The Oncologist®

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,[j] Gang Wu,[j] Hefei Zhang,[j] Renata Zieba,[j] Mohamed Elmeliegy[j]

[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

- **ClinicalTrials.gov Identifier:** NCT01338831
- **Sponsor:** Novartis Pharmaceuticals Corporation
- **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. http://dx.doi.org/10.1634/theoncologist.2015-0502

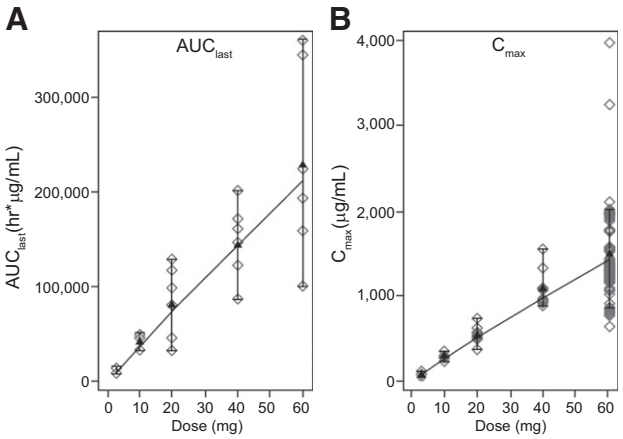


Figure 1. AUC_{last} and C_{max} increase with LFA102 dose in a relatively proportional manner. AUC_{last} **(A)** and C_{max} **(B)** results for individual patients in cycle 1. For each dose, parameter values (open symbols), least-square mean (black triangles), and 90% least-square means confidence 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. C_{max} and AUC_{last} increased in a relatively proportional manner with increasing LFA102 doses.

Abbreviations: AUC_{last}, area under the last measurable concentration; C_{max}, maximum concentration observed.

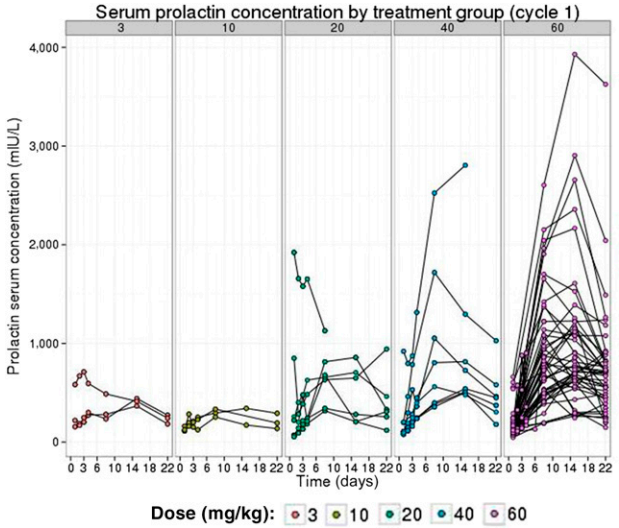


Figure 2. Serum prolactin levels rise with increasing doses of LFA102. Linear views of individual serum prolactin concentration-time profiles grouped by LFA102 dose group are shown. Individual patient serum prolactin increased after LFA102 administration.

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 (C_{max}) and area under the last measurable concentration (AUC_{last}) were approximately linearly dose dependent (Fig. 1) and should provide sufficient exposure to achieve efficacy. However, no objective responses were observed in patients with MBC, and in patients with mCRPC, there were no prostate-specific antigen (PSA) responses.

In vitro data have shown a high binding affinity of LFA102 to PRLR, but because assessing LFA102 binding within tumors is impractical 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.

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

Primary Endpoint	Safety
Primary 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	C_{max} (μg/L) mean ± SD	T_{max}(h) (min–max)	$AUC_{0\text{-}12}$ (h*12 μg/L) mean ± SD	T ½(h) mean ± SD	Cl 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_{max} and AUC_{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 ($\pm$ SD) C_{max} was 1,495 $\pm$ 589 μg/mL (coefficient of variation [CV%]: 39) and mean ($\pm$ SD) AUC_{last} was 230,991 $\pm$ 102,673 hour $\times$ μg/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 patients. 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_{max} and AUC_{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. Thirteen of 73 patients (18%) 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_{max} values were comparable between rodent and human subjects (268 μg/mL and 303 μg/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_{max} of 1,495 $\pm$ 589 μg/mL and a mean steady-state trough concentration of 106 $\pm$ 34 μg/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 xenograft 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 LFA102 monotherapy may not show antitumor activity, it may still have the potential to treat prolactin-dependent tumors in combination with other agents, such as 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.

Acknowledgments

We thank the patients who took part in the trial and their families, as well as the staff who assisted with the study at each site. This study was sponsored by Novartis Pharmaceuticals, which also provided financial support for medical editorial assistance. We thank Karen Beckett for medical editorial assistance with the manuscript.

Disclosures

Jean-Pascal Machiels: Novartis (RF); **Nancy Lewis:** Novartis, Jefferson (E); **Ahmad Awada:** Roche, Pfizer (C/A); **Mark Stein:** Jansen, Medivation, Oncoceutics, Amgen, Advaxis, Merck (RF); **Rebecca Mosher:** Novartis (E); **Ernesto Wasserman:** Novartis (E); **Mohamed Elmeliegy:** Novartis (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

References

1. Ben-Jonathan N, Liby K, McFarland M et al. Prolactin as an autocrine/paracrine growth factor in human cancer. Trends Endocrinol Metab 2002;13: 245–250.

2. Ormandy CJ, Camus A, Barra J et al. Null mutation of the prolactin receptor gene produces multiple reproductive defects in the mouse. Genes Dev 1997;11:167–178.

3. Damiano JS, Wasserman E. Molecular pathways: Blockade of the PRLR signaling pathway as a novel antihormonal approach for the treatment of breast and prostate cancer. Clin Cancer Res 2013;19: 1644–1650.

4. Li H, Ahonen TJ, Alanen K et al. Activation of signal transducer and activator of transcription 5 in human prostate cancer is associated with high histological grade. Cancer Res 2004;64:4774–4782.

5. Clevenger CV, Plank TL. Prolactin as an autocrine/paracrine factor in breast tissue. J Mammary Gland Biol Neoplasia 1997;2:59–68.

6. Hugo ER, Borcherding DC, Gersin KS et al. Prolactin release by adipose explants, primary adipocytes, and LS14 adipocytes. J Clin Endocrinol Metab 2008; 93:4006–4012.

7. Milewicz T, Ryś J, Wójtowicz A et al. Overexpression of P53 protein and local hGH, IGF-I, IGFBP-3, IGFBP-2 and PRL secretion by human breast cancer explants. Neuroendocrinol Lett 2011;32: 328–333.

8. Touraine P, Martini JF, Zafrani B et al. Increased expression of prolactin receptor gene assessed by quantitative polymerase chain reaction in human breast tumors versus normal breast tissues. J Clin Endocrinol Metab 1998;83:667–674.

9. Gill S, Peston D, Vonderhaar BK et al. Expression of prolactin receptors in normal, benign, and malignant breast tissue: An immunohistological study. J Clin Pathol 2001;54:956–960.

10. Leav I, Merk FB, Lee KF et al. Prolactin receptor expression in the developing human prostate and in hyperplastic, dysplastic, and neoplastic lesions. Am J Pathol 1999;154:863–870.

11. Levina VV, Nolen B, Su Y et al. Biological significance of prolactin in gynecologic cancers. Cancer Res 2009;69:5226–5233.

12. Bauernhofer T, Pichler M, Wieckowski E et al. Prolactin receptor is a negative prognostic factor in patients with squamous cell carcinoma of the head and neck. Br J Cancer 2011;104:1641–1648.

13. Harbaum L, Pollheimer MJ, Bauernhofer T et al. Clinicopathological significance of prolactin receptor expression in colorectal carcinoma and corresponding metastases. Mod Pathol 2010;23: 961–971.

14. Tworoger SS, Eliassen AH, Sluss P et al. A prospective study of plasma prolactin concentrations and risk of premenopausal and postmenopausal breast cancer. J Clin Oncol 2007;25: 1482–1488.

15. Wu ZS, Yang K, Wan Y et al. Tumor expression of human growth hormone and human prolactin predict a worse survival outcome in patients with mammary or endometrial carcinoma. J Clin Endocrinol Metab 2011;96:E1619–E1629.

16. Tworoger SS, Eliassen AH, Zhang X et al. A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Res 2013;73:4810–4819.

17. Rose-Hellekant TA, Arendt LM, Schroeder MD et al. Prolactin induces ERalpha-positive and ERalpha-negative mammary cancer in transgenic mice. Oncogene 2003;22:4664–4674.

18. Oakes SR, Robertson FG, Kench JG et al. Loss of mammary epithelial prolactin receptor delays tumor formation by reducing cell proliferation in low-grade preinvasive lesions. Oncogene 2007;26: 543–553.

19. Li H, Zhang Y, Glass A et al. Activation of signal transducer and activator of transcription-5 in prostate cancer predicts early recurrence. Clin Cancer Res 2005;11:5863–5868.

20. Kindblom J, Dillner K, Sahlin L et al. Prostate hyperplasia in a transgenic mouse with prostate-specific expression of prolactin. Endocrinology 2003;144:2269–2278.

21. Rouet V, Bogorad RL, Kayser C et al. Local prolactin is a target to prevent expansion of basal/stem cells in prostate tumors. Proc Natl Acad Sci USA 2010;107:15199–15204.

22. Goffin V, Bernichtein S, Touraine P et al. Development and potential clinical uses of human prolactin receptor antagonists. Endocr Rev 2005;26:400–422.

23. Holtkamp W, Nagel GA. [Bromocriptine in chemotherapy-resistant, metastatic breast cancer. Results of the GO-MC-BROMO 2/82 AIO Study]. Onkologie 1988;11:121–127.

24. Bonneterre J, Mauriac L, Weber B et al. Tamoxifen plus bromocriptine versus tamoxifen plus placebo in advanced breast cancer: Results of a double blind multicentre clinical trial. Eur J Cancer Clin Oncol 1988;24:1851–1853.

25. Bontenbal M, Foekens JA, Lamberts SWJ et al. Feasibility, endocrine and anti-tumour effects of a triple endocrine therapy with tamoxifen, a somatostatin analogue and an antiprolactin in post-menopausal metastatic breast cancer: A randomized study with long-term follow-up. Br J Cancer 1998;77:115–122.

26. Clevenger CV, Zheng J, Jablonski EM et al. From bench to bedside: Future potential for the translation of prolactin inhibitors as breast cancer therapeutics. J Mammary Gland Biol Neoplasia 2008;13:147–156.

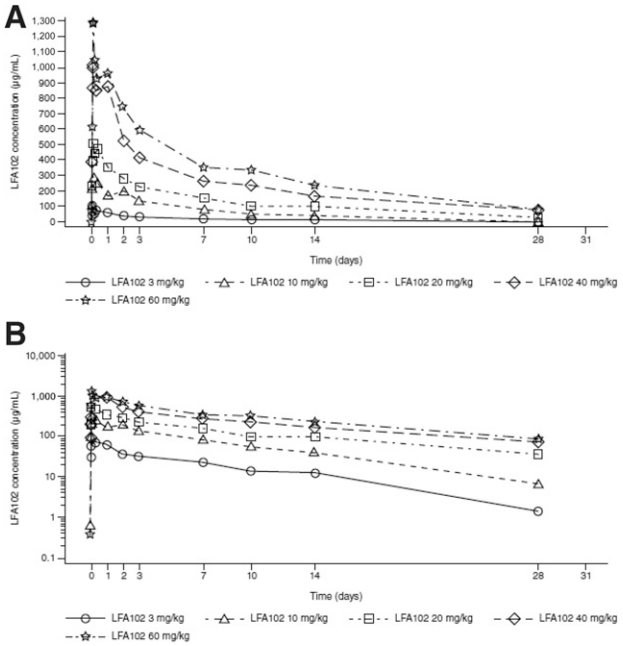
27. Jacobson EM, Hugo ER, Tuttle TR et al. Unexploited therapies in breast and prostate cancer: blockade of the prolactin receptor. Trends Endocrinol Metab 2010;21:691–698.

28. Damiano JS, Rendahl KG, Karim C et al. Neutralization of prolactin receptor function by monoclonal antibody LFA102, a novel potential therapeutic for the treatment of breast cancer. Mol Cancer Ther 2013;12:295–305.

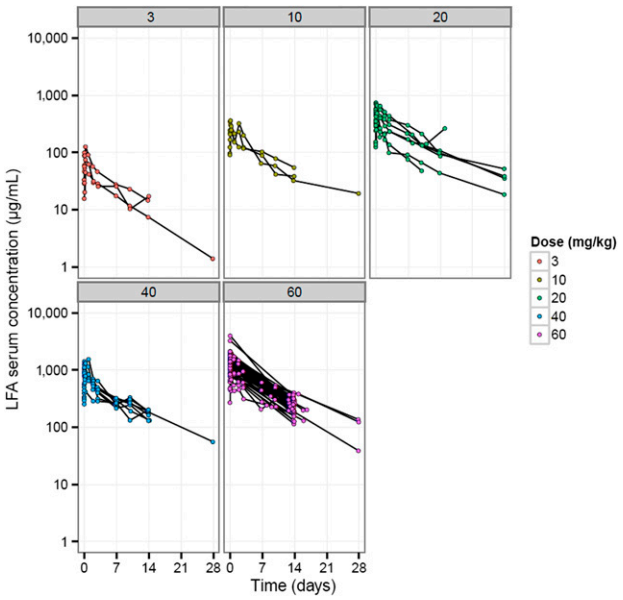
29. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2008;84:548–558.

30. Utama FE, LeBaron MJ, Neilson LM et al. Human prolactin receptors are insensitive to mouse prolactin: implications for xenotransplant modeling of human breast cancer in mice. J Endocrinol 2006; 188:589–601.

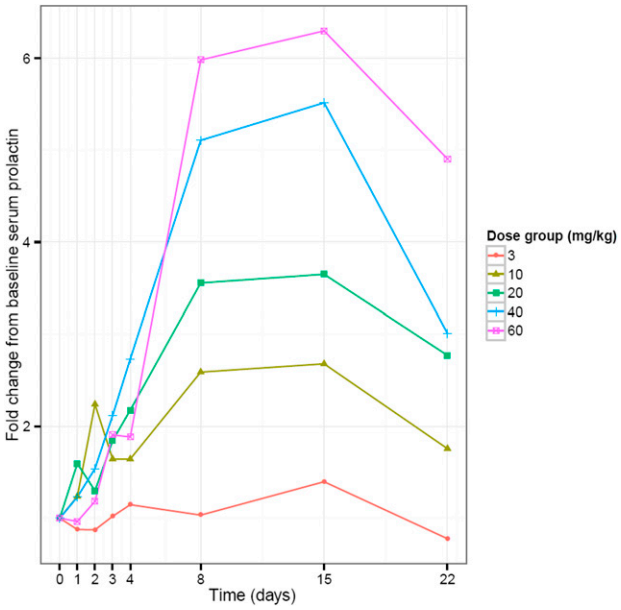
Figures and Tables



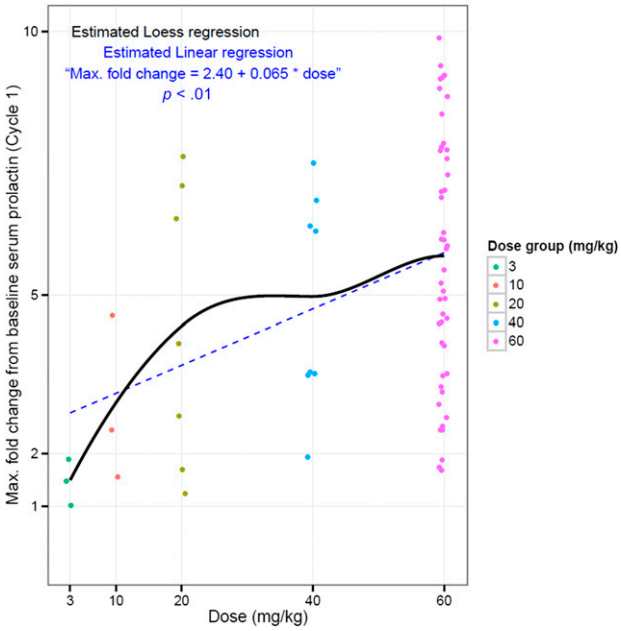
Supplemental Figure 1. **(A)**: Linear view. **(B)**: Semilogarithmic view.



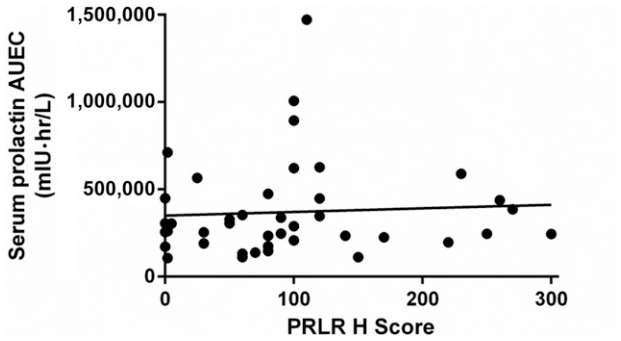
Supplemental Figure 2. Individual LFA102 concentration-time profiles by treatment group: semi-logarithmic view (cycle 1).



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

	All patients					
	LFA102 dose (mg/kg)					
Characteristics	**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 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)

Abbreviations: AE, adverse event; BC, breast cancer; CRCP, castration-resistant prostate cancer; CT, computed tomography; DLT, dose-limiting toxicity; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PD, pharmacodynamics; PK, pharmacokinetics; PRLR, prolactin receptor; RDE, recommended dose for expansion.

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

	LFA102 dose (mg/kg)											
	3 *n* = 3		10 *n* = 3		20 *n* = 7		40 *n* = 8		60 *n* = 52		All *N* = 73	
Adverse event	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total AEs	3 (100)	1(33)	3 (100)	2 (67)	7 (100)	3 (43)	8 (100)	6 (75)	50 (96)	25 (48)	71 (97)	37 (51)
Fatigue	1 (33)	0	1 (33)	0	2 (29)	0	4 (50)	1 (13)	24 (46)	5 (10)	32 (44)	6 (8)
Nausea	1 (33)	0	2 (67)	0	2 (29)	1 (14)	3 (38)	0	16 (31)	0	24 (33)	1 (1)
Constipation	1 (33)	0	0	0	1 (14)	0	1 (13)	0	12 (23)	1 (2)	15 (21)	1 (1)
Decreased appetite	0	0	1 (33)	0	2 (29)	0	2 (25)	0	10 (19)	3 (6)	15 (21)	3 (4)
Vomiting	0	0	1 (33)	0	3 (43)	0	0	0	11 (21)	0	15 (21)	0
Pain in extremity	2 (67)	0	1 (33)	0	0	0	1 (13)	0	9 (17)	1 (2)	13 (18)	1 (1)
Anemia	0	0	0	0	1 (14)	0	2 (25)	0	9 (17)	2 (4)	12 (16)	2 (3)
Increased AST	0	0	0	0	1 (14)	1 (14)	2 (25)	1 (13)	8 (15)	2 (4)	11 (15)	4 (6)
Asthenia	0	0	0	0	2 (29)	1 (14)	1 (13)	1 (13)	7 (14)	3 (6)	10 (14)	5 (7)
Hypophosphatemia	0	0	1 (33)	1 (33)	0	0	1 (13)	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

	LFA102 dose (mg/kg)					
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.