]

Statistical Methods: The primary analysis was performed when 123 PFS events (planned for 120 events) were observed. Descriptive statistics were provided for selected demographic, safety, efficacy, pharmacokinetics, antiganitumab antibodies, PRO, and exploratory endpoints. Summary statistics included mean, median, SD, range, quartiles, 80% CI, and/or 95% confidence interval (CI) of expected values (eg, mean) of continuous and categorical variables.

PFS, time to progression, time to treatment failure, and OS were summarized using Kaplan-Meier estimates. The CIs for 25th percentile, median, and 75th percentile were calculated by the method described by Brookmeyer and Crowley (1982). A Cox model stratified by randomization factors was used to estimate the treatment hazard ratio (ganitumab / placebo) and an 80% CI for PFS, time to progression, time to treatment failure, and OS. The number and percent of subjects

within each category of best overall objective response rate were summarized by treatment group. Time to response and duration of response were descriptively analyzed for subjects who responded. The clinical benefit rate and the maximum reduction in tumor size were also summarized.

Each subscale of the European Organization for the Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ C-30) and the 2 questions from Dermatology Life Quality Index (DLQI) were summarized by cycle. For the QLQ C-30 subscales and the 2 questions from DLQI, a time-adjusted area under the curve (AUC) was also calculated. The time-adjusted AUC was evaluated using an analysis of covariance where the baseline score and the stratification factors were included as the covariates to obtain treatment estimates for each subscale and to obtain estimates of the difference between the 2 treatment groups for each subscale. Responsiveness to change was evaluated by comparing changes in PRO scores to changes in clinical parameters (ECOG performance status and tumor progression).

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received at least 1 dose of ganitumab or placebo; subjects in this analysis set were analyzed according to the treatment received. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, seriousness, and relationship to treatment. The following events of interest were summarized separately: hyperglycemia, thrombocytopenia, hepatotoxicity, rash, infusion reaction, neutropenia, venous thromboembolism, and sensorineural hearing loss. Clinical laboratory parameters and vital signs were summarized using descriptive statistics or shift tables. The incidence of subjects developing antiganitumab antibodies was calculated.

Summary of Results:

Subject Disposition: A total of 156 subjects were randomized in the study, with 106 subjects randomized to the ganitumab treatment group and 50 subjects randomized to the placebo treatment group. As of the primary analysis data cutoff date, 109 (70%) subjects (71 [67%] subjects in the ganitumab treatment group and 38 [76%] subjects in the placebo treatment group) were ongoing in the study. Thirty-five (33%) subjects in the ganitumab treatment group and 12 (24%) subjects in the placebo treatment group had discontinued the study (ie, discontinued treatment and additional protocol assessments). Death was the most common reason for discontinuation of study (ganitumab: 30%, placebo: 20%).

One subject (randomized to ganitumab) never received a dose of investigational product and was excluded from the safety analysis set. Another subject who was randomized to placebo mistakenly received 1 dose of ganitumab at cycle 3 day 1 and was therefore treated as an ganitumab subject for the safety analysis set. Thirty-four subjects in the ganitumab treatment group and 16 subjects in the placebo group received exemestane as endocrine therapy. Seventy-two subjects in the ganitumab treatment group and 33 subjects in the placebo group received fulvestrant as endocrine therapy. Nine subjects received at least 1 dose of open-label ganitumab after having progressed on the placebo treatment group (ie, entered the rollover arm of the study).

As of the primary analysis data cutoff date, 21 (20%) subjects in the ganitumab treatment group and 8 (16%) in the placebo treatment group remained on treatment (ie, investigational product and/or endocrine therapy). Eighty-four percent of subjects in the ganitumab treatment group and 84% of subjects in the placebo treatment group had ended treatment with investigational product, and 83% and 78%, respectively, had also ended treatment with endocrine therapy. Disease progression was the most common reason for discontinuation of investigational product (ganitumab: 64%, placebo: 60%) and was also the most common reason for discontinuation of endocrine therapy (62% and 56%, respectively).

Efficacy Results: The estimated hazard ratio (stratified by endocrine therapy and extent of disease) (80% CI) for PFS for the ganitumab arm relative to the placebo arm was 1.17 (0.91, 1.50) (p = 0.435, stratified log rank test). The median PFS time was 3.9 months in the ganitumab treatment group and 5.7 months in the placebo treatment group.

The objective response rate (80% CI) was 8% (4, 14) in the ganitumab treatment group and 13% (6, 23) in the placebo treatment group. The clinical benefit rate (80% CI) was 35% (27, 44) and 31% (20, 44), respectively. Of the subjects who had a confirmed response, the median duration of response was 30.3 and 33.5 weeks, respectively, and the median time to response was 16.0 and 15.7 weeks, respectively. Among all subjects randomized, the median time to treatment failure was 3.6 and 5.0 months, respectively and median time to progression was 3.9 and 5.7 months, respectively.

The OS data are immature and inconclusive with 73% of subjects censored at the time of the primary analysis. The OS hazard ratio (stratified by the 2 stratification factors) was 1.48 (80% CI: 0.92, 2.37) in favor of the placebo group. The median survival was 22.2 months in the ganitumab treatment group and was not estimable in the placebo treatment group due to a low event rate.

Safety Results: A total of 105 (99%) subjects in the ganitumab treatment group and 47 (96%) subjects in the placebo treatment group had at least 1 treatment-emergent adverse event. The most common adverse events (≥ 20% of subjects), by preferred term, in either treatment group were nausea (ganitumab: 40%, placebo: 39%), fatigue (40%, 24%), diarrhea (31%, 29%), headache (24%, 27%), asthenia (23%, 37%), arthralgia (22%, 22%), vomiting (22%, 20%), back pain (19%, 24%), and hot flush (11%, 24%).

Ninety (85%) subjects in the ganitumab treatment group and 33 (67%) subjects in the placebo treatment group had at least 1 adverse event that was considered by the investigator to be related to investigational product (ganitumab or placebo). The most common adverse events considered by the investigator to be related to investigational product (≥ 20% of subjects) by preferred term in either treatment group were fatigue (ganitumab: 28%, placebo: 18%), asthenia (18%, 24%), and nausea (25%, 18%).

Grade ≥ 3 treatment-emergent adverse events occurred in 45 (42%) subjects in the ganitumab treatment group and 12 (24%) in the placebo treatment group. The most common grade ≥ 3 events (≥ 2 subjects) by preferred term in either treatment group were neutropenia (ganitumab: 6%, placebo: 2%), hyperglycemia (6%, 0%), thrombocytopenia and AST increased (4%, 0%, each), general physical health deterioration (3%, 2%), asthenia (4%, 2%), anemia, dyspnea, and

pulmonary embolism (2%, 2%, each), and fatigue, ALT increased, gamma-glutamyltransferase increased, weight decreased, nausea, vomiting, hypokalemia, arthralgia, hypertension, and breast cancer (2%, 0% each).

Serious adverse events were reported for 27 (25%) subjects in the ganitumab treatment group and 9 (18%) subjects in the placebo treatment group. As reported on the adverse event case report form, 4 (4%) subjects in the ganitumab treatment group and 1 (2%) subject in the placebo treatment group had fatal adverse events while on study. Fatal adverse events were due to progression of disease, with the exception of 1 fatal event of pulmonary embolism in the ganitumab treatment group (which occurred in the post-surgical setting following pathologic femoral fracture). In addition, 2 subjects in the ganitumab treatment group and 1 subject in the placebo treatment group died for a reason noted as "other" per the death case report form and further information noted as sepsis, perforation peritonitis, and ischemic bowel disease with transmural necrosis, respectively. These events occurred > 30 days after the last dose of investigational product.

Eight (8%) subjects in the ganitumab treatment group and 6 (12%) subjects in the placebo treatment group had adverse events leading to permanent discontinuation of treatment or removal from the study.

In the ganitumab treatment group, 103 subjects had a postdose antibody result and 1 subject (1%) developed antiganitumab binding antibodies (negative for neutralizing antibodies); no adverse events were reported that potentially may have been related to the presence of antibodies for this case. In the placebo treatment group, 47 subjects had a postdose antibody result and no subject developed antiganitumab binding antibodies.

[redacted]

Patient-reported Outcomes Results: Overall, there was little evidence of a treatment effect on PROs. Only 1 of the 15 scores derived from the EORTC QLQ C-30 showed a significant difference, which was for the single item constipation symptom measure. The time-adjusted AUC for the global health status/quality of life scale was approximately equal for the 2 treatment groups. DLQI scores (from 2 questions) were generally similar between treatment groups throughout the study.

[redacted]

Conclusions: In conclusion, no evidence of activity was observed in this study with the addition of ganitumab to second-line hormonal therapy in women with HR-positive locally advanced or metastatic breast cancer. The hazard ratio point estimate indicates similar PFS between the ganitumab and placebo treatment groups; based on the 80% CI, this result is interpreted as a PFS effect lies between a 9% improvement and a 50% worsening. Secondary efficacy endpoints of objective response rate, clinical benefit rate, duration of response, time to response, and time to progression were similar between treatment groups. With 73% of subjects censored at the time of the analysis, the OS data are immature and inconclusive.

Overall, the safety profile of ganitumab in this study was consistent with what has been observed to date with ganitumab; no new risks associated with ganitumab treatment were identified.

[redacted]

2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA USA

Name of Finished Product: Not applicable

Name of Active Ingredient: Ganitumab (AMG 479)

Title of Study: An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer

Investigators and Study Centers: This was an international study conducted at 58 centers. Study centers and investigators are listed in Appendix 4.

Publications: Kaufman PA, Ferrero JM, Bourgeois H, et al. A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of AMG 479 With Exemestane (E) or Fulvestrant (F) in Postmenopausal Women With Hormone-Receptor Positive (HR+) Metastatic (M) or Locally Advanced (LA) Breast Cancer (BC). San Antonio Breast Cancer Symposium. 2010:S1-4.

Study Period: 27 March 2008 (first subject enrolled) to 23 September 2011 (data cutoff date for final analysis)

Development Phase: 2

Introduction and Objectives: Ganitumab is a fully human monoclonal IgG1 antibody against human insulin-like growth factor receptor type 1 (IGF-1R) developed to provide inhibitory effects on tumor growth and invasion, likely in combination with standard cancer therapy, molecularly targeted therapy, or both. Ganitumab exerts its antitumor activity by blocking ligand binding (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor-2 [IGF-2]) and inducing receptor internalization and degradation without cross-reacting with the insulin receptor.

This randomized, double-blind, placebo-controlled, phase 2 study was designed with the primary objective to estimate the treatment effect, as measured by progression-free survival (PFS), of ganitumab in combination with endocrine therapy (exemestane or fulvestrant) compared with endocrine therapy (exemestane or fulvestrant) without ganitumab in postmenopausal women with hormone-receptor(HR)-positive, locally advanced, or metastatic breast cancer.

The secondary objectives were to investigate the effect of ganitumab compared with placebo when administered in combination with exemestane or fulvestrant on the safety and tolerability, patient-reported outcomes (PROs), pharmacokinetics of ganitumab, and additional efficacy measures including clinical benefit rate, objective response rate, duration of response, time to progression, time to response, time to treatment failure, and overall survival (OS).

[redacted].

The current report summarizes data for subjects through the data cutoff for the primary analysis and for the final analysis.

Methodology: This was a randomized, double-blind, placebo-controlled, phase 2 study that evaluated the efficacy and safety of the combination of endocrine therapy (exemestane or fulvestrant) with ganitumab (12 mg/kg once every 2 weeks [Q2W]) or placebo in postmenopausal women with confirmed HR-positive, locally advanced, or metastatic breast cancer who had disease progression during or within 12 months after completing prior adjuvant endocrine therapy or during the first prior endocrine therapy for metastatic disease.

Based on investigator discretion, subjects were prescribed an endocrine therapy of either exemestane or fulvestrant to be administered throughout the study. The study planned to randomize 150 subjects in a 2:1 ratio to ganitumab in combination with endocrine therapy (exemestane or fulvestrant) or placebo in combination with endocrine therapy (exemestane or fulvestrant). At least 45 of the 150 subjects randomized were required to be prescribed to each endocrine therapy (exemestane and fulvestrant). Randomization was stratified by prescribed endocrine therapy (exemestane or fulvestrant) and by extent of the subject's disease (soft tissue disease only, bone disease [with or without soft tissue and without visceral disease], or visceral disease [with or without other sites]).

Study treatment with ganitumab or placebo and endocrine therapy (exemestane or fulvestrant) continued until disease progression, unacceptable toxicity, consent withdrawal, investigator discretion, initiation of a new anticancer treatment, or death. Subjects randomized to placebo in combination with endocrine therapy could have the opportunity to continue receiving study treatment as open-label ganitumab in combination with the endocrine therapy originally prescribed ("rollover treatment") upon disease progression. This study was discontinued after an updated OS analysis (when approximately 50% of events had occurred) showed a worse survival outcome for subjects receiving ganitumab in combination with endocrine therapy (see Section 7.10.4 for details).

In order to safeguard the interest of the subjects and maintain the study integrity, an unblinded data review team (DRT) that was external to the study team involved in the daily conduct of the study, but internal to Amgen was formed to review safety data and efficacy analysis results.

Number of Subjects Planned: 150 subjects

Number of Subjects Enrolled: 156 subjects

Sex: 156 women (100%)

Age: mean (standard deviation [SD]) 62.3 (10.3) years (range: 36 to 88 years)

Ethnicity (Race): 147 (94%) white; 4 (3%) black; 3 (2%) Asian; 1 (1%) Hispanic or Latino; 1 (1%) other

Diagnosis and Main Criteria for Eligibility: The main inclusion criteria for subjects in this study included postmenopausal woman ≥ 18 years of age with histologically or cytologically confirmed carcinoma of the breast with locally advanced or metastatic disease not amenable to surgery or radiation with curative intent, HR (estrogen and/or progesterone receptor)-positive disease using institutional standards for analysis of the primary tumor tissue or tissue obtained thereafter (based on medical history review), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable or nonmeasurable disease (as defined by the modified Response Evaluation Criteria in Solid Tumors [RECIST] criteria), adequate renal and hepatic function, and adequate glycemic function for subjects with known diabetes (type 1 or 2). Subjects also had to be amenable to receive endocrine therapy as per investigator discretion and had to have had disease progression while receiving prior endocrine therapy for locally advanced or metastatic breast cancer or recurrence while receiving prior endocrine therapy as adjuvant treatment or within 12 months of treatment discontinuation. A complete list of inclusion/exclusion criteria is provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, and Manufacturing Batch Number: Ganitumab was provided in single-use vials containing 3 mL of a frozen 30-mg/mL sterile solution. Ganitumab or placebo was administered via intravenous (IV) infusion Q2W as defined in the protocol; Ganitumab was administered at a dose of 12 mg/kg. Lot numbers for ganitumab used in this study are provided in Appendix 18 (primary analysis) and Appendix 3 of Appendix 26 (post-primary analysis).

Duration of Treatment: Subjects received ganitumab or placebo in combination with endocrine therapy (exemestane or fulvestrant) until disease progression, unacceptable toxicity, consent withdrawal, investigator discretion, initiation of a new anticancer treatment, or death. Subjects randomized to placebo in combination with endocrine therapy could have the opportunity to continue receiving study treatment as rollover treatment upon disease progression. Estimated median length of individual subject treatment, not including rollover treatment, was 4 months in the placebo treatment group and was 6 months in the ganitumab treatment group.

Reference Therapy, Dose and Mode of Administration, and Manufacturing Batch Number: Placebo was provided by the sponsor in vials identical to ganitumab except containing only vehicle. The dilution method and mode of administration were identical to that of ganitumab. Lot numbers for placebo used in this study are provided in Appendix 18 (primary analysis) and Appendix 3 of Appendix 26 (post-primary analysis).

Based on investigator discretion, subjects were prescribed an endocrine therapy of either exemestane (25 mg tablets once a day [QD] by mouth [PO]) or fulvestrant (loading dose [500 mg intramuscular (IM) on day 1, then 250 mg IM on day 15] then 250 mg IM on day 29 and every 28 days thereafter) to be administered throughout the study.

Study Endpoints

Primary Endpoint: PFS, as measured by modified RECIST per local review

Secondary Endpoints:

- Clinical benefit (complete response, partial response, or stable disease for ≥ 24 weeks as measured by modified RECIST per local review), objective response rate (complete and partial response as measured by modified RECIST per local review), duration of response, time to progression, time to response, time to treatment failure, and OS
- Incidence of adverse events, abnormal laboratory values, and antiganitumab antibody formation
- Pharmacokinetics parameters of ganitumab
- Breast cancer related symptoms, health-related quality of life (HRQOL), and skin toxicity burden

[redacted].

Statistical Methods: The primary analysis was performed when 123 PFS events (planned for 120 events) were observed. A final analysis was performed when all subjects completed long-term follow-up, died, or completed the study early for other reasons (including early termination of the study leading to discontinuation of 4 subjects from blinded study treatment). For the final analyses, only selected summaries were provided. Descriptive statistics were provided for selected demographic, safety, efficacy, pharmacokinetics, antiganitumab antibodies,

PRO, and exploratory endpoints. Summary statistics included mean, median, SD, range, quartiles, 80% CI, and/or 95% confidence interval (CI) of expected values (eg, mean) of continuous and categorical variables.

PFS, time to progression, time to treatment failure, and OS were summarized using Kaplan-Meier estimates. The CIs for 25th percentile, median, and 75th percentile were calculated by the method described by Brookmeyer and Crowley (1982). A Cox model stratified by randomization factors was used to estimate the treatment hazard ratio (ganitumab / placebo) and an 80% CI for PFS, time to progression, time to treatment failure, and OS. The number and percent of subjects within each category of best overall objective response rate were summarized by treatment group. Time to response and duration of response were descriptively analyzed for subjects who responded. The clinical benefit rate and the maximum reduction in tumor size were also summarized.

Each subscale of the European Organization for the Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ C-30) and the 2 questions from Dermatology Life Quality Index (DLQI) were summarized by cycle. For the QLQ C-30 subscales and the 2 questions from DLQI, a time-adjusted area under the curve (AUC) was also calculated. The time-adjusted AUC was evaluated using an analysis of covariance where the baseline score and the stratification factors were included as the covariates to obtain treatment estimates for each subscale and to obtain estimates of the difference between the 2 treatment groups for each subscale. Responsiveness to change was evaluated by comparing changes in PRO scores to changes in clinical parameters (ECOG performance status and tumor progression).

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received at least 1 dose of ganitumab or placebo; subjects in this analysis set were analyzed according to the treatment received. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, seriousness, and relationship to treatment. The following events of interest were summarized separately: hyperglycemia, thrombocytopenia, drug-related hepatic disorders, rash, infusion reaction, neutropenia, venous thromboembolism, and sensorineural hearing loss. Clinical laboratory parameters and vital signs were summarized using descriptive statistics or shift tables. The incidence of subjects developing antiganitumab antibodies was calculated.

Pharmacokinetic measurements for ganitumab, exemestane and fulvestrant were scheduled for subjects who received the specified drugs. Serum ganitumab and plasma exemestane and fulvestrant concentrations were tabulated and the descriptive statistics were summarized for each sampling time point. The parameters included observed minimum concentration (C_{min}) collected prior to the next dose administration, observed maximum concentration (C_{max}) collected at the end-of-infusion for ganitumab, and any concentrations specified in the protocol for ganitumab and exemestane or fulvestrant. Comparisons of pharmacokinetic parameters of ganitumab, exemestane, and fulvestrant between treatments, cycles, and with monotherapy or historical data were performed.

For somatic mutations (K-ras, H-ras, N-ras, b-raf, phosphoinositide-3 kinase [PI3K], phosphatase and tensin homolog [PTEN], and p53), for each analyte, the relationship between mutation status and clinical benefit status was evaluated using a logistic regression model. The relationship between mutation status and PFS was evaluated using a Cox proportional hazard model. For PTEN expression by immunohistochemistry, the relationship between the percent of PTEN+ cells and clinical benefit status was evaluated using a logistic regression model. The relationship between the percent of cells that were PTEN+ and PFS was evaluated using a Cox proportional hazard model. In addition, the relationship between baseline and log ratio of first postdose to baseline circulating biomarkers (free IGF-1, total IGF-1, IGF-2, and IGFBP1- to -3) and clinical benefit status was evaluated using a logistic regression model. The relationship between baseline and log ratio of first postdose to baseline circulating biomarkers and PFS was evaluated using a Cox proportional hazard model.

Summary of Results:

Subject Disposition: A total of 156 subjects were randomized in the study, with 106 subjects randomized to the ganitumab treatment group and 50 subjects randomized to the placebo treatment group. As of the primary analysis data cutoff date, 109 (70%) subjects (71 [67%] subjects in the ganitumab treatment group and 38 [76%] subjects in the placebo treatment group) were ongoing in the study. Thirty-five (33%) subjects in the ganitumab treatment group and 12 (24%) subjects in the placebo treatment group had discontinued the study (ie, discontinued treatment and additional protocol assessments). Death was the most common reason for discontinuation of study (ganitumab: 30%, placebo: 20%).

One subject (randomized to ganitumab) never received a dose of investigational product and was excluded from the safety analysis set. Another subject who was randomized to placebo mistakenly received 1 dose of ganitumab at cycle 3 day 1 and was therefore treated as an ganitumab subject for the safety analysis set. Thirty-four subjects in the ganitumab treatment group and 16 subjects in the placebo group received exemestane as endocrine therapy. Seventy-two subjects in the ganitumab treatment group and 33 subjects in the placebo group received fulvestrant as endocrine therapy. Nine subjects received at least 1 dose of open-label ganitumab after having progressed on the placebo treatment group (ie, entered the rollover arm of the study).

As of the primary analysis data cutoff date, 21 (20%) subjects in the ganitumab treatment group and 8 (16%) in the placebo treatment group remained on treatment (ie, investigational product and/or endocrine therapy). Eighty-four percent of subjects in the ganitumab treatment group and 84% of subjects in the placebo treatment group had ended treatment with investigational product, and 83% and 78%, respectively, had also ended treatment with endocrine therapy. Disease progression was the most common reason for discontinuation of investigational product (ganitumab: 64%, placebo: 60%) and was also the most common reason for discontinuation of endocrine therapy (62% and 56%, respectively).

As of the final analysis data cutoff date, all subjects discontinued the study, most commonly due to death (ganitumab: 60%, placebo: 38%). Of the subjects who received study treatment, all subjects discontinued all study treatments (including 4 subjects who discontinued blinded study treatment due to early discontinuation of the study), most commonly due to disease progression for investigational product (ganitumab: 76%, placebo: 72%) and endocrine therapy (74% and 64%, respectively).

Efficacy Results: At the time of the primary analysis, the estimated hazard ratio (stratified by endocrine therapy and extent of disease) (80% CI) for PFS for the ganitumab arm relative to the placebo arm was 1.17 (0.91, 1.50) (p = 0.435, stratified log rank test). The median PFS time was 3.9 months in the ganitumab treatment group and 5.7 months in the placebo treatment group. At the time of the final analysis, the median PFS times did not change from the primary analysis results. The estimated hazard ratio (stratified by the 2 stratification factors) (80% CI) for PFS for the ganitumab arm relative to the placebo arm was 1.21 (0.95, 1.55) (p = 0.316, stratified log rank test).

At the time of the primary analysis, the objective response rate (80% CI) was 8% (4, 14) in the ganitumab treatment group and 13% (6, 23) in the placebo treatment group. The clinical benefit rate (80% CI) was 35% (27, 44) and 31% (20, 44), respectively. Of the subjects who had a confirmed response, the median duration of response was 30.3 and 33.5 weeks, respectively, and the median time to response was 16.0 and 15.7 weeks, respectively. Among all subjects randomized, the median time to treatment failure was 3.6 and 5.0 months, respectively and median time to progression was 3.9 and 5.7 months, respectively.

At the time of the primary analysis, the OS data are immature and inconclusive with 73% of subjects censored at the time of the primary analysis. The OS hazard ratio (stratified by the 2 stratification factors) was 1.48 (80% CI: 0.92, 2.37) in favor of the placebo group. The median

survival was 22.2 months in the ganitumab treatment group and was not estimable in the placebo treatment group due to a low event rate. At the time of the final analysis, which was based on more mature survival data (with 47% of subjects censored) compared with the primary analysis, the OS hazard ratio was 1.78 (80% CI: 1.27, 2.50), in favor of the placebo treatment group (p = 0.025, stratified log rank test). The median survival was 23.3 months in the ganitumab treatment group and was not estimable in the placebo treatment group.

Safety Results: The summaries of treatment-emergent adverse events in the primary analysis and final analysis were comparable; few changes were noted between the data cutoff dates for the primary and final analyses, and no new safety signals were noted. Safety results are summarized below for the primary analysis.

A total of 105 (99%) subjects in the ganitumab treatment group and 47 (96%) subjects in the placebo treatment group had at least 1 treatment-emergent adverse event. The most common adverse events (≥ 20% of subjects), by preferred term, in either treatment group were nausea (ganitumab: 40%, placebo: 39%), fatigue (40%, 24%), diarrhea (31%, 29%), headache (24%, 27%), asthenia (23%, 37%), arthralgia (22%, 22%), vomiting (22%, 20%), back pain (19%, 24%), and hot flush (11%, 24%).

Ninety (85%) subjects in the ganitumab treatment group and 33 (67%) subjects in the placebo treatment group had at least 1 adverse event that was considered by the investigator to be related to investigational product (ganitumab or placebo). The most common adverse events considered by the investigator to be related to investigational product (≥ 20% of subjects) by preferred term in either treatment group were fatigue (ganitumab: 28%, placebo: 18%), asthenia (18%, 24%), and nausea (25%, 18%).

Grade ≥ 3 treatment-emergent adverse events occurred in 45 (42%) subjects in the ganitumab treatment group and 12 (24%) in the placebo treatment group. The most common grade ≥ 3 events (≥ 2 subjects) by preferred term in either treatment group were neutropenia (ganitumab: 6%, placebo: 2%), hyperglycemia (6%, 0%), thrombocytopenia and aspartate aminotransferase (AST) increased (4%, 0%, each), general physical health deterioration (3%, 2%), asthenia (4%, 2%), anemia, dyspnea, and pulmonary embolism (2%, 2%, each), and fatigue, ALT increased, gamma-glutamyltransferase increased, weight decreased, nausea, vomiting, hypokalemia, arthralgia, hypertension, and breast cancer (2%, 0% each).

Serious adverse events were reported for 27 (25%) subjects in the ganitumab treatment group and 9 (18%) subjects in the placebo treatment group. As reported on the adverse event case report form, 4 (4%) subjects in the ganitumab treatment group and 1 (2%) subject in the placebo treatment group had fatal adverse events while on study. Fatal adverse events were due to progression of disease, with the exception of 1 fatal event of pulmonary embolism in the ganitumab treatment group (which occurred in the post-surgical setting following pathologic femoral fracture). In addition, 2 subjects in the ganitumab treatment group and 1 subject in the placebo treatment group died for a reason noted as “other” per the death case report form and further information noted as sepsis, perforation peritonitis, and ischemic bowel disease with transmural necrosis, respectively. These events occurred > 30 days after the last dose of investigational product.

Eight (8%) subjects in the ganitumab treatment group and 6 (12%) subjects in the placebo treatment group had adverse events leading to permanent discontinuation of treatment or removal from the study.

In the ganitumab treatment group, 103 subjects had a postdose antibody result and 1 subject (1%) developed antiganitumab binding antibodies (negative for neutralizing antibodies); no adverse events were reported that potentially may have been related to the presence of antibodies for this case. In the placebo treatment group, 48 subjects had a postdose antibody result and no subject developed antiganitumab binding antibodies.

Pharmacokinetics Results: Pharmacokinetics results are summarized below for the primary analysis. Ganitumab, fulvestrant, and exemestane pharmacokinetic data were available from 99, 102, and 39 subjects, respectively.

Ganitumab: Following 12 mg/kg Q2W IV infusion, the mean (SD) C_{max} and C_{min} in the first cycle were 226 (50.7) and 30.4 (12.6) μg/mL, respectively, and the exposures increased by 1.2 and 1.8 fold, respectively, in cycle 3. There was no apparent difference in ganitumab exposure when it was co-administered with fulvestrant or with exemestane. Additional analysis was performed to compare the exposures with historical data of ganitumab monotherapy with the same regimen in subjects with advanced solid tumors. The exposure levels were found to be comparable.

Fulvestrant: Following 500 mg Q2W IM injection, the mean (SD) trough concentration in the end of the first cycle was 9.82 (4.12) ng/mL and 8.70 (4.06) ng/mL in the ganitumab and placebo treatment groups, respectively. Little accumulation was observed in cycle 2. The exposure levels were comparable with literature data.

Exemestane: Following 25 mg QD PO administration, blood samples were collected at predose (C_{min}) and 2 hours postdose (C_{2hr}). In the ganitumab treatment group, the mean (SD) C_{2hr} was 9.01 (7.98) ng/mL in the first cycle and C_{min} was 6.48 (4.59) ng/mL prior to the next dose. Less than 2-fold accumulation was observed over multiple dosing. Comparable exposures of exemestane were observed in the placebo and ganitumab treated groups, which were also similar to the literature values.

Patient-reported Outcomes Results: PRO results are summarized below for the primary analysis. Overall, there was little evidence of a treatment effect on PROs. Only 1 of the 15 scores derived from the EORTC QLQ C-30 showed a significant difference, which was for the single item constipation symptom measure. The time-adjusted AUC for the global health status/quality of life scale was approximately equal for the 2 treatment groups. DLQI scores (from 2 questions) were generally similar between treatment groups throughout the study.

Biomarker Results: Biomarker results are summarized below for the primary analysis. No modeling analysis was done to evaluate relationship between efficacy (clinical benefit rate and PFS) and the mutations of K-ras, H-ras, N-ras, b-raf, or PTEN because no mutation was observed in the data. No significant relationship between efficacy (clinical benefit rate and PFS) and mutation status of PIK3CA was observed. Although an apparent significant relationship was observed between TP53 mutation status and PFS, the sample size and mutation rate are too small to be conclusive. No significant relationship between clinical benefit rate and proportional PTEN expression was observed. No significant relationship between PFS and proportional PTEN expression was observed, with the exception for PTEN expression measurement metric of the percent of cells with nuclear staining score greater than 0. However, this relationship was not significantly different between ganitumab and placebo for this metric, suggesting that this metric was associated with unfavorable prognosis and that the effect was not altered by treatment. A statistical significant relationship between baseline insulin-like growth factor binding protein-2 (IGFBP-2) and efficacy (clinical benefit rate and PFS) was observed; however, the relationship was not significantly different between ganitumab and placebo, indicating a prognostic effect of baseline IGFBP-2 and clinical efficacy. No relationship between efficacy (clinical benefit rate and PFS) and any of other baseline circulating markers (free IGF-1, total IGF-1, IGF-2, IGFBP-1, and IGFBP-3) was observed that was significantly different between ganitumab and placebo. Analysis on relationship between change in circulating biomarker (ie, log ratio of first post dose to baseline) and PFS or clinical benefit rate was carried out and no association was found.

Conclusions: In conclusion, no evidence of improvement was observed in this study with the addition of ganitumab to second-line hormonal therapy in women with HR-positive locally advanced or metastatic breast cancer. A trend in favor of the placebo treatment group was observed for PFS. Overall survival was worse among the group of subjects who received ganitumab in combination with endocrine therapy as compared with those who received placebo.

At the time of the primary analysis, the hazard ratio point estimate indicates similar PFS between the ganitumab and placebo treatment groups (HR = 1.17 [80% CI: 0.91, 1.50], p = 0.435); based on the 80% CI, this result is interpreted as a PFS effect lies between a 9% improvement and a 50% worsening. At the time of the final analysis, the hazard ratio estimate for PFS indicates a trend in favor of placebo (HR = 1.21 [80% CI: 0.95, 1.55], p = 0.316); based on the 80% CI, this result is interpreted as a PFS effect lies between a 5% improvement and a 55% worsening.

Secondary efficacy endpoints of objective response rate, clinical benefit rate, duration of response, time to response, and time to progression were similar between treatment groups.

With 73% of subjects censored at the time of the primary analysis, the OS data were immature and inconclusive. At the time of the final analysis, which was based on more mature survival data (with 47% of subjects censored) compared with the primary analysis, the hazard ratio point estimate for OS indicates worse OS in the ganitumab treatment group (HR = 1.78 [80% CI: 1.27, 2.50], p = 0.025); based on the 80% CI, this result is consistent with a 27% to 150% worsening in OS in the ganitumab treatment group.

The safety profile of ganitumab in this study was consistent with what has been observed to date with ganitumab; no new risks associated with ganitumab treatment were identified. No pattern in the types of adverse events and serious adverse events was apparent to explain the worse survival in the ganitumab treatment arm.

Pharmacokinetic properties of ganitumab in combination with fulvestrant or exemestane were similar and were also comparable to historical data with ganitumab monotherapy. The fulvestrant and exemestane concentrations were similar with and without co-administration of ganitumab. No predictive marker was identified in this patient population for PFS and clinical benefit rate.