Ribociclib Plus Trastuzumab in Advanced HER2-Positive Breast Cancer: Results of a Phase 1b/2 Trial

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Abstract

Preclinical studies have demonstrated that cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors can resensitize HER2-positive breast cancers to anti-HER2 therapies. We conducted a phase 1b/2 study of ribociclib (400 mg per day) plus trastuzumab in heavily pretreated patients with advanced HER2-positive disease. Continuous low-dose ribociclib plus trastuzumab was safe, but only 1 of 12 patients experienced stable disease. These findings suggest that further study of CDK4/6 inhibitor/anti-HER2 combinations should focus on a less pre-treated population.

Background: Signaling through the cyclin-dependent kinase 4 and 6 (CDK4/6) pathway can mediate therapeutic resistance in HER2-positive breast cancer. Preclinical studies have demonstrated that CDK4/6 inhibitors can resensitize resistant HER2-positive breast cancer to anti-HER2 therapies. **Patients and Methods:** We conducted a phase 1b/2 study of ribociclib (400 mg per day on a continuous schedule) plus trastuzumab (6 mg/kg every 3 weeks) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine. There were no restrictions on the number of prior therapy lines. Primary objective was clinical benefit rate at 24 weeks, and secondary objectives included safety, objective response, rate and progression-free survival. The study was enrolled at ClinicalTrials.gov as NCT02657343. **Results:** From March 2016 to March 2017, 13 patients were enrolled. One patient was found to have HER2-negative disease and did not receive treatment. Median number of prior lines in the metastatic setting was 5 (range, 0-14); 67% had hormone receptor–positive disease. No dose-limiting toxicities were observed during the safety run-in phase, and ribociclib was thus dosed at 400 mg per day continuously for the expansion cohort. Grade 3 adverse events were observed in 4 patients (33.3%) and included neutropenia ($n = 2$) as well as fatigue and pain in 1 patient each. No grade 4/5 adverse events or QTc prolongation were observed. One patient (8.3%) experienced stable disease > 24 weeks; no objective responses were observed, and median progression-free survival was 1.33 months (95% confidence interval, 0.92-2.57). **Conclusion:** Continuous low-dose ribociclib (400 mg) plus trastuzumab is safe, with no new safety concerns. The limited activity observed in this study suggests that further study of CDK4/6 inhibitor/anti-HER2 combinations should focus on a less pretreated population.

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Introduction

Despite outstanding improvements in survival with the introduction of anti-HER2 therapies in the treatment of advanced HER2-positive breast cancer,[1-3] most tumors ultimately develop therapeutic resistance, leading to disease progression. To date, there is no standard of care treatment for patients with advanced HER2-positive tumors with disease progression despite treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1). Treatment options in this setting include lapatinib plus capecitabine, combinations of trastuzumab with other chemotherapies, or chemotherapy-free regimens including combinations of trastuzumab and/or lapatinib, with concomitant endocrine therapy for patients with hormone receptor (HR)-positive disease. A better understanding of the underlying mechanisms of resistance to anti-HER2 therapy is essential for the development of new strategies to further improve patient outcomes.[4]

Ribociclib is an orally bioavailable, highly selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor that has demonstrated antiproliferative activity, particularly in HR-positive cell lines. It demonstrates in vitro drug concentration causing 50% inhibition for CDK4/6 of approximately 10 and 40 nM, respectively.[5] The US Food and Drug Administration initially approved ribociclib to be used in combination with an aromatase inhibitor as first-line endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer, based on the results of the phase 3 MONALEESA-2 study.[6] More recently, on the basis of the results of other phase 3 trials, the US Food and Drug Administration has expanded ribociclib's indication in HR-positive, HER2-negative advanced breast cancer to include the treatment of pre- or perimenopausal women (together with ovarian function suppression) and to be used in combination with fulvestrant as initial or second-line treatment.[7,8] The currently approved ribociclib dose schedule is a starting dose of 600 mg daily provided for the first 21 consecutive days of a 28-day cycle.

Notably, cyclin D1 lies downstream of HER2-signaling and the cyclin D1−CDK4 axis plays an important role in the initiation and growth of HER2-driven breast cancers.[9] Moreover, preclinical studies have demonstrated synergy between anti-HER2 therapy and CDK4/6 inhibitors in HER2-positive cancers that are resistant to anti-HER2 treatments.[10-12] Our group has described that tumor cells surviving HER2-blockade retain high expression of cyclin D1 and targeting these cells with CDK4/6 inhibitors resensitizes them to anti-HER2 therapy not only by reducing retinoblastoma phosphorylation but also by suppressing mTORC1/S6K/S6RP activity and increasing tumor cell dependence on the epidermal growth factor receptor family kinases.[10] Furthermore, the combination of anti-HER2 therapy and CDK4/6 inhibition is more potent than either agent alone, as demonstrated in transgenic mouse models of inducible HER2-driven mammary carcinomas.[10] As such, there is a strong rationale to assess the activity of CDK4/6 inhibitors in HER2-positive breast cancers.[13]

Limited clinical data exist regarding the combination of CDK4/6 and HER2 inhibition in HER2-positive breast cancer. However, early results from ongoing clinical trials suggest that the combination is clinically active, especially in patients with HER2-positive, HR-positive disease.[14-16]

To explore the relevance of these biological findings in the clinical arena, we conducted a phase 1b/2 clinical trial to assess the safety and efficacy of ribociclib (LEE011) in combination with trastuzumab or T-DM1 in patients with advanced HER2-positive breast cancer (NCT02657343). Here, we present the results of the ribociclib plus trastuzumab cohort. In addition, a continuous daily dosing of ribociclib was selected in this study to be combined with anti-HER2 therapy. Continuous low dose of ribociclib at 400 mg demonstrated both preliminary activity and a manageable safety profile when combined with fulvestrant compared to an intermittent dose of ribociclib in the treatment of patients with HR-positive, HER2-negative advanced breast cancer.[17] The rationale for dosing at 400 mg daily continuously instead of on the 600 mg daily 3 weeks on−1 week off schedule was to prevent a break in therapy that could potentially allow cancer cells to escape cell-cycle arrest and to reduce rates of toxicity, including neutropenia and risk of cardiac toxicity, when combined with anti-HER2 therapy.

Patients and Methods

Study Design and Treatment Plan

We conducted an open-label phase 1b/2 clinical trial designed to assess the safety and activity of ribociclib in combination with anti-HER2 therapies among women with metastatic or locally advanced treatment-refractory HER2-positive breast cancer. In this study, there were two separate cohorts: one cohort of ribociclib provided in combination with T-DM1 (cohort A) and another cohort of ribociclib in combination with trastuzumab (cohort B). Here we report the results of cohort B.

The phase 1b component assessed the safety of ribociclib in combination with trastuzumab in 6 patients, and a de-escalation design was included to establish the maximum tolerated dose. Patients received intravenous trastuzumab (6 mg/kg 3 weekly with a loading dose of 8 mg/kg in cycle 1) and ribociclib at 400 mg by mouth daily on a continuous schedule for a 21-day cycle of treatment. Accrual was paused after the first 6 patients had been enrolled onto the study, and observation of these patients continued until all 6 had completed 1 cycle of therapy (3 weeks) and had been assessed for dose-limiting toxicities during that cycle. Treatment was continued until radiographic or symptomatic progression, unacceptable toxicity, or withdrawal of informed consent.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP) and the Declaration of Helsinki, approved by Dana-Farber Cancer Institute's institutional review board, and registered at ClinicalTrials.gov (NCT02657343). All patients provided written informed consent before the initiation of any study-related treatment or procedures.

Patient Population

Patients aged ≥ 18 years with histologically confirmed unresectable, locally advanced, or metastatic HER2-positive breast cancer and measurable disease per response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were eligible.[18] HER2 positivity was defined by 3+ staining by immunohistochemistry or by fluorescence in-situ hybridization amplification, in accordance to the 2013 American Society of Clinical

Table 1 Characteristics of 12 Patients

Characteristic	Value
Age (y)	51 (42-72)
White race/ethnicity	12 (100%)
ECOG Performance Status	
0	10 (83%)
1	2 (17%)
ER and/or PR positive	8 (67%)
No. of metastatic sites	4 (1-4)
Previous Therapy in Any Setting	
Trastuzumab	12 (100%)
Pertuzumab	12 (100%)
T-DM1	12 (100%)
No. of prior lines of systemic therapy for metastatic disease	5 (0[a]-14)
No. of prior chemotherapies for metastatic disease	4 (0[a]-11)

Data are presented as n (%) or median (range).
Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = progesterone receptor; T-DM1 = trastuzumab emtansine.
[a]This patient had received trastuzumab/pertuzumab and T-DM1 for early-stage disease.

Oncology–College of American Pathologists guidelines.[19] All patients must have received prior trastuzumab, pertuzumab, and T-DM1 as (neo)adjuvant or metastatic therapy, and there was no limit on the number of prior lines of treatment. The protocol required patients to have an Eastern Cooperative Oncology Group performance status of ≤ 2; adequate bone marrow, liver, and renal function; a left ventricular ejection fraction of at least 50% (determined by echocardiography or multiple-gated acquisition multigated acquisition scan) at screening; adequate contraception; and a negative pregnancy test for women of childbearing potential. Patients with previous CDK4/6 inhibitor exposure, QTcF > 450 ms, or unstable brain metastases were excluded.

Statistical Analysis

This was a single-arm nonrandomized trial. The primary objective was to assess the clinical benefit rate (defined as the proportion of patients with complete response, partial response, and stable disease at 24 weeks) with ribociclib in combination with trastuzumab. Secondary end points included objective response rate (defined as complete plus partial response) and progression-free survival (defined as the time from the date of the first dose of study treatment to the date of objectively determined progressive disease or death from any cause, whichever occurred first). For patients not known to have disease that progressed or who died as of the data cutoff date, progression-free survival was censored at the date of the last objective progression free assessment before the initiation of a new anticancer therapy. Another secondary objective was the assessment of adverse events (AEs), including a specific 6 patient safety run-in phase to evaluate the maximum tolerated dose for continuously dosed ribociclib in conjunction with trastuzumab.

We proposed that a clinical benefit rate at 24 weeks of 45% among patients with advanced breast cancer would be considered worthy of further study, and that a rate of 24% or less would not be of clinical interest (null hypothesis). The expansion cohort (ie, all patients enrolled after the 6 patient safety run-in) used a Simon 2-stage design: the first stage was designed to enroll 20 patients, and 6 of these patients were required to demonstrate clinical benefit (complete response + partial response + stable disease > 24 weeks) in order proceed to the second stage, where a further 15 patients would be recruited. The sample size was chosen to have a high power (90%) and a type I error rate of no more than 10%. The time to event variables were analyzed using the Kaplan-Meier estimator. Demographics, baseline characteristics, and AEs were summarized among patients who received at least one dose of either ribociclib or trastuzumab.

Table 2 Adverse Events According to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03

	Grade, N (%)		
Adverse Event	**1**	**2**	**3**
Fatigue	5 (42%)	3 (25%)	1 (8%)
Neutropenia	2 (17%)	1 (8%)	2 (17%)
Anemia	2 (17%)	1 (8%)	0
Nausea	4 (33%)	0	0
Headache	0	3 (25%)	0
Vomiting	2 (17%)	0	0
Anorexia	1 (8%)	1 (8%)	0
Dyspnea	1 (8%)	2 (17%)	0
Rash	2 (17%)	0	0
Pain	1 (8%)	1 (8%)	1 (8%)

No grade 4 toxicities were observed.

Safety and Efficacy Assessments

Tumors assessments were performed every 2 cycles (6 weeks) until disease progression or cycle 8, and then every 3 cycles with the same imaging modality as screening. Response and progression were evaluated using the new international criteria proposed by the RECIST guideline (version 1.1). AEs were graded accordingly to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Results

Between March 2016 and March 2017, a total of 13 patients were enrolled onto this cohort of the study. One patient was found to have HER2-negative disease, so therefore only 12 patients initiated protocol therapy (6 patients in the phase 1b part and 6 in the phase 2). In March 2017, the accrual for this study cohort was closed early because of the limited clinical activity observed.

Baseline patient and disease characteristics are listed in Table 1. Overall, median age at inclusion was 51 years old (range, 42-72 years), and most patients (67%) had HR-positive disease. The median number of prior lines of systemic therapy for metastatic disease was 5 (range, 0-14).

No dose-limiting toxicities were observed during the safety run-in phase, and ribociclib was thus dosed at 400 mg by mouth daily on a continuous schedule for the expansion cohort. Regarding dose modifications, 4 patients (33.3%) required a hold in ribociclib treatment as a result of grade 3 AEs; however, only one of these required dose reduction of ribociclib in a subsequent treatment

Table 3 Best Response of 12 Subjects by RECIST 1.1

Characteristic	N (%)
Complete response	0
Partial response	0
Stable Disease	
< 12 wk	1 (8.3%)
12-24 wk	1 (8.3%)
> 24 wk	1 (8.3%)
Progressive disease+	9 (75%)

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors.

cycle. No patient discontinued or held trastuzumab. The main reason for treatment discontinuation was progressive disease in 11 patients (91.7%); one patient withdrew from the study.

Table 2 lists all toxicities or AEs, most of which were grade 1 or 2. Grade 3 toxicities were observed in 4 patients (33.3%) and included neutropenia in 2 patients (17%), and fatigue and pain in 1 patient each (8%). There were no grade 4 or greater events. No patient demonstrated a significant decrease in left ventricular ejection fraction (< 50%), QTc prolongation > 480 ms, or grade 3/4 increase of liver function tests.

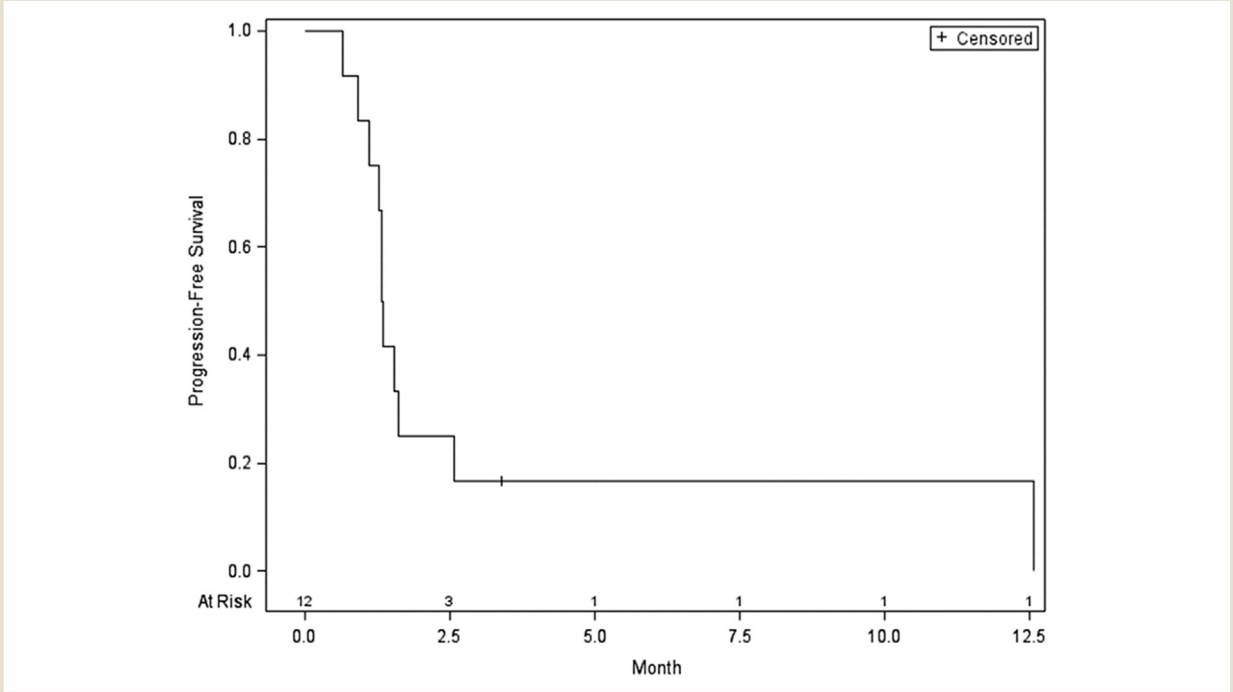
Regarding efficacy, of the 12 patients included in the study, only one (8.3%; 95% confidence interval, 0.4-5.4) experienced stable disease > 24 weeks. This patient had HR-positive/HER2-positive disease and a median of 10 prior lines in the metastatic setting, including several lines of endocrine therapy plus trastuzumab. After a median follow-up of 5 months, no objective responses were observed (Table 3), and median progression-free survival was 1.33 months (95% confidence interval, 0.92-2.57) (Figure 1).

Discussion

In this phase 1/2b study, continuous daily dosing of ribociclib at 400 mg in combination with trastuzumab was well tolerated, and no new safety concerns arose. To our knowledge, this is the first report evaluating ribociclib activity in combination with anti-HER2 therapy in advanced HER2-positive breast cancer. The toxicity profile of ribociclib is similar to that of palbociclib, with neutropenia and thrombocytopenia being the most frequent grade 3/4 AEs in large trials.[6] Transaminitis has also been observed with ribociclib, with grade 3/4 aspartate aminotransferase and alanine aminotransferase elevations occurring in 5% to 10% of patients when ribociclib is provided with endocrine therapy. We did not observe any grade 2 or higher transaminitis, possibly due to lower dosing of ribociclib (400 mg), as liver function test increase with ribociclib appears to be dose dependent. Moreover, we did not observe any episodes of QTc prolongation of > 480 ms or left ventricular dysfunction in this small cohort of patients, which is reassuring, given that both ribociclib and trastuzumab have known cardiotoxic properties (albeit through different mechanisms). Results from ongoing studies exploring daily dosing of ribociclib at 400 mg, including a phase 3 trial evaluating the efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment in patients with HR-positive, HER2-negative early breast cancer (NCT03701334), are awaited.

In our study, the activity of ribociclib in combination with trastuzumab was limited. Only one patient derived clinical benefit

Figure 1 Progression-Free Survival After Median Follow-Up of 5 Months, Median Progression-Free Survival was 1.33 Months (95% Confidence Interval, 0.92-2.57)



lasting over 24 weeks, and no objective responses were seen. On account of these results, we chose to close accrual to this cohort early. The lack of efficacy might be explained by several factors. First, patients included in this study were heavily pretreated, with a median of 4 prior lines of chemotherapy received in the metastatic setting. Thus, it appears that, as is seen with other targeted therapies, responses to CDK4/6 inhibitors are also less likely in heavily pretreated patients even though these agents target more fundamental drivers of cell division. Second, endocrine therapy was not permitted in patients with HR-coexpressing tumors in this study. Patients with HR-positive tumors comprised 67% of the study cohort, and given the existence of bilateral cross talk between the estrogen receptor and HER2 pathways and that estrogen receptor blockade is likely important when utilizing CDK4/6 inhibitors, this could potentially contribute to the lack of response observed in the study. Third, we included patients with HR-negative disease. Although definitive data are not available, preliminary reports suggest that CDK4/6 inhibitor activity in HER2-positive breast cancer is mainly restricted to HR-positive tumors.[14,20] For example, initial results from the phase 2 SOLTI-1303 PATRICIA trial (NCT02448420), which evaluates the combination of palbociclib and trastuzumab with or without letrozole in pretreated HER2-positive breast cancer patients, suggest that the combination is active, particularly in luminal tumors (as assessed by PAM50 subtyping), which are more likely to be HR positive.[15,20] Moreover, in the neoadjuvant setting, the phase 2 open-label NA-PHER trial[16] explored the combination of trastuzumab, pertuzumab, palbociclib, and fulvestrant in patients with HER2-positive, HR-positive breast cancer in the neoadjuvant setting.[16] This chemotherapy-free regimen induced a significant decrease of Ki-67 expression at 2 weeks and at surgery (primary end point), and notably, 27% of patients experienced a pathologic compete response in breast and nodes. These results, together with the preclinical data supporting dual inhibition of CDK4/6 and HER2, support ongoing efforts exploring this approach. Currently, there are other clinical trials evaluating the role of CDK4/6 inhibitors in advanced HER2-positive breast cancer, including 2 global randomized trials. The phase 2 MonarcHER study (NCT02675231) evaluates the role of abemaciclib in combination with trastuzumab with or without fulvestrant in pretreated metastatic disease, and the phase 3 PATINA study (NCT02947685) explores the benefits of adding palbociclib to first-line trastuzumab, pertuzumab and an aromatase inhibitor (after standard induction therapy with chemotherapy, trastuzumab, and pertuzumab). Both studies are restricted to patients with HR-positive tumors. Other ongoing investigator-initiated trials are evaluating the combination of palbociclib plus TDM-1 (NCT03530696) and tucatinib plus palbociclib and letrozole (NCT03054363).

In conclusion, we describe for the first time the activity of ribociclib, a CDK4/6 inhibitor, at a daily continuous dose of 400 mg in combination with trastuzumab in advanced HER2-positive breast cancer. In this cohort, it appears that continuous daily dosing of ribociclib at 400 mg is feasible and safe. The limited activity observed in this study suggests that further study of CDK4/6 inhibitor/anti-HER2 combinations should focus on a less pretreated population.

Clinical Practice Points

- Signaling through the CDK4/6 pathway can mediate therapeutic resistance in HER2-positive breast cancer. Preclinical studies have demonstrated that CDK4/6 inhibitors can resensitize resistant HER2-positive breast cancer to anti-HER2 therapies.
- Limited clinical data exist regarding the combination of CDK4/6 and HER2 inhibition in advanced HER2-positive breast cancer.
- We conducted a phase 1b/2 study of ribociclib plus trastuzumab in patients with advanced HER2-positive disease previously treated with trastuzumab, pertuzumab, and T-DM1.
- Combining continuous low-dose ribociclib (400 mg per day) plus trastuzumab is safe, but limited activity was observed in a patient population with a median of 5 prior lines of therapy in the metastatic setting.
- These findings suggest that further study of CDK4/6 inhibitor/anti-HER2 combinations in advanced HER2-positive breast cancer should focus on a less pretreated population.
- Although there have been some previous reports, to our knowledge, this is the first report of the activity of a CDK4/6 inhibitor plus trastuzumab in advanced HER2-positive breast cancer.

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