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Randomized phase II study of lonaprisan as second-line therapy for progesterone receptor-positive breast cancer

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Background: The progesterone-receptor (PR) antagonists onapristone (type I) and mifepristone (type II) showed modest activity in hormone-receptor-positive breast cancer; however, onapristone in particular was associated with hepatotoxicity. Lonaprisan is a novel, type III PR antagonist that was well tolerated in phase I studies.
Patients and methods: This randomized, open-label, phase II study evaluated the efficacy and tolerability of lonaprisan as second-line endocrine therapy in postmenopausal women with stage IV, PR-positive, HER2-negative, metastatic breast cancer.
Results: Patients received once-daily lonaprisan 25 mg ($n = 34$) or 100 mg ($n = 34$). The primary objective was not met (≥35% clinical benefit rate: complete/partial responses at any time until month 6 or stable disease [SD] for ≥6 months from start of treatment). There were no complete/partial responses. In the 25 mg and 100 mg groups, 6 of 29 patients (21%) and 2 of 29 patients (7%), respectively, had SD ≥6 months. Overall, 61 of 68 patients (90%) had ≥1 adverse event (AE), the most frequent (≥10% overall) being fatigue, hot flush, dyspnoea, nausea, asthenia, headache, constipation, vomiting, and decreased appetite; 33 patients had serious AEs.
Conclusion: Lonaprisan showed limited efficacy as second-line endocrine therapy in postmenopausal women with PR-positive metastatic breast cancer.
Key words: antiprogestin, breast cancer, lonaprisan, progesterone-receptor antagonist, progesterone-receptor positive

introduction

Endocrine therapy is the most important systemic treatment for patients with hormone-receptor-positive breast cancer (BC), and multiple endocrine therapies are available in this setting. However, all these agents aim at oestrogen deprivation. Furthermore, the effectiveness of current endocrine therapies is limited by the development of drug resistance [1]. This resistance is thought to be mediated, at least in part, by interactions between oestrogen-receptor (ER) and growth-factor-receptor signalling pathways—so-called molecular cross-talk—that lead to modulation of hormone receptor function [2]. Therefore, there is an unmet need for therapies with novel mechanisms of action for postmenopausal women with hormone-receptor-positive, stage IV, systemic BC.

As well as agents that target oestrogen deprivation, various agents targeting the progesterone receptor (PR) have been investigated. PR modulators compete with progesterone for the PR ligand-binding site. There are three types of steroidal PR antagonist. Type I agents prevent DNA binding and inhibit PR phosphorylation. Type II agents promote DNA binding and promote PR phosphorylation. Type III agents promote DNA binding, recruit co-repressors, and strongly promote PR phosphorylation. Studies with onapristone (type I) and mifepristone (type II) suggested that PR antagonism, either alone or in combination therapy, may be a viable treatment strategy in postmenopausal women with advanced BC [3–6]. Both were studied in first- and second-line settings, and mifepristone has also been used as a third-line treatment. Beneficial effects were mainly observed in patients with PR-positive tumours. Together, the study of mifepristone as second-line therapy ($n = 11$) and the study of onapristone as second-line therapy ($n = 90$) reported an objective response rate (ORR; complete response plus partial response) of around 10% [3, 6]. The first-line studies reported ORRs of 11% for mifepristone

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and 56% for onapristone [4, 5]. However, transient liver function test abnormalities in some patients (mainly during the first 6 weeks) halted the clinical development of onapristone [4].

Lonaprisan (ZK230211) is a type III PR antagonist. *In vitro* studies show that lonaprisan has strong antiproliferative properties that are greater than those of mifepristone and onapristone [7–9]. In two randomized, placebo-controlled, phase I studies in healthy postmenopausal women, lonaprisan (single dose of 1–200 mg or repeated doses of 5–100 mg) was well tolerated without hepatotoxicity [10]. The aim of the present prospective, multicentre, randomized, open-label, parallel-group, phase II study was to evaluate the efficacy, tolerability, and pharmacokinetics of lonaprisan, 25 or 100 mg once daily, as second-line endocrine therapy for postmenopausal women with stage IV, PR-positive, human epidermal growth factor receptor 2 (HER2)-negative, metastatic BC.

materials and methods

study design

This was an open-label, prospective, randomized, parallel-group, phase II study (clinicaltrials.gov identifier: NCT00555919; EudraCT Number: 2005–005581-36), carried out at 28 centres in Austria, Finland, France, Germany, UK, Italy, Poland, Spain, Sweden, and Switzerland. It was conducted in accordance with the principles of the Declaration of Helsinki, the ICH-GCP guidelines, and appropriate local regulatory authorities. The objective of the study was to evaluate the efficacy, safety, tolerability, and pharmacokinetics of two doses of lonaprisan, 25 and 100 mg, given orally, once daily.

study population

Patients included were postmenopausal women with: PR-positive, histologically, or cytologically confirmed metastatic (stage IV, Union Internationale Contre le Cancer [UICC] criteria version 6) BC; disease progression after first-line endocrine therapy for advanced BC (i.e. with tumour remission or stabilization lasting at least 3 months under endocrine therapy); at least one measurable or non-measurable tumour lesion (according to Response Evaluation Criteria in Solid Tumours [RECIST] [11]); WHO performance status score ≤1.

Postmenopausal was defined as: aged ≥50 years with amenorrhoea for ≥12 months; or aged ≤50 years with 6 months of spontaneous amenorrhoea and follicle-stimulating hormone levels within postmenopausal range (>40 mIU/ml); or having undergone bilateral oophorectomy. This is a standard definition for postmenopausal, and is consistent with, for example, draft guidance from the FDA regarding clinical evaluation of hormone-replacement therapy to treat the symptoms of the menopause [12].

Exclusion criteria included: more than one prior endocrine treatment for advanced BC; previous combination of endocrine treatment with any other type of treatment (except chemotherapy); previous sequential endocrine treatments (if there was disease progression between treatments); HER2 status positive or unknown.

interventions and outcomes

Patients were randomized to receive lonaprisan 25 mg once daily (one 25-mg tablet) or 100 mg once daily (two 50-mg tablets) until they had disease progression, became unable to tolerate therapy, developed any condition that precluded study treatment, were non-compliant with therapy, withdrew consent, or died. Treatment was taken as a fasting morning dose at least 1 h before food. Randomization was carried out centrally according to a computer-generated list produced by the sponsor using randomization blocks. Patients were equally distributed between treatment groups with stratification for disease status (measurable/non-measurable disease) and previous chemotherapy (yes/no).

The primary efficacy outcome was clinical benefit, defined as the proportion of patients with: complete response or partial response at any time up to month 6; or stable disease for 6 months from the start of study treatment. Secondary efficacy outcomes were: ORR (best overall response out of partial response or complete response in patients with measurable disease); progression-free survival (PFS); duration of response; duration of clinical benefit; and overall survival (OS). Tumour response was evaluated at 3-monthly intervals until study end, and lesions were evaluated according to RECIST 1.0 [11].

Safety outcomes included adverse events (AEs), serious AEs (SAEs), laboratory assessments, and electrocardiograms (ECGs).

Other outcomes included pharmacokinetic analysis of lonaprisan and its metabolites (subgroup of patients at selected centres only).

statistical methods

Planned enrolment was 72 patients (36 per dose group). This was based on one-sided significance testing within each group at test level 10%. With 36 assessable patients per group, a power of ≥90% was guaranteed if the anticipated clinical benefit rate of 35% were met. The primary objective of the study was not inferential comparison between the two groups, but hypothesis testing within each group. The study was designed to demonstrate a positive effect of lonaprisan (within each group) compared with a threshold clinical benefit rate of 15%. Within each treatment group, the primary efficacy outcome was analysed in a single-stage design. The outcome was considered successful if 9 of 36 assessable patients in one treatment group showed clinical benefit. The main analysis of efficacy was to be carried out after all patients had been treated for 6 months or had dropped out before month 6, whichever came soonest. The analysis sets for efficacy and safety were consistent (all patients with at least one intake of study drug). Data are displayed by descriptive statistics.

results

patients

The first patient enrolled in March 2008. The study was terminated earlier than planned (April 2010) owing to slow recruitment and anticipation of negative study findings; expected futility was based on a data review carried out by two senior investigators (the coordinating investigator and a site principal investigator) when 68 of the proposed 72 patients had been treated. Of 83 patients screened, 69 were randomized (supplementary Figure S1, available at *Annals of Oncology* online). All but one patient (100 mg group) received at least one dose of lonaprisan; the full analysis set as well as the safety analysis set included 68 patients.

Overall, the median (range) patient age was 66 (42–94) years (Table 1). All patients except one were Caucasian and all had UICC stage IV BC. Initial diagnosis for 72.1% of patients was ductal carcinoma (including invasive ductal carcinoma, ductal carcinoma *in situ*, and inflammatory, mucinous, scirrhous, papillary, or other subtypes) and for 23.5% of patients was lobular carcinoma (including invasive lobular carcinoma with lobular carcinoma *in situ*). The remaining 4.4% of patient had other subtypes of BC. Overall, the two treatment groups were

Table 1. Baseline patient characteristics and demographics (full analysis set)

	Lonaprisan 25 mg/day ($n = 34$)	Lonaprisan 100 mg/day ($n = 34$)	Total ($n = 68$)
Age (years)			
Median (range)	64.5 (42–82)	67.0 (54–94)	66.0 (42–94)
Race, *n* (%)			
Caucasian	33 (97.1)	34 (100)	67 (98.5)
Hispanic	1 (2.9)	0 (0)	1 (1.5)
Histology at initial diagnosis, *n* (%)			
Ductal carcinoma[a]	25 (73.5)	24 (70.6)	49 (72.1)
Lobular carcinoma[b]	8 (23.5)	8 (23.5)	16 (23.5)
Other[c]	1 (2.9)	2 (5.9)	3 (4.4)
HER2 receptor status, *n* (%)			
Negative	31 (91.2)	33 (97.1)	64 (94.1)
Positive	0 (0)	0 (0)	0 (0)
Unknown/missing[d]	3 (8.8)	1 (2.9)	4 (5.9)
Progesterone receptor status, *n* (%)			
Positive	32 (94.1)	34 (100)	66 (97.1)
Negative	0 (0)	0 (0)	0 (0)
Unknown/missing[e]	2 (5.9)	0 (0)	2 (2.9)
Oestrogen receptor status, *n* (%)			
Positive	29 (85.3)	31 (91.2)	60 (88.2)
Negative	2 (5.9)	3 (8.8)	5 (7.4)
Unknown/missing	3 (8.8)	0 (0)	3 (4.4)
Previous breast cancer therapy, *n* (%)			
Adjuvant/neoadjuvant hormone therapy	21 (61.8)	14 (41.2)	35 (51.5)
Adjuvant/neoadjuvant chemotherapy	18 (52.9)	10 (29.4)	28 (41.2)
Chemotherapy for advanced/metastatic disease	7 (20.6)	11 (32.4)	18 (26.5)
Radiotherapy	24 (70.6)	20 (60.6)[f]	44 (65.7)[g]
Previous endocrine therapy for metastatic/advanced disease, *n* (%)[h]			
Aromatase inhibitors			
Letrozole	13 (38.2)	14 (41.2)	27 (39.7)
Anastrozole	12 (36.4)	13 (38.2)	25 (36.8)
Exemestane	3 (8.8)	1 (2.9)	4 (5.9)
Oestrogen receptor antagonists			
Tamoxifen	4 (11.8)	7 (20.6)	11 (16.2)
Fulvestrant	6 (17.6)	1 (2.9)	7 (10.3)
Number of sites of metastasis, *n* (%)			
1	17 (50.0)	9 (26.5)	26 (38.2)
2	9 (26.5)	15 (44.1)	24 (35.3)
≥3	8 (23.5)	10 (29.4)	18 (26.5)
Most common[i] sites of metastasis, *n* (%)			
Bone	20 (58.8)	23 (67.6)	43 (63.2)
Liver	9 (26.5)	13 (38.2)	22 (32.4)
Lymph nodes	9 (26.5)	9 (26.5)	18 (26.5)
Lung	6 (17.6)	8 (23.5)	14 (20.6)
Breast	3 (8.8)	6 (17.6)	9 (13.2)
Pleura	2 (5.9)	7 (20.6)	9 (13.2)

[a]Includes ductal carcinoma, e.g. ductal carcinoma *in situ*, and all subtypes, such as inflammatory, mucinous, papillary, scirrhous, and other subtypes.
[b]Includes lobular carcinoma, e.g. invasive and carcinoma *in situ*.
[c]Includes Paget's disease and breast carcinoma (not otherwise specified).
[d]Although this was an exclusion criterion, four patients with unknown/missing HER2 status were enrolled (minor protocol deviation in three patients; no protocol deviation in one patient, as HER2 was available at screening).
[e]Although this was an inclusion criterion, two patients with unknown/missing progesterone receptor status were enrolled (major protocol deviation in one patient; no protocol deviation in one patient as PR was available at screening).
[f]$n = 33$.
[g]$n = 67$.
[h]Patients could have received more than one previous endocrine therapy for metastatic/advanced disease.
[i]>10% of total patients.
HER2, human epidermal growth factor receptor 2.

comparable in terms of demographics and baseline characteristics.

efficacy

The primary efficacy variable was clinical benefit (defined as the proportion of patients with complete or partial response at any time point up to month 6 or stable disease for 6 months from the start of study treatment). Of the evaluable patients ($n = 58$), 8 (14%) had stable disease ≥6 months: 6 of 29 (21%) in the 25 mg group and 2 of 29 (7%) in the 100 mg group. There were no confirmed complete or partial responses. Therefore, the primary objective of at least 35% clinical benefit rate was not met.

The best overall response during the study was stable disease for ≥3 months in 18 patients (9 of 29 [31.0%] in each group). For the remaining patients, best overall response was therefore progressive disease (20 of 29 [69.0%] in each group). Time-to-event analyses were omitted due to the lack of responders. Some patients had prolonged stable disease: three in the 25 mg group and one in the 100 mg group still showed stable disease at month 12.

pharmacokinetics

Dose-related increases in exposure to lonaprisan and its metabolites occurred when the lonaprisan dose increased from 25 to 100 mg.

safety

Twenty-nine (85.3%) of the 34 patients in the 25 mg group and 32 (94.1%) of the 34 patients in the 100 mg group experienced at least one AE (Table 2). The most common AEs (≥10% overall) were fatigue, hot flush, dyspnoea, nausea, asthenia, headache, constipation, vomiting, and decreased appetite. Drug-related AEs were reported for 18 patients (52.9%) in the 25 mg group and 24 patients (70.6%) in the 100 mg group; the most common (≥10% overall) were fatigue and hot flush.

In all, 21 patients (30.9%) experienced an SAE (9 [26.5%] in the 25 mg group and 12 [35.3%] in the 100 mg group). SAEs reported in more than one patient were endometrial hypertrophy (one patient in the 25 mg group and two patients in the 100 mg group); myocardial infarction (MI; two patients in the 100 mg group); and ascites, subileus, and dyspnoea (one patient in each group for each).

Treatment was discontinued due to AEs in three patients in the 25 mg group (increase of alanine aminotransferase and gamma-glutamyl transpeptidase, increase of endometrial thickness, elevated liver enzymes) and in three patients in the 100 mg group (non-ST-elevated MI, fatigue/chills, liver failure due to disease progression).

There were no consistent trends observed for any laboratory parameters in either dose group. Most laboratory abnormalities were CTCAE grade 1 or 2. Few notable changes in heart rate or blood pressure were observed.

Twelve patients died during the study (four in the lonaprisan 25 mg group and eight in the lonaprisan 100 mg group). In the 25 mg group, all four deaths were due to disease progression. In the 100 mg group, six deaths were due to disease progression, one to cardiorespiratory distress, and one to 'other' ('reduced general condition' with 'nausea, upper abdominal pain'). No deaths were considered related to study treatment.

discussion

This prospective, multicentre, randomized, open-label, parallel-group, phase II study evaluated the efficacy, tolerability, and pharmacokinetics of once-daily lonaprisan 25 or 100 mg as second-line endocrine therapy for postmenopausal women with stage IV, PR-positive, HER2-negative metastatic BC. Although disease stabilization was observed in some patients for a clinically useful period (overall 14% of patients had stable disease for ≥6 months), the study did not meet its primary end point. The study terminated earlier than planned owing to slow recruitment and anticipation of negative study findings (futility analysis).

Based on observations for second-line therapy with type I and II PR antagonists in hormone-receptor-positive BC, an overall clinical benefit rate of ~35%–50% was expected for lonaprisan, a type III steroidal PR antagonist [3, 6, 13, 14]. In our study, no

Table 2. Adverse events (safety analysis set)

	Lonaprisan 25 mg/day ($n = 34$)		Lonaprisan 100 mg/day ($n = 34$)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any adverse event, *n* (%)	29 (85.3)	8 (23.5)	32 (94.1)	12 (35.3)
Most common adverse events, *n* (%)[a]				
Fatigue	6 (17.6)	1 (2.9)	11 (32.4)	2 (5.9)
Hot flush	7 (20.6)	1 (2.9)	6 (17.6)	0
Dyspnoea	5 (14.7)	1 (2.9)	7 (20.6)	1 (2.9)
Nausea	6 (17.6)	0	6 (17.6)	0
Asthenia	9 (26.5)	0	2 (5.9)	1 (2.9)
Headache	5 (14.7)	0	3 (8.8)	0
Constipation	4 (11.8)	0	3 (8.8)	0
Vomiting	4 (11.8)	0	3 (8.8)	0
Decreased appetite	3 (8.8)	1 (2.9)	4 (11.8)	0
Ascites	1 (2.9)	1 (2.9)	2 (5.9)	1 (2.9)
Myocardial infarction	0	0	2 (5.9)	2 (5.9)

[a]Any grade adverse events occurring in ≥10% of patients overall, or grade ≥3 adverse events occurring in ≥2 patients overall.

objective responses were observed, compared with ORRs of ~10%–50% in previous studies of second-line endocrine therapy [3, 6, 13–15]; thus, the clinical benefit rate here included only patients who had stable disease. The limited efficacy demonstrated by lonaprisan in this study suggests that either the drug is ineffective in this population or it is effective in only a limited number of patients. In our study, four patients had prolonged stable disease (>12 months); however, there is considerable debate about the value of stable disease as a measure of efficacy in BC. Given our findings, a clinical benefit rate of <20% should be the definition of an ineffective second-line therapy after an aromatase inhibitor. While there is an argument for setting this at <15% (the clinical benefit rate across both doses of lonaprisan) we feel that the more conservative figure of <20% is appropriate.

This study differs from studies of other PR antagonists in postmenopausal women with metastatic BC in terms of study design and patient population, but the results of the studies may also vary because of the type of PR antagonist used—i.e. a type III agent compared with a type I or II agent (such as onapristone and mifepristone, respectively). Further investigation would require a deeper understanding of the mechanism of action of lonaprisan, especially of the implications of being a type III PR antagonist, and which characteristics make tumour cells sensitive to type III PR antagonism. Understanding the effects of therapy and selecting individuals who are likely to respond to treatment are two key challenges we face in using endocrine therapies for BC [16].

Clinical and molecular factors may both have led to the limited efficacy of lonaprisan. Potentially relevant clinical factors include advanced metastatic disease, multiple sites of metastases, large tumour burden, poor performance status, and aggressive tumour biology. Notably, there were 10 deaths from progressive disease, emphasizing the advanced BC stage of the enrolled patients. In terms of molecular factors, cross-talk between ER and growth-factor-receptor signalling pathways is thought to be a significant cause of *de novo* or acquired resistance to endocrine treatment for hormone-receptor-positive BC [2]. These alterations in signalling may induce not only the development of an endocrine-insensitive phenotype but also a cellular phenotype with enhanced migratory and invasive behaviour [1]. Cross-talk between PR and growth-factor signalling pathways also occurs [17] and this cross-talk, or dysregulation of this mechanism, may underlie the limited efficacy of lonaprisan in this study.

Five patients had ER-negative, PR-positive disease. There has been much debate on this topic, with compelling arguments both for [18, 19] and against [20, 21] the existence of ER-negative, PR-positive disease. Either way, we do not believe that the ER status of patients in our study affected our results, given that we assessed a PR antagonist in patients with PR-positive BC.

In conclusion, lonaprisan showed very limited efficacy as second-line endocrine therapy in postmenopausal women with PR-positive metastatic BC. Our findings set a definition for an ineffective agent (clinical benefit rate <20%) in the second-line setting after an aromatase inhibitor—a setting for which no endocrine agent has a licensed indication. While there may be a number of potential reasons for the observed lack of efficacy, future research should look to find a deeper understanding of the mechanism of action of lonaprisan, including better comprehension of the implications of being a type III PR antagonist.

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