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

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Clinical Trial Results

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

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Author Summary

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;21:535–536

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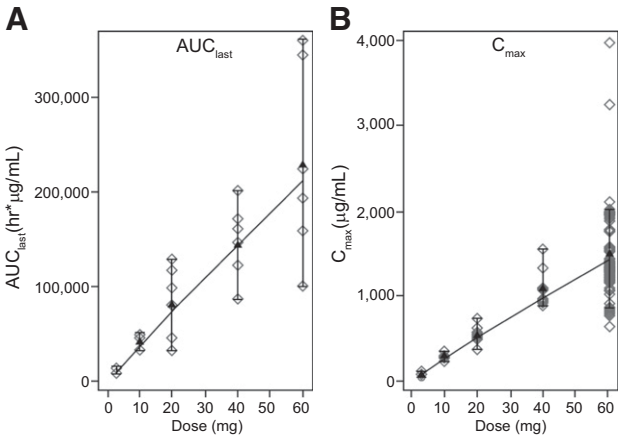

Figure 1. AUC_{last} and C_{max} increase with LFA102 dose in a relatively proportional manner. AUC_{last} **(A)** and C_{max} **(B)** results for individual patients in cycle 1. For each dose, parameter values (open symbols), least-square mean (black triangles), and 90% least-square means confidence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

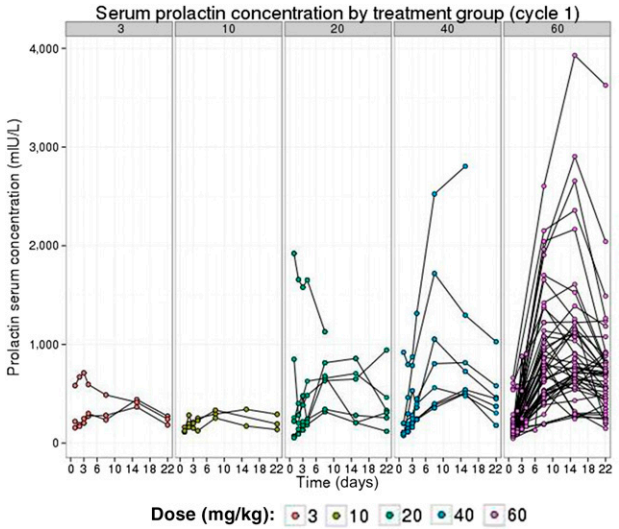

Figure 2. Serum prolactin levels rise with increasing doses of LFA102. Linear views of individual serum prolactin concentration-time profiles grouped by LFA102 dose group are shown. Individual patient serum prolactin increased after LFA102 administration.

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.

Author disclosures available online.

Editor's Note: See the related commentary, "Targeting Prolactin Receptor (PRLR) Signaling in PRLR-Positive Breast and Prostate Cancer," by Ciara C. O'Sullivan and Susan E. Bates on page 523 of this issue.