Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Endocrine therapy-based neoadjuvant treatment for luminal breast cancer allows efficient testing of new combinations before surgery. The activation of the phosphatidylinositol-3-kinase (PI3K) pathway is a known mechanism of resistance to endocrine therapy. Taselisib is an oral, selective PI3K inhibitor with enhanced activity against *PIK3CA*-mutant cancer cells. The LORELEI trial tested whether taselisib in combination with letrozole would result in an increased proportion of objective responses and pathological complete responses.

Methods In this multicentre, randomised, double-blind, parallel-cohort, placebo-controlled phase 2, study, we enrolled postmenopausal women (aged ≥18 years) with histologically confirmed, oestrogen receptor (ER)-positive, HER2-negative, stage I–III, operable breast cancer, from 85 hospitals in 22 countries worldwide. To be eligible, patients had have an Eastern Cooperative Oncology Group (ECOG) performance status 0–1, adequate organ function, and had to have evaluable tumour tissue for *PIK3CA* genotyping. Patients were randomly assigned (1:1) by means of a permuted block algorithm (block size of four) via an interactive voice or web-based response system, to receive letrozole (2·5 mg/day orally, continuously) with either 4 mg of oral taselisib or placebo (on a 5 days-on, 2 days-off schedule) for 16 weeks, followed by surgery. Randomisation was stratified by tumour size and nodal status. Site staff, patients, and the sponsor were masked to treatment assignment. Coprimary endpoints were the proportion of patients who achieved an objective response by centrally assessed breast MRI and a locally assessed pathological complete response in the breast and axilla (ypT0/Tis, ypN0) at surgery in all randomly assigned patients and in patients with *PIK3CA*-mutant tumours. Analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02273973, and is closed to accrual.

Findings Between Nov 12, 2014, and Aug 12, 2016, 334 participants were enrolled and randomly assigned to receive letrozole and placebo (n=168) or letrozole and taselisib (n=166). Median follow-up was 4·9 months (IQR 4·7–5·1). The study met one of its primary endpoints: the addition of taselisib to letrozole was associated with a higher proportion of patients achieving an objective response in all randomly assigned patients (66 [39%] of 168 patients in the placebo group *vs* 83 [50%] of 166 in the taselisib group; odds ratio [OR] 1·55, 95% CI 1·00–2·38; p=0·049) and in the *PIK3CA*-mutant subset (30 [38%] of 79 *vs* 41 [56%] of 73; OR 2·03, 95% CI 1·06–3·88; p=0·033). No significant differences were observed in pathological complete response between the two groups, either in the overall population (three [2%] of 166 in the taselisib group *vs* one [1%] of 168 in the placebo group; OR 3·07 [95% CI 0·32–29·85], p=0·37) or in the *PIK3CA*-mutant cohort (one patient [1%] *vs* none [0%]; OR not estimable, p=0·48). The most common grade 3–4 adverse events in the taselisib group were gastrointestinal (13 [8%] of 167 patients), infections (eight [5%]), and skin–subcutaneous tissue disorders (eight [5%]). In the placebo group, four (2%) of 167 patients had grade 3 or worse vascular disorders, two (1%) had gastrointestinal disorders, and two (1%) patients had grade 3 or worse infections and infestations. There was no grade 4 hyperglycaemia and grade 3 cases were asymptomatic. Serious adverse events were more common in the taselisib group (eight [5%] patients with infections and seven [4%] with gastrointestinal effects) than in the placebo group (one [1%] patient each with grade 3 postoperative wound and haematoma infection, grade 4 hypertensive encephalopathy, grade 3 acute cardiac failure, and grade 3 breast pain). One death occurred in the taselisib group, which was not considered to be treatment-related.

Interpretation The increase in the proportion of patients who achieved an objective response from the addition of taselisib to endocrine therapy in a neoadjuvant setting is consistent with the clinical benefit observed in hormone receptor-positive, HER2-negative, metastatic breast cancer.

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Introduction

Oestrogen receptor (ER)-positive, HER2-negative breast cancer accounts for about 70% of all diagnosed breast cancer cases, and endocrine therapy is its cornerstone treatment, both in the early and advanced disease settings. However, not all ER-positive breast cancer responds optimally to endocrine therapy. Upregulation of the PI3K–AKT–mTOR pathway is one of the mechanisms that can lead to primary or secondary endocrine resistance, or both.[1] Genes in the PI3K–AKT–mTOR pathway are frequently mutated or amplified in breast cancer, especially in the ER-positive subtype. *PIK3CA* (encoding p110α, the catalytic subunit of PI3Kα) is mutated in about 35% of all breast cancers, and is more frequent in ER-positive tumours.[2]

Targeting the PI3K–AKT–mTOR pathway in ER-positive breast cancer has proved beneficial both in the neoadjuvant and in the advanced settings.[3,4] In the BOLERO-2 trial, the addition of everolimus to exemestane improved progression-free survival in patients with hormone receptor-positive disease, but efficacy was not increased in those with *PIK3CA*-mutant tumours,[4,5] suggesting that direct inhibitors of PI3K could be a preferred option in these patients. In line with this hypothesis, a phase 3 trial testing the pan-PI3K inhibitor buparlisib in combination with fulvestrant showed increased activity in those patients with a *PIK3CA* mutation detected in circulating tumour DNA (ctDNA).[6] Although these results were encouraging, pan-PI3K inhibitors were frequently associated with hyperglycaemia, dermatological and gastrointestinal adverse events, fatigue, and pneumonitis.[6–8] Mood disorders were reported in nearly a third of patients and a higher proportion of patients receiving buparlisib showed suicidal ideations and attempts,[6,7] which discouraged its approval. Conversely, PI3K isoform-specific agents, such as taselisib and alpelisib, have shown a better safety profile and their most common adverse events (eg, hyperglycaemia, rash, diarrhoea, and mucositis) are amenable to medical management if early interventions are indicated.[9–11]

Taselisib (GDC-0032) inhibits the PI3K-β isoform 30 times less potently than the α-isoform and shows enhanced activity against *PIK3CA*-mutant versus wild-type forms.[12] Taselisib as single agent is well tolerated and has shown antitumour activity across multiple tumour types.[13] The combination of taselisib with letrozole or fulvestrant induced several partial responses in heavily pretreated patients with metastatic, ER-positive breast cancer, especially in tumours harbouring a *PIK3CA* mutation,[14] suggesting that the addition of taselisib to hormone therapy might be a potential therapeutic choice for patients with *PIK3CA*-mutant breast cancer.[15]

The neoadjuvant setting provides a unique opportunity to identify predictive biomarkers of response to novel therapeutic agents. Pretreatment biopsies are easily accessible, on-treatment biopsies can monitor treatment

Research in context

Evidence before this study

We searched PubMed for publications between Jan 1, 2001, and Sept 30, 2017, with the search terms "*PIK3CA* mutation", "PI3K alpha-specific inhibitors", "neoadjuvant endocrine", and "ER+/HER2-negative early breast cancer". We also searched PubMed for publications in the same period describing assessment of taselisib using the terms "taselisib" or "GDC-0032". No previous randomised trials had investigated the targeting of PI3K specifically in oestrogen receptor (ER)-positive, HER2-negative early breast cancer. Analyses of preclinical studies and single-group phase 1 or phase 2 studies in ER-positive, HER2-negative, metastatic breast cancer have suggested a more pronounced effect of isoform selective inhibitors in cell lines, preclinical models, and patients harbouring a *PIK3CA* mutation.

Added value of this study

Our results suggest that taselisib increases the efficacy of letrozole in postmenopausal women with hormone receptor-positive, HER2-negative, operable breast cancer, because this combination results in a higher proportion of patients who achieved an objective response, especially in patients harbouring *PIK3CA*-mutant tumours. The safety profile of taselisib was consistent with previous reports and related toxicities were tolerable and manageable with early medical interventions.

Implications of all the available evidence

Targeting the mTOR–PI3K pathway combined with endocrine therapy is an active treatment option in this setting for hormone receptor-positive, HER2-negative, advanced breast cancer. The efficacy of taselisib in the neoadjuvant setting is consistent with the clinical benefit reported in the SANDPIPER trial in which taselisib plus fulvestrant resulted in longer progression-free survival than fulvestrant alone in patients with *PIK3CA*-mutant metastatic cancer. Our results and available data from phase 1–3 trials of taselisib in advanced disease, although limited by differences in sample sizes, tissues analysed, and populations included, suggest that *PIK3CA* mutations might help in selecting patients who benefit from targeting PI3K. Further studies are required to identify response and resistant biomarkers for these agents.

response at a biological level and, if a pathological complete response is not achieved, the surgical specimen can be examined for mechanisms of resistance to therapy. The biological information obtained from all specimens can be correlated with clinical data, such as objective response and pathological complete response, a surrogate endpoint that strongly associates with disease-free and overall survival in patients with some subtypes of breast cancer.[16]

However, MRI has been shown to be more accurate than clinical palpation, ultrasound, and mammogram for measuring residual tumour size after neoadjuvant therapy in several prospective trials.[17] In the I-SPY1 trial,[18] breast functional tumour volume by MRI (tumour volume enhancement >70% after neoadjuvant chemotherapy) was a strong predictor of relapse-free survival in patients with ER-positive, HER2-negative breast cancer. In another study including ER-positive, HER2-negative tumours, absolute tumour size by MRI after neoadjuvant chemotherapy and radiological complete response but not pathological complete response was associated with relapse-free survival.[19]

In the LORELEI trial, we aimed to assess the efficacy and safety of neoadjuvant taselisib and letrozole in the treatment of patients with ER-positive, HER2-negative, early breast cancer and investigated the presence of a *PIK3CA* mutation as a biomarker for response.

Methods

Study design and participants

LORELEI is a multicentre, randomised, double-blind, parallel cohort, placebo-controlled, phase 2 trial. Patients were enrolled at 85 hospitals in 22 countries worldwide (appendix p 16). Eligible patients were women aged 18 years or older who were postmenopausal (by bilateral oophorectomy or 12 months of amenorrhoea plus follicle-stimulating hormone and oestradiol amounts in the postmenopausal range) with histologically confirmed, operable stage I–III, invasive breast cancer, defined as ER-positive, HER2-negative by local assessment. The minimum size of the primary tumour was 2 cm in largest diameter (cT1c–3) by MRI. In case of multifocal tumours (defined as two or more foci of cancer within the same breast quadrant), the largest lesion had to be at least 2 cm in diameter and was designated as a target lesion for all subsequent tumour evaluations. Radiologically suspicious nodes without a cytological confirmation were classified as node-negative disease.

See Online for appendix

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, adequate glucose metabolism, and adequate haematological, renal, and hepatic functions (appendix p 85).

Patients were ineligible if they had received any previous treatment for primary invasive breast cancer, or presented with metastatic, inoperable, bilateral, or multicentric breast cancer, or had already undergone excisional biopsy of the primary tumour or sentinel or axillary lymph nodes. Patients for whom upfront chemotherapy was clinically judged as indicated, owing to tumour features suggestive of primary endocrine resistance or immediate surgery, were also excluded. History of diabetes requiring treatment, malabsorption syndrome, and active large or small intestine inflammatory conditions also precluded participation (appendix p 86).

All patients provided written, informed consent before any study-specific procedures were done. The study was done in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and independent institutional ethics committees at all participating hospitals approved the protocol and respective study related documents (appendix p 20).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to taselisib plus letrozole or placebo plus letrozole by stratified permuted blocks (block size of four) by means of a permuted block randomisation algorithm via an interactive voice or web-based response system. After approximately the first 100 patients had been enrolled, *PIK3CA* mutation status of the enrolled patients was evaluated to establish whether the groups were sufficiently balanced, and to assess whether a cap on enrolment of either wild-type or mutant cohorts was required. Neither was deemed necessary, and full enrolment of the trial continued without study modification. Randomisation was stratified by tumour size (T1–T2 *vs* T3) and nodal status (cytologically positive *vs* radiologically or cytologically negative). In this double-blinded study, all patients, sites, principal investigators, Roche-Genentech, Austrian Breast & Colorectal Cancer Study Group, Breast International Group, and SOLTI Breast Cancer Research Group were masked to study treatment assignments. There were no accidental unblindings of any type during the conduct of the trial.

Procedures

A formalin-fixed paraffin-embedded tumour specimen from a core biopsy confirmed as evaluable by a central histopathological laboratory was retrieved from all patients for central analysis of *PIK3CA* mutation status. *PIK3CA* mutation status was established by a central laboratory (HistoGeneX, Belgium) by means of the Roche cobas PIK3CA Mutation Test (Roche Diagnostics; Indianapolis, IN, USA) according to the manufacturer's instructions (appendix p 1). As per protocol, local hormone receptors and HER2 status were assessed for enrolment according to local laboratories' definition. Central assessment was done retrospectively on the basis of international guidelines.[20,21] Concordance between local and central testing for hormone receptor status and HER2 status are shown in the appendix (p 1). Ki67 proliferative index was centrally established by two independent readers blinded to treatment groups

following the recommendations of the International Ki67 in Breast Cancer Working Group.[22]

Patients received letrozole at 2·5 mg once daily orally plus either taselisib at 4 mg or matching placebo on a 5 days-on, 2 days-off schedule orally for a total of 16 weeks. Letrozole, but not taselisib, could be continued up until surgery per investigator's discretion. Patients could discontinue treatment for unacceptable toxicity, loss to follow-up, non-compliance, physician decision, progressive disease, protocol deviation, participant or guardian decision, or death. Up to two dose reductions of taselisib were allowed in case a patient was unable to tolerate the protocol-specified dose as follows: 2 mg at 5 days on, 2 days off, and 2 mg at 3 days on, 4 days off. If the patient continued to have drug-related adverse events (appendix pp 104–112) after the second dose reduction, treatment was permanently discontinued. Once a dose had been reduced, re-escalation was not permitted. No dose modifications were allowed for letrozole.

Before starting study treatment, a breast MRI, ultrasound, and mammogram were done. At weeks 1, 5, 9, 13, and 16, the primary breast tumour and axillary lymph nodes were assessed by clinical breast examination (palpation and calliper measurement). At week 9, a breast ultrasound was done to rule out progressive disease. Suspicion of progressive disease by clinical examination or ultrasound had to be confirmed by investigator-assessed MRI. Patients with primary disease not evaluable by ultrasound at baseline had to be assessed by MRI at week 9. Suspected progression in the lymph nodes also had to be confirmed by needle aspiration when these nodes had not been previously shown to be cytologically positive. Patients with progressive disease could either proceed directly to surgery or were removed from the study, according to the investigator's decision. During week 16, MRI was done for the primary endpoint analysis. Imaging centres received training (appendix pp 151–153) and implemented a specific standardised protocol for all MRI examinations. An independent review facility was used to establish the proportion of patients who achieved an objective response via MRI. Objective response for all assessment modalities was defined by a modified version of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (appendix pp 2–6), in which malignant lymph nodes were assessed as non-target lesions, because size alone might not adequately characterise disease status. Clinical examination, ultrasound, and mammogram were done before surgery in addition to blood sample extractions for the secondary endpoint analyses.

The following laboratory assessments were done locally: haematology, coagulation, fasting serum chemistry, lipid profile, insulin and glucose, glycated haemoglobin (HbA1c), and urinalysis (appendix pp 95–97). Safety monitoring was done at baseline, every 4 weeks, and on week 16 before surgery by laboratory workup, assessments of vital signs, physical examination, 12-lead electrocardiogram, ECOG performance status, and patient-reported outcome questionnaires (European Organisation for the Research and Treatment of Cancer [EORTC] QLQ-C30 and the Modified Breast Cancer module QLQ-BR23) for quality of life. Adverse events were assessed and graded according to Common Terminology Criteria for Adverse Events version 4.0. In addition, patients were contacted by telephone for a general assessment of adverse events at weeks 7 and 11.

A second biopsy was done in week 3 for biomarker analyses. Blood samples for exploratory endpoint analyses were collected on day 1 before dosing, at week 9, before surgery (week 16 visit), and at the 4 weeks post-surgical follow-up visit. Surgery took place after at least 16 weeks of treatment and had to be done within 4 days after the last dose of taselisib, if possible. Delays in surgery owing to toxicity or other safety issues were allowed. Breast and axillary surgery followed local practice. Information on the type of surgery was recorded. Surgical specimens were collected for histological examination to assess for pathological complete response and for other endpoint analyses. The pathological complete response assessment was done

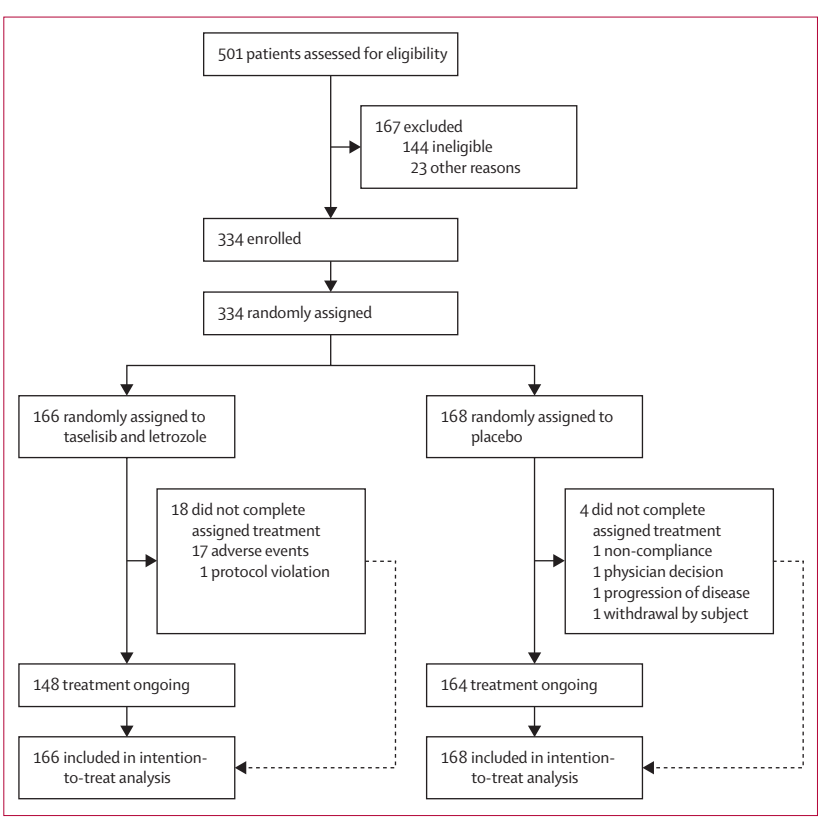

Figure 1: **Trial profile**
For the safety analysis, 167 patients were included in the taselisib plus letrozole group and 167 patients were assessed in the placebo plus letrozole group because one patient assigned to placebo received taselisib by mistake. Patients who did not complete assigned treatment include those who discontinued and ended treatment early.

locally but it was reviewed by the study pathologist who examined for inconsistencies before the final pathological complete response category assignment.

Following surgery, the study protocol did not recommend any adjuvant therapy after the study treatment, but it was deemed that decisions about any further

	All patients in intention-to-treat population		*PIK3CA*-mutant patients		*PIK3CA* wild-type patients	
	Taselisib group (n=166)	Placebo group (n=168)	Taselisib group (n=73)	Placebo group (n=79)	Taselisib group (n=92)	Placebo group (n=89)
Age, years						
Mean (SD)	64·6 (8·5)	64·7 (8·7)	64·8 (9·1)	63·6 (9·0)	64·5 (8·1)	65·6 (8·4)
Median (IQR)	64·0 (57·0–70·0)	63·5 (58·0–73·0)	64·0 (59·0–71·0)	61·0 (59·0–69·5)	64·5 (58·0–72·0)	65·0 (59·0–71·0)
Race						
White	143 (86%)	140 (83%)	65 (89%)	62 (78%)	77 (84%)	78 (88%)
American Indian or Native Alaskan	11 (7%)	11 (7%)	3 (4%)	9 (11%)	8 (9%)	2 (2%)
Asian	6 (4%)	6 (4%)	4 (5%)	4 (5%)	2 (2%)	2 (2%)
Black or African-American	1 (1%)	5 (3%)	0	2 (3%)	1 (1%)	3 (3%)
Other	4 (2%)	6 (4%)	1 (1 %)	2 (3%)	3 (3%)	4 (4%)
Missing	1 (1%)	0	0	0	1 (1%)	0
Ethnicity						
Hispanic or Latino	36 (22%)	48 (29%)	14 (19%)	25 (32%)	22 (24%)	23 (26%)
Not Hispanic or Latino	114 (69%)	109 (65%)	51 (70%)	50 (63%)	62 (67%)	59 (66%)
Not reported	13 (8%)	10 (6%)	6 (8%)	4 (5%)	7 (8%)	6 (7%)
Unknown	3 (2%)	1 (1%)	2 (3%)	0	1 (1 %)	1 (1%)
ECOG performance status score						
0	147 (89%)	146 (87%)	65 (89%)	70 (89%)	81 (88%)	76 (85%)
1	18 (11%)	22 (13%)	8 (11%)	9 (11%)	10 (11%)	13 (15%)
Missing	1 (1%)	0	0	0	1 (1%)	0
Oestrogen receptors Allred score						
0–2	2 (1%)	1 (1%)	0	1 (1 %)	2 (2%)	0
3–8	158 (95%)	161 (96%)	70 (96%)	77 (97%)	88 (96%)	85 (96%)
Missing	6 (4%)	6 (4%)	4 (5%)	2 (3%)	2 (2%)	4 (4%)
Progesterone receptors Allred score						
0–2	13 (8%)	17 (10%)	4 (6%)	6 (8%)	8 (9%)	11 (12%)
3–8	143 (86%)	145 (86%)	64 (88%)	70 (89%)	79 (86%)	76 (84%)
Missing	10 (6%)	6 (4%)	5 (7%)	3 (4%)	5 (5%)	3 (3%)
T stage						
T1	9 (5%)	8 (5%)	3 (4%)	5 (6%)	6 (7%)	3 (3%)
T2	127 (77%)	135 (80%)	61 (84%)	62 (78%)	65 (71%)	73 (82%)
T3	30 (18%)	23 (14%)	9 (12%)	11 (14%)	21 (23%)	12 (13%)
T4	0	2 (1%)	0	1 (1%)	0	1 (1%)
N stage*						
N0	108 (65%)	109 (65%)	47 (64%)	55 (70%)	61 (66%)	54 (61%)
N1	52 (31%)	50 (30%)	23 (32%)	22 (28%)	28 (30%)	28 (31%)
N2	6 (4%)	8 (5%)	3 (4%)	2 (3%)	3 (3%)	6 (7%)
N3	0	1 (1%)	0	0	0	1 (1 %)
Histological grade						
GX	14 (8%)	14 (8%)	11 (15%)	6 (8%)	3 (3%)	8 (9%)
G1	32 (19%)	22 (13%)	14 (19%)	11 (14%)	18 (20%)	11 (12 %)
G2	103 (62%)	104 (62%)	41 (56%)	53 (67%)	61 (66%)	51 (57%)
G3	13 (8%)	22 (13%)	4 (5%)	6 (8%)	9 (10%)	16 (18%)
Missing	4 (2%)	6 (4%)	3 (4%)	3 (4%)	1 (1%)	3 (3%)

(Table 1 continues on next page)

	All patients in intention-to-treat population		*PIK3CA*-mutant patients		*PIK3CA* wild-type patients	
	Taselisib group (n=166)	Placebo group (n=168)	Taselisib group (n=73)	Placebo group (n=79)	Taselisib group (n=92)	Placebo group (n=89)
(Continued from previous page)						
Stage						
Stage I	4 (2%)	6 (4%)	1 (1%)	4 (5%)	3 (3%)	2 (2%)
Stage II	147 (89%)	145 (86%)	67 (92%)	67 (85%)	79 (86%)	78 (88%)
Stage III	15 (9%)	17 (10%)	5 (7%)	8 (10%)	10 (11%)	9 (10%)
Nodal status						
Cytologically positive	52 (31%)	53 (32%)	24 (33%)	23 (29%)	27 (29%)	30 (34%)
Radiologically or cytologically negative	114 (69%)	115 (68%)	49 (67 %)	56 (71%)	65 (71%)	59 (66%)
Ki67 expression						
Data available	150 (90%)	157 (93%)	64 (88%)	75 (95%)	85 (92%)	82 (92%)
Mean, % (SD)	23·3% (18·0)	21·7% (15·8)	20·9% (16·5)	16·6% (11·1)	25·3% (18·9)	26·5% (17·9)
Median, % (IQR)	18·0% (11·0–30·0)	17·0% (10·0–28·0)	15·0% (10·0–29·0)	15·0%(8·0–22·0)	20·0% (12·0–31·0)	21·5% (15·0–35·0)
Missing	16 (10%)	11 (7%)	9 (12%)	4 (5%)	7 (8%)	7 (8%)
<14%	53 (32%)	52 (31%)	27 (37%)	34 (43%)	25 (27%)	18 (20%)
≥14%	97 (58%)	105 (63%)	37 (51%)	41 (52%)	60 (65%)	64 (72%)

Data are n (%) unless stated otherwise. *Including 198 clinical and 136 pathological stages. Numbers in total column include patients with missing mutation status information (one patient assigned to taselisib).

Table 1: **Baseline characteristics**

treatment could be made according to each investigator's discretion following local practice and guidelines. The post-surgery visit marked the end of the study.

Outcomes

The coprimary endpoints for this study were the following: the proportion of patients who achieved an objective response (defined as the percentage of patients with complete or partial responses, and measured by centrally assessed MRI via modified RECIST version 1.1 criteria) in all enrolled patients and in patients with *PIK3CA*-mutant tumours; and the proportion of patients with pathological complete responses in breast and axilla (defined as ypT0/Tis, ypN0) by local evaluation in all enrolled patients and in patients with *PIK3CA*-mutant tumours.

Secondary efficacy objectives were the proportion of patients with *PIK3CA* wild-type tumours who achieved an objective response (centrally assessed), pathological complete responses in breast and axilla by local evaluation in patients with *PIK3CA* wild-type tumours, and the following evaluations in all enrolled patients and separated by *PIK3CA* mutation status: local comparison of objective responses by ultrasound, clinical breast examination, and mammogram; centrally assessed changes in Ki67 index from baseline to week 3, baseline to surgery at week 17–18, after 16 weeks of treatment, and week 3 to surgery; centrally derived Preoperative Endocrine Prognostic Index score; MRI changes in enhancing tumour volume from baseline to surgery; comparison of different definitions of pathological complete response, including ypT0, ypN0 and ypT0/is, ypNX; breast pathological complete response), and safety and quality-of-life assessments. For safety evaluation, the prevalence and severity of adverse events in the taselisib plus letrozole group were compared with the placebo plus letrozole group.

Only the first two secondary efficacy objectives referring to *PI3KCA* wild-type tumours will be reported in this manuscript. The remaining secondary objectives will be reported separately. Exploratory objectives were also defined, focused on translational research to describe the tumour biology and sensitivity or resistance to taselisib. Comparisons of objective responses by ultrasound, clinical breast exam and mammogram before and after treatment (at baseline and at week 16), as well as quality-of-life assessments, and translational endpoints will be reported separately.

Statistical analysis

LORELEI was considered positive if either one of the coprimary endpoints was significant in all enrolled patients and in patients with *PIK3CA*-mutant tumours. Since this was an exploratory phase 2 study focused on the estimation of treatment effects, multiplicity adjustment aimed not to be too restrictive. Therefore, an overall, two-sided, family-wise type I error of 20% was used and was divided within each population into 16% for the proportion of patients who achieved an objective response and 4% for total pathological complete responses. Acknowledging that improvement in objective response is clinically meaningful and that significant improvement in

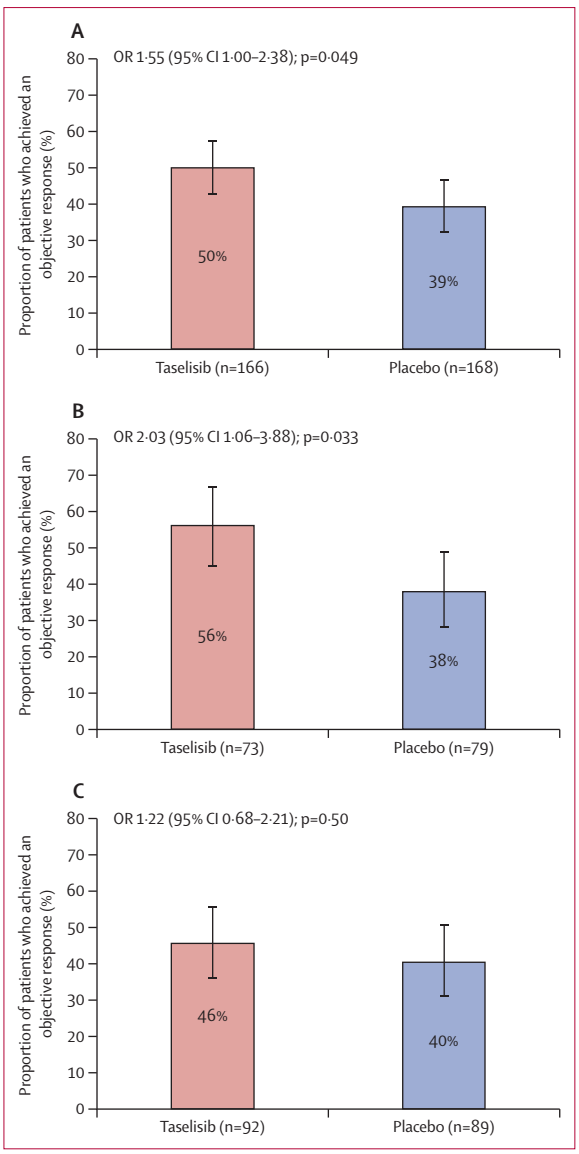

Figure 2: **Objective responses**
Objective responses in all enrolled patients (A), patients with *PIK3CA*-mutant tumours (B), and patients with *PIK3CA* wild-type tumours (C). OR=odds ratio.

pathological complete response is difficult to achieve, more emphasis (4:1) was put on objective response compared with the pathological complete response endpoint, with the goal to detect differences in the proportion of patients with an objective response detectable by MRI given the moderate study sample size. No adjustment for multiple comparisons was done.

The sample size was calculated on a χ^2 test with continuity correction, based on a conservative scenario that assumed that the treatment assignment imbalance in *PIK3CA*-mutant tumour biology and sensitivity or resistance to taselisib was 40% versus 60%.

A sample size of 120 patients in the *PIK3CA*-mutant cohort would allow detection of an absolute percentage increase of 24% (from 40% to 64%, minimal detectable difference 15%; two-sided α=16%) in MRI-assessed objective response (assuming 10% of patients would be unevaluable) and an increase of 18% (from 1% to 19%; minimal detectable difference 13%; two-sided α=4%) in pathological complete response prevalence in all patients, at 80% power for each coprimary endpoint. Overall, 330 patients were required assuming that the prevalence of patients with *PIK3CA* mutations would be 40%.

Efficacy analyses were based on the intention-to-treat population, which comprised all randomly assigned patients. Patients with non-evaluable MRI were classified as non-responders. The coprimary endpoints tumour objective response and pathological complete response were compared by treatment group in all randomised patients and in the *PIK3CA*-mutant population with a Cochran-Mantel-Haenszel test, stratified by tumour size and nodal status or Fisher's exact test, depending on the underlying data distribution. Differences between all randomised and *PIK3CA*-mutant patients were not formally tested. Hence, comparisons are indirect and should be interpreted with caution. Decrease in Ki67 was measured by proportional change and compared between groups with regression models.

Safety analyses were done in all patients who received at least one dose of study treatment. Patients were analysed according to the treatment received. Therefore, patients who wrongly received the study drug at any timepoint were included in the experimental group. Frequencies of adverse events were compared by trial group. An independent data monitoring committee monitored accumulating patient safety data approximately every 6 months after the start of recruitment or more frequently as needed until the last patient had completed study treatment. No interim analyses for efficacy were planned. All analyses were done with SAS (version 9.3). This trial is registered with ClinicalTrials.gov, number NCT02273973, and is closed to accrual follow-up ended at last visit 1 month after surgery.

Role of the funding source

This study was done under an academic–pharma partnership. The funder of the study was involved in the study design, execution, data interpretation, and reviewing the report. The trial was done under an academic collaboration from Breast International Group and all the academic groups and Roche. The agreement was made from the beginning and a contract was signed with all the tasks assigned: data collection, data analysis, and writing of the results report were done by the Austrian Breast and Colorectal Cancer Study Group. The sponsor was blinded to all efficacy data until after the conclusion of the study and top-line readouts were presented. All parties had full access to all the data in the study and had joint responsibility for the decision to submit for publication. The Steering Committee of the LORELEI trial had the final decision to submit to publication.

Results

From Nov 12, 2014, to Aug 12, 2016, 501 patients were assessed for eligibility and 334 patients were enrolled and randomly assigned to treatment with letrozole plus taselisib (166 patients) or placebo (168 patients; figure 1). *PIK3CA* mutation was detected in 152 (46%) patients, 73 (44%) of 166 randomly assigned to taselisib and 79 (47%) of 168 assigned to placebo. Of the 181 (54%) patients without a *PIK3CA* mutation detected, 92 (55%) were randomly assigned to taselisib and 89 (53%) to placebo. One patient with an unknown *PIK3CA* mutation status was randomly assigned to the taselisib group. All patients received at least one dose of study treatment. One patient randomly assigned to placebo received taselisib by mistake; this patient was included in the placebo group for efficacy analyses and the taselisib group for safety analyses. Overall, 312 (93%) patients completed treatment as planned and 22 (7%) discontinued treatment (figure 1).

Baseline characteristics were well balanced between treatment groups (table 1). Most of the patients had T2 stage disease (78%), node-negative disease (65%), and high Ki67 expression (60%) in tumours, defined as baseline Ki67 of more than 14%.

At a median follow-up of 4·9 months (IQR 4·7–5·1), an objective response measured by centrally assessed MRI was recorded in 66 (39%) of 168 patients in the placebo group versus 83 (50%) of 166 patients in the taselisib group (OR 1·55 [95% CI 1·00–2·38], p=0·049; figure 2). In patients with tumours harbouring *PIK3CA* mutations, 30 (38%) of 79 patients in the placebo group versus 41 (56%) of 73 patients in the taselisib group had an objective response (OR 2·03 [95% CI 1·06–3·88], p=0·033; figure 2). Partial responses seemed to be more frequent with taselisib than placebo in patients harbouring *PIK3CA* mutations, although the study was not powered for this comparison (table 2). The proportion of patients with pathological complete responses in the breast and axilla (ypT0/Tis, ypN0) was low and no differences were observed in the overall population (three [2%] patients in the taselisib group *vs* one [1%] in the placebo group; OR 3·07 [95% CI 0·32–29·85], p=0·37) or in patients with *PIK3CA* mutations (one [1%] *vs* none; OR not estimable, p=0·48; figure 3; appendix p 19).

In patients with *PIK3CA* wild-type tumours, there was no significant difference between the treatment groups in the proportion of patients achieving an objective response (36 [40%] of 89 patients in the placebo group *vs* 42 [46%] of 92 patients in the taselisib group; OR 1·22, 95% CI 0·68–2·21; p=0·50; figure 2) or a pathological complete response in the breast and axilla (two [2%] *vs* one [1%]; OR 1·96, 95% CI 0·17–21·96, p=1·00; figure 3).

Ki67 decreased after 3 weeks of treatment in both groups (appendix p 8). No significant differences were observed in the change in Ki67 index between taselisib and placebo treatment, the decrease in the Ki67 value was –85 (95%CI –79 to –89) in patients in the *PI3KCA*-mutant cohort treated with taselisib and –82 (–78 to –87) in the patients in the placebo group; appendix p 8). Ki67 increased from week 3 to surgery in both cohorts (appendix p 8), but 126 (90%) of 140 had stopped taselisib more than 48 h before surgery (median time 11 days; IQR 6–16).

	All patients in intention-to-treat population		*PIK3CA*-mutant patients		*PIK3CA* wild-type patients	
	Taselisib group (n=166)	Placebo group (n=168)	Taselisib group (n=73)	Placebo group (n=79)	Taselisib group (n=92)	Placebo group (n=89)
Complete response	8 (5%)	3 (2%)	5 (7%)	2 (3%)	3 (3%)	1 (1%)
Partial response	75 (45%)	63 (38%)	36 (49%)	28 (35%)	39 (42%)	35 (39%)
Stable disease	67 (40%)	86 (51%)	28 (38%)	39 (49%)	38 (41%)	47 (53%)
Non-complete response/non-progressive disease*	0	1 (1%)	0	1 (1%)	0	0
Progressive disease	6 (4%)	5 (3%)	1 (1%)	3 (4%)	5 (5%)	2 (2%)
Missing, not evaluable	10 (6%)	10 (6%)	3 (4%)	6 (8%)	7 (8%)	4 (4%)

Data are n (%). Numbers in total column include patients with missing mutation status information (one patient assigned to taselisib). *No target lesions (target non-nodal) are identified at baseline due to unability to define margins.

Table 2: **Responses in the intention-to-treat population**

The median number of weeks of drug exposure was near the targeted 16 weeks (15·7 [IQR 15·0–15·7] in the taselisib group; 15·7 [15·4–15·7] in the placebo group), and the median dose intensity of taselisib or placebo was 100% (IQR 99–100) in the taselisib group and 100% (100–100) in the placebo group.

All participants in the taselisib group who achieved a pathological complete response received the full treatment dose, but 11 patients in the taselisib group discontinued letrozole early. Five patients in the placebo group did not receive their complete letrozole treatment owing to adverse events (oedema), including one patient who achieved a pathological complete response. 48 (29%) of 166 patients in the taselisib group had taselisib dose interruptions, and 35 (21%) of 168 patients in the placebo group had placebo dose interruptions. The main reasons were participant non-compliance and adverse events (appendix pp 11–13). Dosing of taselisib was reduced in 19 (11%) patients and in placebo was reduced in 16 patients (10%), mainly owing to adverse events (13 taselisib patients [8%] and five controls [3%]; appendix pp 14–15). Overall, 18 (11%) patients in the taselisib group and four (2%) patients in the placebo group did not complete treatment. Of those patients, 17 (10%) in the taselisib group and none in the placebo group did not complete talelisib treatment owing to adverse events (appendix p 13). One patient in the taselisib group discontinued due to a protocol violation, and four in the placebo group had to permanently discontinue treatment owing to reasons other than adverse events (non-compliance, physician decision, progressive disease, and withdrawal of informed consent).

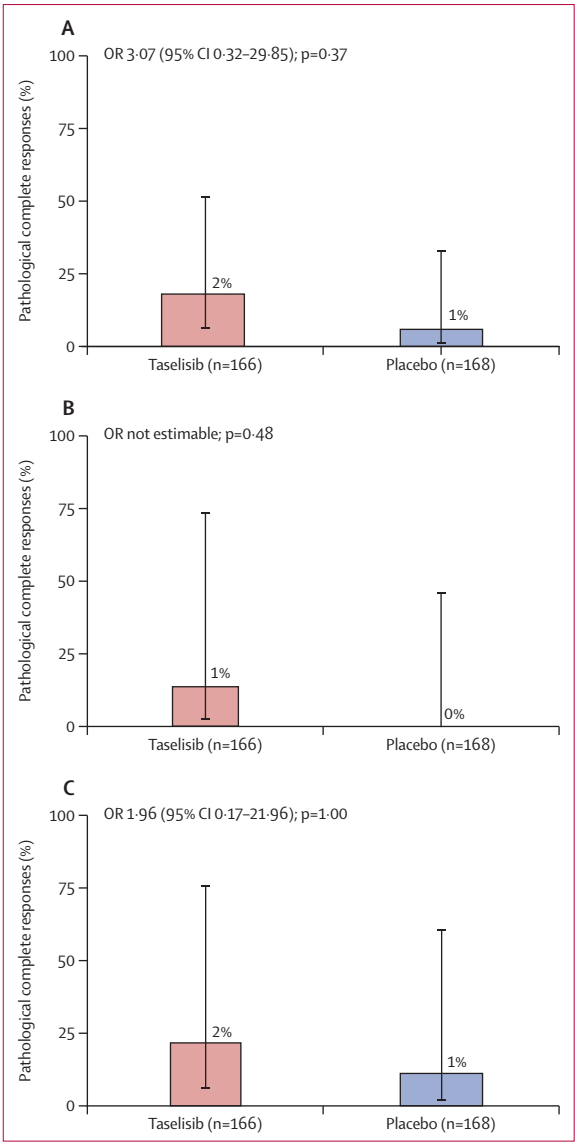

Figure 3: **Pathological complete responses in breast and axilla (ypT0/Tis, ypN0)**
Total pathological complete response by local evaluation in all enrolled patients (A), patients with *PIK3CA*-mutant tumours (B), and patients with *PIK3CA* wild-type tumours (C). OR=odds ratio.

The most common adverse events in the taselisib group were gastrointestinal (diarrhoea, nausea, and stomatitis), fatigue, hyperglycaemia, rash, arthralgia, and hot flush (table 3). These were typically grade 1 or 2 in severity. Grade 3 or worse adverse events occurred in 43 (26%) of 167 patients who received taselisib and 13 (8%) of 167 patients who received placebo (table 3). The most common individual grade 3 or worse adverse events in the taselisib group were diarrhoea, skin and subcutaneous tissue disorders, and infections or infestations (eight patients [5%] with each adverse event). The prevalence of grade 3 or worse adverse events did not exceed 5% for any individual adverse event. There was no grade 4 hyperglycaemia events and grade 3 cases were asymptomatic. In the placebo group, four (2%) of 167 patients had grade 3 or worse vascular disorders, two (1%) had grade 3 or worse gastrointestinal disorders, and two (1%) patients had grade 3 or worse infections and infestations.

Serious adverse events of any cause were more common in the taselisib group (20 [12%] of 167 patients), and were predominantly infections (eight [5%] patients) and gastrointestinal effects (seven [4%] patients) than in the placebo group (four [2%] patients; one patient each with grade 3 postoperative wound and haematoma infection, grade 4 hypertensive encephalopathy, grade 3 acute cardiac failure, and grade 3 breast pain; appendix pp 9–10). One death occurred in the overall population in one patient assigned to the taselisib group—a 73-year old woman with previous medical history of paroxysmal atrial fibrillation, type 2 diabetes, arterial hypertension, hyperlipoproteinaemia, and hyperuricaemia. On day 114, the patient died suddenly and it was believed by the physician who assessed the death not to be related to the study drugs, an autopsy was not done, and a cause was not established.

Discussion

The LORELEI study met one of its coprimary endpoints by showing that the addition of taselisib to letrozole significantly increased the proportion of patients achieving an objective response measured by centrally assessed MRI in ER-positive, HER2-negative postmenopausal patients with early breast cancer. The taselisib effect seemed to be more pronounced in patients whose tumour harboured a *PIK3CA* mutation, however, the 95% CIs overlap to a substantial degree and therefore further research is needed to confirm this. Conversely, we did not observe any difference between the treatments in the proportion of patients achieving a pathological complete response, which was low in both study groups. Overall, adverse events were manageable and consistent with the previously reported toxicity profile of taselisib and more tolerable than the toxicities observed with pan-PI3K inhibitors.[6–8]

PI3K-mTOR inhibition combined with endocrine therapy in advanced breast cancer has shown meaningful clinical benefit in several previous studies, but comparisons between trial outcomes are limited by differences in intrinsic activity and toxicity profiles of PI3K inhinitors, sample sizes, and heterogeneity in endocrine resistance and previous treatments received by the patients included.[6–11,13–15] Short neoadjuvant studies have accurately predicted the outcomes of larger studies in the advanced settings for endocrine and targeted therapies.[3,23] Everolimus plus letrozole as neoadjuvant treatment resulted in more objective responses compared with placebo plus letrozole, although this difference was not significant (68% *vs* 59%, p=0·062),[3] in line with an increase in median progression-free survival in

metastatic breast cancer when everolimus was added to exemestane (6·9 months *vs* 2·8 months, hazard ratio [HR] 0·43; 95% CI 0.35–0.54; p<0·001),[4] which led to the approval of this combination in advanced breast cancer. Similarly, the clinical benefit from the addition of taselisib to endocrine therapy, which increased the proportion of patients with an objective response in the LORELEI study is consistent with the longer progression-free survival with taselisib or placebo plus fulvestrant] reported in the SANDPIPER trial.[10] Hence, the neo-adjuvant model might accelerate the development of drugs and could be a platform for biomarker validation and discovery of primary or acquired mechanisms of drug resistance in breast cancer.[3–5,23]

The study met one of its coprimary endpoints for a significant improvement in objective responses measured by centrally assessed MRI with the addition of taselisib to letrozole in the overall population and in the subset of patients with *PIK3CA*-mutant tumours. In the taselisib group, objective responses and partial responses were higher in patients with tumours harbouring *PIK3CA* mutations than in those with wild-type *PIK3CA* status, which supports the idea that taselisib is potentially more active in *PIK3CA*-mutant tumours and is consistent with data reporting activity of PI3K inhibitors in postmenopausal patients with ER-positive, HER2-negative, metastatic breast cancer. Thus, in the phase 1 trial combining taselisib plus letrozole in this setting, the proportion of patients with *PIK3CA*-mutant tumours achieving an objective response was 40%, compared with just 14% of those with *PIK3CA* wild-type tumours.[14] Similarly, in a single group phase 2 trial of taselisib plus fulvestrant, the proportion of responders in patients with *PIK3CA*-mutant tumours was 42% and of patients with *PIK3CA* wild-type tumours was 14%.[15] The detection of a *PIK3CA* mutation either in plasma ctDNA collected just before the beginning of treatment[6,7] or in archival tumour tissue, or both, has been shown to be predictive of the efficacy of buparlisib combined with fulvestrant in postmenopausal patients resistant to aromatase inhibitors[6] or aromatase inhibitors and everolimus.[5] The SANDPIPER trial, a phase 3 study in ER-positive, HER2-negative, postmenopausal women, showed that addition of taselisib to fulvestrant resulted in the proportion of patients achieving objective responses from 12% to 28% (p=0·002) compared with placebo, and increased progression-free survival from 5·4 months to 7·4 months (HR 0·7 [95% CI 0·56–0·89], p=0·0037) in patients with tumours harbouring *PIK3CA* mutations.[10] The SOLAR-1 trial also showed that the PI3Kαspecific inhibitor alpelisib combined with fulvestrant obtains more objective responses than treatment with fulvestrant alone (36% *vs* 16%, p=0·0002), and also significantly improved progression-free survival in a *PIK3CA*-mutant, ER-positive, HER2-negative, metastatic breast cancer population (11·0 months *vs* 5·7 months, HR 0·65 [95% CI 0·50–0·85]; p=0·00065).[11]

We chose to use objective response by modified RECIST version 1.1 criteria measured by MRI as a coprimary endpoint in the LORELEI trial because MRI is highly accurate for assessing residual tumour size after neoadjuvant therapy compared with clinical palpation, ultrasound, and mammogram.[17,18] As per US Food and Drug Administration recommendations in phase 2 studies, centrally established objective response is preferred over investigator assessment.[24] In two studies with endocrine neoadjuvant therapy, the objective response by MRI varied from 54%[25] to 70%.[26] These results are higher than that those seen in LORELEI, but

	Taselisib group (n=167)				Placebo group (n=167)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Gastrointestinal disorders	79 (47%)	12 (7%)	1 (1%)	0	53 (32%)	2 (1%)	0	0
Diarrhoea	44 (26%)	8 (5%)	0	0	19 (11%)	1 (1%)	0	0
Nausea	34 (20%)	1 (1%)	0	0	19 (11%)	0	0	0
Stomatitis	21 (13%)	1 (1%)	1 (1%)	0	5 (3%)	0	0	0
Abdominal pain	6 (4%)	1 (1%)	0	0	0	0	0	0
Colitis	0	2 (1%)	0	0	0	0	0	0
Enterocolitis haemorrhagic	0	1 (1%)	0	0	0	0	0	0
Haemorrhoids	0	1 (1%)	0	0	0	0	0	0
Pancreatitis	0	1 (1%)	0	0	0	0	0	0
Food poisoning	0	0	0	0	1 (1%)	1 (1%)	0	0
General disorders and administration site conditions	59 (35%)	1 (1%)	0	1 (1%)	66 (40%)	0	0	0
Fatigue	33 (20%)	0	0	0	40 (24%)	0	0	0
Asthenia	17 (10%)	0	0	0	16 (10%)	0	0	0
Impaired healing	0	1 (1%)	0	0	0	0	0	0
Sudden death	0	0	0	1 (1%)	0	0	0	0
Skin and subcutaneous tissue disorders	48 (29%)	7 (4%)	1 (1%)	0	33 (20%)	0	0	0
Rash	13 (8%)	3 (2%)	0	0	5 (3%)	0	0	0
Rash macular	1 (1%)	1 (1%)	0	0	0	0	0	0
Drug eruption	0	1 (1%)	0	0	0	0	0	0
Erythema multiforme	0	0	1 (1%)	0	0	0	0	0
Perivascular dermatitis	0	1 (1%)	0	0	0	0	0	0
Rash erythematous	0	1 (1%)	0	0	0	0	0	0
Metabolism and nutrition disorders	37 (22%)	6 (4%)	0	0	25 (15%)	0	0	0
Hyperglycaemia	24 (14%)	2 (1%)	0	0	12 (7%)	0	0	0
Hypokalaemia	2 (1%)	2 (1%)	0	0	0	0	0	0
Dehydration	0	1 (1%)	0	0	0	0	0	0
Diabetes mellitus	0	1 (1%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	37 (22%)	1 (1%)	0	0	53 (32%)	0	0	0
Arthralgia	19 (11%)	0	0	0	36 (22%)	0	0	0
Myalgia	4 (2%)	1 (1%)	0	0	5 (3%)	0	0	0

(Table 3 continues on next page)

	Taselisib group (n=167)				Placebo group (n=167)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Infections and infestations	30 (18%)	7 (4%)	1 (1%)	0	38 (23%)	2 (1%)	0	0
Postoperative wound infection	0	2 (1%)	0	0	0	1 (1%)	0	0
Erysipelas	0	2 (1%)	0	0	0	0	0	0
Pneumonia	0	1 (1%)	0	0	2 (1%)	0	0	0
Bacterial diarrhoea	0	0	1 (1%)	0	0	0	0	0
Diarrhoea infectious	0	0	1 (1%)	0	0	0	0	0
Gastroenteritis	0	1 (1%)	0	0	0	0	0	0
Wound infection	0	1 (1%)	0	0	0	0	0	0
Influenza	0	0	0	0	3 (2%)	1 (1%)	0	0
Haematoma infection	0	0	0	0	0	1 (1%)	0	0
Vascular disorders	29 (17%)	6 (4%)	0	0	42 (25%)	4 (2%)	0	0
Hot flush	25 (15%)	0	0	0	33 (20%)	0	0	0
Hypertension	5 (3%)	5 (3%)	0	0	7 (4%)	4 (2%)	0	0
Varicose ulceration	0	1 (1%)	0	0	0	0	0	0
Nervous system disorders	32 (19%)	0	0	0	33 (20%)	0	1 (1%)	0
Headache	16 (10%)	0	0	0	18 (11%)	0	0	0
Hypertensive encephalopathy	0	0	0	0	0	0	1 (1%)	0
Investigations	25 (15%)	3 (2%)	1 (1%)	0	12 (7%)	2 (1%)	0	0
Alanine aminotransferase increased	8 (5%)	1 (1%)	0	0	3 (2%)	1 (1%)	0	0
Amylase increased	4 (2%)	2 (1%)	0	0	1 (1%)	0	0	0
Lipase increased	2 (1%)	1 (1%)	1 (1%)	0	2 (1%)	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders	24 (14%)	1 (1%)	0	0	17 (10%)	0	0	0
Pneumonitis	1 (1%)	1 (1%)	0	0	0	0	0	0
Psychiatric disorders	19 (11%)	0	0	0	26 (16%)	0	0	0
Reproductive system and breast disorders	15 (9%)	0	0	0	13 (8%)	1 (1%)	0	0
Breast pain	6 (4%)	0	0	0	7 (4%)	1 (1%)	0	0
Cardiac disorders	4 (2%)	0	0	0	1 (1%)	1 (1%)	0	0
Cardiac failure acute	0	0	0	0	0	1 (1%)	0	0

Data are number of patients (%). Treatment grouping is based on treatment as received, not treatment as randomised. If a single patient had more than one occurrence of a specific system organ class or adverse event, only the occurrence with the highest grade has been included in the table.

Table 3: **Treatment-emergent adverse events of any causality**

there were some differences in response criteria and the treatment period was longer (6 months *vs* 4 months in LORELEI), which might have an effect on response to neoadjuvant endocrine therapy.[27]

Regarding the second coprimary endpoint, pathological complete response was established by local assessment because it is a more common endpoint in neoadjuvant studies and is routinely used in clinical practice. However, sites were asked to complete a pathological complete response evaluation sheet, which was centrally checked by the study pathologist for inconsistencies before a central pathological complete response status was assigned to each patient. Pathological complete responses in breast and axilla were low and owing to the small number of events, no conclusions can be drawn. Pathological complete response correlates with long-term outcomes such as event-free survival after neoadjuvant chemotherapy, but with neoadjuvant endocrine therapy, pathological complete response evidence is anecdotal.[3] We aimed to explore whether the addition of taselisib to letrozole increased the proportion of patients with pathological complete responses with the consequent potential effect on long-term outcomes, on the basis of the sustained partial responses reported in trials which combined taselisib and letrozole or fulvestrant in the metastatic setting.[14,15] Hence, we split the overall alpha error within the two coprimary endpoints (16% for objective response and 4% for total pathological complete response) in order to detect only a large magnitude of benefit in pathological complete response and a smaller benefit in objective response. Importantly, 3–4 months of neoadjuvant endocrine therapy virtually never produces pathological complete responses[27] and one of the limitations of the LORELEI study was the inability to explore this endpoint after a longer period of at least 6 months of therapy.

Reduction in Ki67 after neoadjuvant treatment with aromatase inhibitors is a surrogate marker of suppression of cellular proliferation and correlates with better relapse-free survival.[28] A composite score—the preoperative endocrine prognostic index score derived from Ki67, tumour size, number of axillary lymph nodes, and ER status measured in the surgical specimen after neoadjuvant endocrine therapy—can also be used to distinguish between sensitive and resistant disease as a function of the risk of relapse.[29] Changes in Ki67 at week 3 were higher in subset of patients with *PIK3CA* mutations, but no significant differences were observed between the taselisib and placebo groups.

Most of the patients in the taselisib group with available Ki67 samples (126 [90%] of 140) had stopped taselisib more than 2 days before surgery. Taselisib's half-life is around 40 h, which might explain the increase of Ki67 at time of tissue collection at surgery compared with the week 3 value, and impedes interpretation of the centrally derived Preoperative Endocrine Prognostic Index score. This increase in Ki67 in surgery specimens has been described in other neoadjuvant approaches. The NeoPalAna study[30] was a phase 2 trial that aimed to establish the antiproliferative effect of the CDK4/6 inhibitor palbociclib combined with anastrozole versus anastrozole alone in stage II–III ER-positive, HER2-negative breast cancer. Prevalence of cell cycle arrest (Ki67 ≤2·7%) was higher at 2 weeks of treatment in the palbociclib plus anastrozole group (87% *vs* 26%, p<0·001). Nevertheless, in patients who stopped

palbociclib 1 month before surgery (median 29 days, IQR 8–49), Ki67 was increased at surgery to near baseline amounts, an effect that was reversed when palbociclib was reintroduced immediately before surgery. These observations emphasise the importance of identifying predictive biomarkers after neoadjuvant treatment.

Adverse events were more frequent in the taselisib group than in the placebo group as expected, but the safety profile was generally good. The most common adverse events in the taselisib-treated group were consistent with previous trials with this drug.[10,14,15] Most cases of diarrhoea were grade 1–2 in severity, and were grade 3 in 5% of patients. Overall, diarrhoea was manageable and reversible with dose interruptions and reductions. The prevalence of grade 3 colitis was low at 2%, and no cases of grade 4 gastrointestinal toxicities were observed. Other class-related adverse events, such as hyperglycaemia, stomatitis, and rash, occurred infrequently. Importantly, the prevalence of grade 3 or worse adverse events did not exceed 5% in any case. Adverse events leading to taselisib reduction (8%) or discontinuation (10%) were acceptable and lower than dosing adjustments required in the SANDPIPER (37% and 17%) and SOLAR-1 (up to 62% and 25%) trials, as might be expected with a shorter exposure to treatment. No depression or anxiety were observed in the patients treated with taselisib, in contrast to what has been reported with other PI3K inhibitors.[6,7]

A major limitation of this study is that it was not powered to detect a difference in relapse-free survival between groups. Even so, long-term follow-up is of finite value to assess whether or not the benefit obtained in the proportion of patients who achieved an objective response by MRI translates to better relapse-free survival in ER-positive, HER2-negative populations. Another limitation was the duration of 16 weeks of treatment. This period was chosen on the basis of safety data available at the time of the study design, but a greater benefit might have been obtained with longer exposure to treatment.[27]

In conclusion, this study showed that taselisib increased the efficacy of letrozole in the treatment of newly diagnosed, ER-positive, HER2-negative early breast cancer, in terms of objective response as measured by centrally reviewed MRI, especially in those patients with *PIK3CA*-mutant tumours. The safety profile of the combination is acceptable, and toxicity in the taselisib group was consistent with historical data. Comprehensive biomarker analyses will provide further insight into patient and tumour profiles and correlation with response. Taken together, our results support future investigation of specific PI3K inibitors plus endocrine treatment in ER-positive, HER2-negative breast cancer, especially in patients with *PIK3CA*-mutant tumours.

Contributors

All authors have contributed to a greater or lesser extent to the design of the trial, recruitment of patients, data collection, results interpretation, as well as writing the manuscript.

Declaration of interests

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