Clinical Trial Results

Phase I Study of the Prolactin Receptor Antagonist LFA102 in Metastatic Breast and Castration-Resistant Prostate Cancer

NEERAJ AGARWAL, a JEAN-PASCAL MACHIELS, b CRISTINA SUÁREZ, c NANCY LEWIS, d MICHAELA HIGGINS, e KARI WISINSKI, f AHMAD AWADA, g MICHELA MAUR, h MARK STEIN, i ANDY HWANG, j REBECCA MOSHER, ERNESTO WASSERMAN, k GANG WU, l HFEI ZHANG, m RENATA ZIEBA, n MOHAMED ELMELIEGY

a Huntsman Cancer Institute, Division of Medical Oncology, Department of Medicine, University of Utah, Salt Lake City, Utah, USA; b Roi Albert II Institute, Medical Oncology Service, University Clinic Saint Luc and Institute of Experimental and Clinical Research (Pôle Molecular Imaging, Radiotherapy & Oncology), Catholic University of Louvain, Brussels, Belgium; c Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology, Barcelona, Spain; d Thomas Jefferson University, Philadelphia, Pennsylvania, USA; e Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA; f University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA; g Jules Bordet Institute, Brussels, Belgium; h Oncology Unit, Department of Oncology, Hematology and Respiratory Disease, University Hospital Policlinico of Modena, Modena, Italy; i Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA; j Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA

TRIAL INFORMATION

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• Principal Investigator: Neeraj Agarwal
• IRB Approved: Yes

LESSONS LEARNED

• Despite evidence for a role for prolactin signaling in breast and prostate tumorigenesis, a prolactin receptor-binding monoclonal antibody has not produced clinical efficacy.
• Increased serum prolactin levels may be a biomarker for prolactin receptor inhibition.
• Results from the pharmacokinetic and pharmacodynamics (PD) studies suggest that inappropriately long dosing intervals and insufficient exposure to LFA102 may have resulted in lack of antitumor efficacy.
• Based on preclinical data, combination therapy of LFA102 with those novel agents targeting hormonal pathways in metastatic castration-resistant prostate cancer and metastatic breast cancer is promising.
• Given the PD evidence of prolactin receptor blockade by LFA102, this drug has the potential to be used in conditions such as hyperprolactinemia that are associated with high prolactin levels.

ABSTRACT

Background. Prolactin receptor (PRLR) signaling is implicated in breast and prostate cancer. LFA102, a humanized monoclonal antibody (mAb) that binds to and inhibits the PRLR, has exhibited promising preclinical antitumor activity.

Methods. Patients with PRLR-positive metastatic breast cancer (MBC) or metastatic castration-resistant prostate cancer (mCRPC) received doses of LFA102 at 3–60 mg/kg intravenously once every 4 weeks. Objectives were to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) to investigate the safety/tolerability of LFA102 and to assess pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity.

Results. A total of 73 patients were enrolled at 5 dose levels. The MTD was not reached because of lack of dose-limiting toxicities. The RDE was established at 60 mg/kg based on PK and PD analysis and safety data. The most common all-cause adverse events (AEs) were fatigue (44%) and nausea (33%) regardless of relationship. Grade 3/4 AEs reported to be related to LFA102 occurred in 4% of patients. LFA102 exposure increased approximately dose proportionally across the doses tested. Serum prolactin levels increased in response to LFA102 administration, suggesting its potential as a biomarker for PRLR inhibition. No antitumor activity was detected.

Conclusion. Treatment with LFA102 was safe and well tolerated, but did not show antitumor activity as monotherapy at the doses tested. The Oncologist 2016; 21:535–536i

Correspondence: Neeraj Agarwal, M.D., Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope, Suite 2123, Salt Lake City, Utah 84112, USA. Telephone: 801-585-0255; E-Mail: neeraj.agarwal@hci.utah.edu. Received December 9, 2015; accepted for publication January 11, 2016; published Online First on April 18, 2016. ©AlphaMed Press; the data published online to support this summary is the property of the authors. http://dx.doi.org/10.1634/theoncologist.2015-0502

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DISCUSSION

Prolactin, a pituitary-derived polypeptide hormone, is implicated in breast and prostate tumorigenesis. Expression of the PRLR has been confirmed in breast and prostate cancers. This phase I study evaluated LFA102 in 73 patients with PRLR-positive MBC or mCRPC, treated at doses of 3–60 mg/kg. During dose escalation, LFA102 demonstrated favorable safety and tolerability at all doses. No dose-limiting toxicities (DLTs) occurred; therefore, the MTD was not reached, although the RDE was established at 60 mg/kg based on safety, PK, and PD data supported by Bayesian logistic regression modeling. Dose proportionality analysis showed that serum LFA102 maximum concentration observed (Cmax) and AUClast increased in a relatively proportional manner with increasing LFA102 doses.

Abbreviations: AUClast, area under the last measurable concentration; Cmax, maximum concentration observed.

TRIAL INFORMATION

| Disease                  | Breast cancer                      |
|--------------------------|------------------------------------|
| Disease                  | Prostate cancer                     |
| Stage of disease / treatment | Metastatic / Advanced             |
| Prior Therapy            | 1 prior regimen                    |
| Type of study - 1        | Phase I                             |
| Type of study - 2        | Adaptive Design                    |
| Primary Endpoint         | Recommended Phase II Dose          |
| Primary Endpoint         | Maximum Tolerated Dose             |

Figure 1. AUClast and Cmax increase with LFA102 dose in a relatively proportional manner. AUClast (A) and Cmax (B) results for individual patients in cycle 1. For each dose, parameter values (open symbols), least-square mean (black triangles), and 90% least-square means confidence interval (vertical bars) are shown. Serum LFA102 concentrations were measured up to day 28 of cycle 1 via dense sampling followed by trough concentration measurement in subsequent cycles. Concentration-time profiles show biexponential disposition typical for monoclonal antibodies. Cmax and AUClast increased in a relatively proportional manner with increasing LFA102 doses.

Figure 2. Serum prolactin levels rise with increasing doses of LFA102. Linear views of individual serum prolactin concentration-time profiles grouped by LFA102 dose group are shown. Individual patient serum prolactin increased after LFA102 administration. In patients, our study used serum prolactin levels as a surrogate marker for PRLR inhibition. A sixfold change in serum prolactin levels from baseline was observed in patients treated with LFA102 60 mg/kg, indicative of inhibition of PRLR and ruling out poor target binding as causing lack of efficacy (Fig. 2). Other potential explanations for the lack of LFA102 efficacy include that prolactin may not be an oncogenic driver in breast and prostate cancer in humans, unforeseen compensatory modulation of downstream signaling pathways in response to PRLR inhibition, or upregulation of other tumorigenic signaling pathways that compensate for PRLR inhibition. Nevertheless, preclinical data show that letrozole potentiates the efficacy of LFA102 when administered in combination in a rat mammary cancer model. Therefore, although LFA102 monotherapy may not show antitumor activity, it may have potential for treating prolactin-dependent tumors in combination with other recently approved, novel hormonal pathway targeting agents in MBC and mCRPC. Furthermore, given the PD evidence of prolactin receptor blockade by LFA102, this drug has the potential to be used in conditions such as hyperprolactinemia that are associated with high prolactin levels.
Primary Endpoint: Safety
Secondary Endpoint: Tolerability
Secondary Endpoint: Pharmacokinetics
Secondary Endpoint: Pharmacodynamic
Secondary Endpoint: Efficacy
Additional Details of Endpoints or Study Design: Exploratory: Effects of LFA102 on serum prolactin levels.
Investigator’s Analysis: Evidence of target inhibition but no or minimal antitumor activity

**Drug Information**

Drug 1
Generic/Working name: LFA102
Drug type: Antibody
Dose: mg/kg
Route: IV
Schedule of Administration: 10 mg/kg once every 4 weeks.

**Dose Escalation Table**

| Dose Level | Dose of Drug: LFA102 | Number Enrolled | Number Evaluable for Toxicity |
|------------|-----------------------|-----------------|-----------------------------|
| 1          | 3 mg/kg               | 3               | 3                           |
| 2          | 10 mg/kg              | 3               | 3                           |
| 3          | 20 mg/kg              | 7               | 7                           |
| 4          | 40 mg/kg              | 8               | 8                           |
| 5          | 60 mg/kg              | 52              | 52                          |

**Patient Characteristics**

Number of patients, male: 39
Number of patients, female: 34
Stage: Locally advanced or metastatic disease.
Age: Median (range): 66.0 years (41.0–89.0 years)
Number of prior systemic therapies: Median (range): Not Collected
Performance Status: ECOG
0 — 30
1 — 38
2 — 5
3 — 0
unknown —

Cancer Types or Histologic Subtypes: Breast and prostate, 73

**Primary Assessment Method**

Control Arm: Breast And Prostate
Number of patients screened: 73
Number of patients enrolled: 73
Number of patients evaluable for toxicity: 73
Number of patients evaluated for efficacy: 73
Response assessment CR: \( n = 0 \) (0%)
Response assessment PR: \( n = 0 \) (0%)
Response assessment SD: \( n = 13 \) (18%)
Response assessment PD: \( n = 41 \) (56%)
Response assessment OTHER: \( n = 19 \) (26%)

Control Arm: Total Patient Population
Number of patients screened: 73
Number of patients enrolled: 73
Number of patients evaluable for toxicity: 73
Number of patients evaluated for efficacy
73

Response assessment CR
n = 0 (0%)

Response assessment PR
n = 0 (0%)

Response assessment SD
n = 13 (18%)

Response assessment PD
n = 41 (56%)

Response assessment OTHER
n = 19 (26%)

**Adverse Events**

Adverse Events At All Dose Levels, Cycle 1

| Name                                      | *NC/NA | 1     | 2     | 3     | 4     | 5     | All Grades |
|-------------------------------------------|--------|-------|-------|-------|-------|-------|------------|
| Nausea                                    | 57%    | 29%   | 11%   | 3%    | 0%    | 0%    | 43%        |
| Anemia                                    | 72%    | 14%   | 11%   | 3%    | 0%    | 0%    | 28%        |
| Anorexia                                  | 73%    | 15%   | 7%    | 5%    | 0%    | 0%    | 27%        |
| Pain in extremity                         | 74%    | 14%   | 11%   | 1%    | 0%    | 0%    | 26%        |
| Constipation                               | 79%    | 15%   | 5%    | 1%    | 0%    | 0%    | 21%        |
| Aspartate aminotransferase increased      | 78%    | 14%   | 3%    | 5%    | 0%    | 0%    | 22%        |
| Vomiting                                  | 79%    | 14%   | 7%    | 0%    | 0%    | 0%    | 21%        |
| Fatigue                                   | 82%    | 4%    | 7%    | 7%    | 0%    | 0%    | 18%        |
| Hypophosphatemia                          | 89%    | 1%    | 4%    | 5%    | 1%    | 0%    | 11%        |
| General disorders and administration site conditions - Asthenia | 82% | 4% | 7% | 7% | 0% | 0% | 18% |

Adverse Events Legend
*No Change from Baseline/No Adverse Event

**Serious Adverse Events**

| Name             | Grade | Attribution |
|------------------|-------|-------------|
| Dyspnea          | NA    | Unrelated   |

Serious Adverse Events Legend
Serious adverse events occurring in three or more patients are listed.
Abbreviation: NA, not available.

**Dose Limiting Toxicities**

| Dose Level | Dose of Drug: LFA102 | Number Enrolled | Number Evaluable for Toxicity | Number with a Dose Limiting Toxicity | Dose Limiting Toxicity Information |
|------------|----------------------|-----------------|-------------------------------|--------------------------------------|-----------------------------------|
| 1          | 3 mg/kg              | 3               | 3                             | 0                                     |                                  |
| 2          | 10 mg/kg             | 3               | 3                             | 0                                     |                                  |
| 3          | 20 mg/kg             | 7               | 7                             | 0                                     |                                  |
| 4          | 40 mg/kg             | 8               | 8                             | 0                                     |                                  |
| 5          | 60 mg/kg             | 52              | 52                            | 0                                     |                                  |

**Pharmacokinetics/Pharmacodynamics**

| Dose Level | Dose of Drug: LFA102 | Number Enrolled | Cmax (µg/L) mean ± SD | Tmax(h) min–max | AUC 0-12 (h*12 µg/L) mean ± SD | T ½(h) mean ± SD | CI F (L/h) mean ± SD | AUC (0–tlast) (hour × µg/mL) mean (SD) |
|------------|----------------------|-----------------|-----------------------|-----------------|-------------------------------|-----------------|---------------------|----------------------------------------|
| 1          | 3 mg/kg              | 3               | 85.9 (35.8)           | 7.77 (2.0–8.03) | —                             | 5.6 d (0.24)    | —                   | 11,636.1 (3,320.4)                      |
| 2          | 10 mg/kg             | 3               | 303.0 (58.5)          | 4.00 (2.4–4.0)  | —                             | 7.13 d (4.25)   | —                   | 44,450.0 (6,925.7)                      |
| 3          | 20 mg/kg             | 7               | 545.4 (115.9)         | 3.92 (1.02–7.75) | —                             | 8.72 d (2.54)   | —                   | 84,349.1 (38,746.8)                     |
| 4          | 40 mg/kg             | 8               | 1,092.4 (235.2)       | 2.36 (2.0–23.9) | —                             | 8.89 d (2.71)   | —                   | 145,779.0 (37,900.8)                    |
| 5          | 60 mg/kg             | 52              | 1,495.2 (589.3)       | 2.07 (1.87–4.00) | —                             | 8.75 d (0.99)   | —                   | 230,990.6 (102,673.3)                   |

**Assessment, Analysis, and Discussion**

Completion
Study completed

Investigator’s Assessment
Evidence of target inhibition but no or minimal antitumor activity
Prolactin is a pituitary-derived polypeptide hormone implicated in breast and prostate tumorigenesis [1–3]. Prolactin is also expressed in several extrapituitary sites, in addition to breast and prostate tumors themselves [1, 4–7]. Expression of PRLR has been confirmed in various cancers, including breast and prostate [8–13]. Data suggest that increased serum prolactin levels may increase breast cancer risk and correlate with worse prognosis [14–16]. Overexpression of prolactin in murine mammary glands leads to tumor formation, and transplanted PRLR-negative tumors exhibit delays in tumor expansion compared with PRLR-positive tumors in mice [17, 18]. Although prolactin is expressed in normal human prostate, high expression in prostate tumors is associated with high-grade prostate cancer and worse prognosis [4, 19]. Overexpression of prolactin in mouse prostate causes hyperplasia and tumorigenesis [20, 21]. Therefore, blocking prolactin signal transduction is an attractive target in breast and prostate cancers.

Attempts made to inhibit PRLR signaling in vivo have been unsuccessful [22–27]. LFA102 is a humanized mAb that binds to the extracellular domain of PRLR. LFA102 inhibits PRLR signal transduction and cell proliferation in human breast cancer cells and causes tumor regression in animal xenograft models. Rats treated with LFA102 showed increased serum prolactin levels, suggesting this may be a potential biomarker for PRLR inhibition [28]. These data suggest that LFA102 has the potential to be an effective therapeutic agent in patients with breast or prostate cancer.

This phase I study evaluated LFA102 in patients with PRLR-positive MBC or mCRPC. Between September 2011 and March 2014, 73 patients were treated with LFA102 at doses of 3–60 mg/kg. During dose escalation, no DLTs occurred and the MTD was not reached. The RDE was established at 60 mg/kg, the highest tested dose level. The most common AEs, regardless of study drug relationship, were fatigue (44%), nausea (33%), constipation, decreased appetite, and vomiting (21% each). Of the 73 patients treated, 3 patients (4%) had grade 3 or 4 AEs suspected to be related to the study drug: decreased blood phosphorus, increased serum lipase, and decreased blood lymphocyte count, each in 1 patient (1%).

The serum LFA102 concentration-time profiles showed biexponential disposition typical for mAbs. $C_{\text{max}}$ and $AUC_{\text{last}}$ increased in a relatively proportional manner with increasing LFA102 doses (Fig. 1). The geometric mean apparent volume of distribution at steady state ($Vss$) and clearance across the treatment groups were similar, indicating linear PK. The geometric mean of $Vss$ for doses of 3–60 mg/kg ranged from 4 to 6 L. The geometric mean half-life ranged from 6 to 9 days. At the RDE of 60 mg/kg, the mean (± SD) $C_{\text{max}}$ was $1,495 \pm 589$ $\mu$g/mL (coefficient of variation [CV%]: 39) and mean (± SD) $AUC_{\text{last}}$ was $230,791 \pm 102,673$ hour $\times \mu$g/mL (CV% = 45), indicating moderate interindividual variability. No antidrug-antibody-positive samples were detected.

An exploratory objective of the study was to determine the effect of LFA102 treatment on serum prolactin levels in patients. The fold change from baseline increased in a dose-dependent manner, reached a maximum between days 8 and 15, and declined after day 15. The maximum fold-change in serum prolactin levels increased with doses up to 20 mg/kg and reached a plateau between 40 and 60 mg/kg. The temporal delay between PK and PD response is suspected to reflect the time needed for LFA102 to distribute to peripheral tissues, inhibit peripheral PRLR, and, consequently, lead to increased serum prolactin as a compensatory feedback mechanism.

The primary objective of this study was to determine the MTD and/or RDE of LFA102 in patients with MBC or mCRPC. An RDE of 60 mg/kg was established based on safety, PK, and PD, supported by the Bayesian logistic regression model. LFA102 demonstrated a favorable safety profile and tolerability at all doses tested. Dose proportionality analysis showed that serum LFA102 $C_{\text{max}}$ and $AUC_{\text{last}}$ were approximately linearly dose-dependent. LFA102 $Vss$ was close to the volume of plasma, suggesting limited peripheral distribution typical of mAbs. At 60 mg/kg, the LFA102 half-life was 9 days, which, although within the reported range of mAbs, is slightly lower than the typical immunoglobulin G (IgG) with a half-life of approximately 25 days [29]. A possible explanation for this might be a lower affinity for the neonatal Fc receptor for IgG, which protects IgG from proteolytic degradation, leading to faster clearance.

No objective responses were observed in patients with MBC during this study. In patients with mCRPC, there were no PSA responses. Thirty-eight of 73 patients (52%) experienced stable disease as their best response to LFA102 treatment. The majority of patients (67 of 73 patients; 92%) discontinued the study because of disease progression. One explanation for the lack of antitumor activity is the possibility of insufficient exposure. After a single dose of LFA102 10 mg/kg by i.v., serum LFA102 $C_{\text{max}}$ values were comparable between rodent and human subjects (268 $\mu$g/mL and 303 $\mu$g/mL, respectively; data not shown). Administration of a single dose of LFA102 10 mg/kg showed antitumor activity in a prolactin-dependent mouse tumor xenograft model (Nb2-11-luc) [28]. Consequently, the 60 mg/kg LFA102 dose in patients, which resulted in a mean $C_{\text{max}}$ of $1,495 \pm 589$ $\mu$g/mL and a mean steady-state trough concentration of 106 ± 34 $\mu$g/mL, would be anticipated to provide sufficient LFA102 exposure to achieve efficacy.

In vitro data showed a high binding affinity of LFA102 to PRLR [28]. Assessing LFA102 binding to PRLR directly within tumors is impractical in patients; therefore, serum prolactin levels were used as a surrogate marker for PRLR inhibition. A sixfold change in serum prolactin levels from baseline was observed in patients treated with LFA102 60 mg/kg, indicative of inhibition of PRLR. The compensatory increase in serum prolactin indicates that LFA102 binds to PRLR in patients, ruling out poor target binding as causative of lack of efficacy. However, the source of serum prolactin increase could either be the tumor or the pituitary gland. No correlation between tumor PRLR expression and serum prolactin response was observed. Therefore, the observed increase in serum prolactin is more likely to be a pituitary-driven feedback to LFA102 as a result of peripheral, nontumoral PRLR inhibition rather than a tumor-specific process. Furthermore, the increase in serum prolactin was transient; it was maintained up to 15 days following LFA102 administration (supplemental online Fig. 3). Based on this observation, more frequent LFA102 dosing (e.g., every 2 weeks) could have resulted in sustained PRLR inhibition and perhaps a better efficacy profile.

Another potential explanation for the lack of LFA102 efficacy is that prolactin may not be an oncogenic driver in breast and prostate cancer in humans. Prolactin activity as an oncogenic driver in human tumors has been difficult to assess.
directly in preclinical models of human breast and prostate cancers [28]. Mouse prolactin does not activate human PRLR; therefore, human breast or prostate cancer cells or primary tumors cannot be used for xenograph models in mice to assess the requirement for PRLR signaling in driving oncogenesis [30]. Other explanations for the lack of LFA102 efficacy include unforeseen compensatory modulation of downstream signaling pathways in response to PRLR inhibition, or upregulation of other compensatory tumorigenic signaling pathways.

Finally, letrozole potentiates the efficacy of LFA102 when administered in combination in a rat mammary cancer model [28]. These preclinical results raise the possibility that although administered in combination in a rat mammary cancer model other compensatory tumorigenic signaling pathways.

unforeseen compensatory modulation of downstream signal– the requirement for PRLR signaling in driving oncogenesis [30].

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**FIGURES AND TABLES**

Supplemental Figure 1. **(A):** Linear view. **(B):** Semilogarithmic view.

Supplemental Figure 2. Individual LFA102 concentration-time profiles by treatment group: semi-logarithmic view (cycle 1).
Supplemental Figure 3. Geometric mean for fold change from baseline for serum prolactin versus time profiles by treatment group (cycle 1).

Supplemental Figure 4. Correlation of maximum fold change from baseline serum prolactin with dose.

Supplemental Figure 5. Correlation of serum prolactin exposure with baseline prolactin receptor expression, 60 mg/kg dose group. 

$R^2 = .003; p = .7$.

Abbreviations: AUEC, area under the effect curve; PRLR, prolactin receptor.
Table 1. Patients' characteristics

| Characteristics                        | All patients |
|----------------------------------------|--------------|
|                                        | LFA102 dose (mg/kg) |
|                                        | 3 10 20 40 60 All |
| Patients, no.                          | 3 3 7 8 52 73   |
| Age (years), mean (range)              | 77 (71–80) 70 (56–78) 57 (45–76) 69 (52–85) 65 (41–89) 65 (41–89) |
| Sex, no. (%)                           |              |
| Female                                 | 0 2 (67) 4 (57) 2 (25) 26 (50) 34 (47) |
| Male                                   | 3 (100) 1 (33) 3 (43) 6 (75) 26 (50) 39 (53) |
| Race, no. (%)                          |              |
| White                                  | 3 (100) 3 (100) 7 (100) 7 (88) 48 (92) 68 (93) |
| Black                                  | 0 0 0 0 4 (8) 4 (6) |
| Other                                  | 0 0 0 1 (13) 0 1 (1) |
| Baseline ECOG performance status, no. (%) |              |
| 0                                      | 1 (33) 1 (33) 3 (43) 4 (50) 21 (40) 30 (41) |
| 1                                      | 1 (33) 2 (67) 2 (29) 4 (50) 29 (56) 38 (52) |
| 2                                      | 1 (33) 0 2 (29) 0 2 (4) 5 (7) |
| Primary site of cancer, no. (%)        |              |
| Prostate                               | 3 (100) 1 (33) 3 (43) 6 (75) 26 (50) 39 (53) |
| Breast                                 | 0 2 (67) 4 (57) 2 (25) 26 (50) 34 (47) |
| Prostate cancer (primary site)         |              |
| Patients, no.                          | 3 1 3 6 26 39 |
| Gleason score at initial diagnosis (prostate), no.; mean (range) | 3; 8 (7–9) 1; 7 (—) 3; 7 (3–9) 6; 8 (6–10) 25; 8 (3–10) 38; 8 (3–10) |
| PSA level at baseline (prostate), ng/mL |              |
| No.; mean (±SD)                        | 3; 147 (60) 1; 392 (392) 3; 48 (60) 6; 138 (161) 26; 204 (356) 39; 182 (301) |
| Median (range)                         | 160 (82–199) 392 (—) 28 (1–115) 52 (9–372) 47 (1–1,676) 49 (1–1,676) |
| Breast cancer (primary site)           |              |
| Patients, no.                          | 0 2 4 2 26 34 |
| Molecular subtype (breast), no. (%)    |              |
| HER2-positive                          | 0 0 0 0 2 (8) 2 (6) |
| ER-positive                            | 0 1 (50) 3 (75) 1 (50) 20 (77) 25 (74) |
| PR-positive                            | 0 1 (50) 2 (50) 0 13 (50) 16 (47) |
| Triple negative                        | 0 1 (50) 1 (25) 1 (50) 4 (15) 7 (21) |

Abbreviations: —, not applicable; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; PSA, prostate-specific antigen; SD, standard deviation; Triple negative, HER2-, ER-, and PR-negative.
### Supplemental Table 1. Trial information

| Parameter                  | Description                                                                 |
|----------------------------|-----------------------------------------------------------------------------|
| Disease                    | CRPCBC (all subtypes), PRLR-positive                                        |
| Stage of disease/treatment | CRPC: metastatic<br>MBC: locally advanced or metastatic                      |
| Prior therapy              | ≥1 prior regimen                                                            |
| Type of study              | Phase I                                                                     |
| Eligible patients          | ECOG PS 0–2, life expectancy ≥12 weeks                                       |
| Primary objectives         | MTD or RDE of LFA102 (dose escalation part) Safety and tolerability (dose expansion part) |
| Secondary objectives       | PK, PD, and preliminary antitumor activity                                  |
| Exploratory objective      | Effects of LFA102 on serum prolactin levels                                 |
| LFA102 administration      | IV infusion once every 4 weeks until disease progression, unacceptable toxicity, or withdrawal by patient or physician decision |
| AE grading                 | CTCAE version 4.03                                                          |
| DLT definition             | AE or abnormal laboratory value assessed as unrelated to progressive disease, intercurrent illness, or concomitant medications, occurring in cycle 1 |
| MTD definition             | Highest drug dosage not expected to cause DLT in >33% of patients in cycle 1 |
| Response evaluation        | CT scan and MRI, where appropriate, every 8 weeks Investigator assessed using PCWG2 (CRPC) or RECIST version 1.1 (MBC) |

**Supplemental Table 2.** Most common AEs (≥15% for all grades or ≥5% for grade 3/4 in all patients) regardless of study drug relationship

| Adverse event            | 3 n = 3 | 10 n = 3 | 20 n = 7 | 40 n = 8 | 60 n = 52 | All N = 73 |
|--------------------------|---------|----------|----------|----------|-----------|------------|
| Total AEs                | 3 (100)| 3 (100)| 2 (67)   | 8 (100)| 50 (96)| 71 (97)   | 51 (51)   |
| Fatigue                  | 1 (33)| 0       | 2 (29)   | 4 (50)| 24 (46)| 32 (44)   | 6 (8)     |
| Nausea                   | 1 (33)| 2 (67)| 2 (14)   | 3 (38)| 16 (31)| 24 (33)| 1 (1)     |
| Constipation             | 1 (33)| 0       | 1 (14)   | 1 (13)| 12 (23)| 15 (21)| 1 (1)     |
| Decreased appetite       | 0      | 1 (33)| 2 (29)   | 2 (25)| 10 (19)| 15 (21)| 3 (4)     |
| Vomiting                 | 0      | 1 (33)| 3 (43)   | 0     | 11 (21)| 15 (21)| 0         |
| Pain in extremity        | 2 (67)| 1 (33)| 0       | 1 (13)| 9 (17)| 13 (18)| 1 (1)     |
| Anemia                   | 0      | 0       | 1 (14)   | 2 (25)| 9 (17)| 12 (16)| 2 (3)     |
| Increased AST            | 0      | 0       | 1 (14)   | 2 (25)| 8 (15)| 11 (15)| 4 (6)     |
| Asthenia                 | 0      | 0       | 1 (14)   | 1 (13)| 7 (14)| 10 (14)| 5 (7)     |
| Hypophosphatemia         | 0      | 1 (33)| 1 (33)| 0| 1 (13)| 4 (8)| 2 (4)     | 6 (8)| 4 (6) |

Data given as no. (%)  
Abbreviations: AE, adverse event; AST, aspartate aminotransferase.
Supplemental Table 3. Safety, tolerability, dose changes, and exposure to LFA102

| Event                                                   | No. (%) |
|---------------------------------------------------------|---------|
| Grade 3/4 AEs suspected to be related to study treatment |         |
| Decreased blood phosphorus                              | 1 (1)   |
| Increased serum lipase                                  | 1 (1)   |
| Decreased blood lymphocyte count                        | 1 (1)   |
| LFA102 dose changes                                     |         |
| Discontinued because of AEs                             | 5 (7)   |
| Adjustments or interruptions because of AEs             | 4 (6)   |
| Delay because of AE/scheduling conflict                 | 3 (4)   |
| ≥1 change                                               | 4 (6)   |
| Death\(^a\)                                             | 4 (6)   |
| Median (range) exposure to LFA102, weeks                | 12 (1–48)|
\(^a\)Regarded as not related to LFA102 treatment.
Abbreviation: AE, adverse event.

Supplemental Table 4. Best overall response to LFA102 treatment

| Response                  | 3 n = 3 | 10 n = 3 | 20 n = 7 | 40 n = 8 | 60 n = 52 | All N = 73 |
|---------------------------|---------|----------|----------|----------|-----------|------------|
| Complete response         | 0       | 0        | 0        | 0        | 0         | 0          |
| Partial response          | 0       | 0        | 0        | 0        | 0         | 0          |
| Stable disease            | 1       | 1        | 1        | 0        | 10        | 13         |
| Progressive disease       | 1       | 1        | 5        | 4        | 30        | 41         |
| Unknown/NCRNPD            | 1       | 1        | 1        | 4        | 12        | 19         |

Based on investigator-reported results.
Abbreviation: NCRNPD, noncompleted response, nonprogressive disease.