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Clinical Trial Results

Bosutinib in Combination With the Aromatase Inhibitor Letrozole: A Phase II Trial in Postmenopausal Women Evaluating First-Line Endocrine Therapy in Locally Advanced or Metastatic Hormone Receptor-Positive/HER2-Negative Breast Cancer

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Author Summary

Abstract

Background. Endocrine therapy resistance in hormone receptor-positive (HR+) breast cancer (BC) may involve crosstalk between HRs and growth factor signaling pathways. We evaluated bosutinib, a dual Src/Abl tyrosine kinase inhibitor that has previously demonstrated some antitumor activity in BC, plus letrozole as first-line endocrine therapy in locally advanced or metastatic HR+/HER2− BC.

Methods. Sixteen postmenopausal women were enrolled in a phase II study evaluating the safety/efficacy of bosutinib plus letrozole. In the single-arm safety/dose-confirming lead-in (part 1), patients received oral bosutinib at 400 mg/day plus letrozole at 2.5 mg/day; adverse events (AEs) and dose-limiting toxicities (DLTs) were monitored, and initial efficacy was assessed. A randomized efficacy/safety phase (part 2) was planned to evaluate the combination versus letrozole monotherapy.

Results. Fifteen of 16 subjects experienced treatment-related AEs, most commonly diarrhea (69%). Treatment-related hepatotoxicity AEs (primarily alanine aminotransferase [ALT] or aspartate aminotransferase [AST] elevations) occurred in 6 of 16 patients (38%). Four of 15 evaluable patients (27%) experienced a DLT (grade 3/4 ALT/AST elevations, $n = 2$; grade 3 rash, $n = 1$; grade 3 diarrhea or vomiting, $n = 1$), including 1 Hy's law hepatotoxicity case. All DLTs resolved following treatment discontinuation. One patient achieved confirmed partial response; one had stable disease for >24 weeks. Study termination occurred before part 2.

Conclusion. The unfavorable risk-benefit ratio did not warrant further investigation of bosutinib plus letrozole. ***The Oncologist*** 2014;19:348–349

Discussion

This phase II study was designed to evaluate bosutinib plus letrozole versus letrozole as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic HR+/HER2− BC (Table 1). The DLT-evaluable population included all part 1 patients who received ≥21 of 28 planned cycle 1 bosutinib and letrozole doses or who experienced a DLT in cycle 1, regardless of the number of doses received. Hepatotoxicity was common in part 1. Two patients experienced serious AEs of ALT/AST elevations that led to treatment discontinuation and met DLT criteria, including one case that met Hy's law criteria, an indicator of drug-induced hepatic injury [1]; liver function test abnormalities resolved after bosutinib discontinuation. Specific class II human leukocyte antigen alleles may play a role in tyrosine kinase inhibitor-induced hepatotoxicity [2]. One patient achieved a confirmed partial disease response. Although the safety profile for bosutinib plus letrozole was not fully determined because the upper bound of the 80% confidence interval (CI) for the 12% DLT rate (80% CI: 12%–46%) was not ≤34%, per protocol, it was decided that the observed risks exceeded potential benefits, and the study was terminated prematurely by the sponsor before part 2.

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Table 1. Treatment summary (safety population)

Parameter	Bosutinib 400 mg + letrozole 2.5 mg ($n = 16$)
Duration of treatment, weeks, median (range)	8.5 (1.6−32.3)
Dose delay due to an AE, *n* (%)	
Bosutinib	6 (38)
Letrozole	3 (19)
Dose reduction due to an AE, *n* (%)	
Bosutinib	1 (6)
Letrozole	0
Dose-limiting toxicities, *n* (% [80% CI])[a]	4 (27 [12−46])
ALT/AST increased	2 (13)
Diarrhea/vomiting	1 (7)
Rash	1 (7)
Discontinued treatment, *n* (%)	16 (100)
Reason for treatment discontinuation, *n* (%)	
AE	0
Death	0
Disease progression	2 (13)
Terminated by sponsor	12 (75)
Withdrawal by patient	1 (6)
Protocol violation	1 (6)

[a]$n = 15$ evaluable patients.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval.

In another phase II trial with a similar design evaluating bosutinib at 400 mg/day plus exemestane at 25 mg/day as second-line therapy in postmenopausal women with HR+/HER2− BC (ClinicalTrials.gov identifier NCT00793546), 5 of 13 evaluable patients had a DLT, and these were all hepatic or gastrointestinal events [3]. The recommended phase II dose (RP2D) of bosutinib 300 mg/day plus exemestane 25 mg/day had a generally acceptable safety profile: 3 of 26 evaluable patients (12% [80% CI: 4%–24%]) had a DLT, and again, all were hepatic or gastrointestinal events. No hepatic toxicity met Hy's law criteria; however, the treatment-related hepatotoxicity rate of 26% did not support further evaluation of this combination. One patient achieved a confirmed partial disease response on the RP2D; however, the 80% CI upper boundary for median progression-free survival (PFS) was below the benchmark of 16 weeks for exemestane [3].

Preclinical studies had demonstrated that bosutinib inhibits BC cell proliferation, invasion, and migration, as well as tumor growth and metastasis in vivo [4–6]. A phase II trial of bosutinib monotherapy utilizing a dose of 400 mg/day in heavily pretreated advanced BC patients unselected for HR status demonstrated a clinical benefit rate of 27% and a 16-week PFS rate of 40%; all four patients whose tumors responded had HR+ BC [7]. Common toxicities included gastrointestinal events (diarrhea [66%], nausea [55%], vomiting [47%]), and grade 3/4 ALT/AST laboratory elevations (19%) [7]. A similar safety profile was observed in a phase I study of bosutinib in advanced solid tumors [8].

Bosutinib plus letrozole has a worse safety profile than single-agent bosutinib, which is characterized by manageable events and the absence of life-threatening events [7, 8]. Given the efficacy of bosutinib monotherapy in metastatic BC, Src/Abl inhibition remains a novel treatment strategy. Alternative combination regimens with bosutinib warrant consideration in metastatic BC.

Author disclosures and references available online.