Neoadjuvant atirmociclib plus letrozole versus letrozole alone in HR+/HER2– breast cancer: results from FourLight-2, a randomized phase 2 window of opportunity study

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Objective

- To evaluate the effects of atirmociclib + letrozole and letrozole alone on Ki-67 expression in HR+/HER2– breast cancer tumors after 14 days of treatment in the preoperative (neoadjuvant) setting (FourLight-2).

Conclusion

- Atirmociclib + letrozole demonstrated substantially greater antiproliferative effects than letrozole alone, with a tolerable safety profile in patients with HR+/HER2– breast cancer, suggesting that atirmociclib + letrozole may have therapeutic value in early breast cancer.

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Poster

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Abstract PLS

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Background

- In the neoadjuvant setting, endocrine therapy is a standard of care option in patients with HR+/HER2– breast cancer.[1]
- Atirmociclib (PF-07220060) is a potent and selective CDK4 inhibitor and has shown favorable tolerability and promising early activity as a first-line treatment in patients with HR+/HER2– metastatic breast cancer.[2]
- CDK4 selectivity limits hematologic and gastrointestinal toxicities that may be dose limiting. As atirmociclib allows for greater CDK4 target coverage, it results in deeper antitumor responses in vitro with the potential of reducing toxicities.[3]
- Ki-67 is a biomarker used to assess the antiproliferative activity of anti-cancer therapies.[4]
- Complete cell cycle arrest (CCCA, defined as Ki-67-positive tumor cells ≤2.7%) in the neoadjuvant setting is correlated with reduced breast cancer tumor recurrence.[5,6]

Methods

STUDY DESIGN AND TREATMENTS

- This window-of-opportunity study was an international (13 countries), phase 2, open-label, randomized trial (FourLight-2; NCT06465368; **Figure 1**).
- Postmenopausal women with newly diagnosed, histologically confirmed HR+/HER2– breast cancer who received no prior systemic therapy and Ki-67 score of ≥10% (locally-assessed), primary tumor size ≥1.5 cm, and ECOG PS 0 or 1 were enrolled.
- Patients with prior and/or current systemic therapy (eg, chemotherapy or hormonal therapy), radiation, surgery, or any investigational agents for the treatment of breast cancer were excluded.
- Breast lesion biopsies were performed prior to treatment (baseline) and on day 14 of treatment (on-treatment).
- Eligible patients were randomly assigned 1:1 to atirmociclib (300 mg, orally twice daily) + letrozole (2.5 mg, orally once daily) or letrozole alone (2.5 mg, orally once daily), for 14 days.

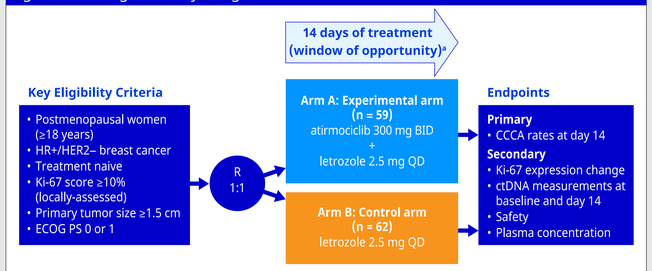
ASSESSMENTS

- The primary endpoint was centrally-assessed CCCA rate at day 14.
- Secondary endpoints included tumor Ki-67 expression change (centrally-assessed), ctDNA assessments, safety, and PK.
- Tumor Ki-67 expression was centrally assessed by immunohistochemistry (IHC).

STATISTICAL ANALYSIS

- Participants with evaluable Ki-67 results from baseline (locally or centrally-assessed) and day 14 (centrally assessed) visits were included in the primary analysis.
- No formal hypotheses for treatment effects were tested in this study.
- The rate of patients with CCCA in each group was calculated along with the 2-sided 95% confidence interval (CI). Bayesian analyses were performed to assess the CCCA rates using posterior probabilities.

Figure 1. FourLight-2 study design



[a]After day 14, patients received physician's choice of standard of care.
BID, twice daily; CCCA, complete cell cycle arrest; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; QD, once daily.

Results

PATIENTS

- 121 patients were randomized to atirmociclib + letrozole (n = 59) or letrozole alone (n = 62).
- Median age was 66 years for atirmociclib + letrozole and 63 years for letrozole alone; the proportion of patients with tumor grade 1/2 was 75% for the atirmociclib + letrozole arm and 81% for the letrozole alone arm (**Table 1**).
- Median duration of treatment was 15.0 days (range, 14–17) for atirmociclib and 15.0 days (range, 13–17) for letrozole in the atirmociclib + letrozole arm and 15.0 days (range, 10–16) for the letrozole alone arm.

Table 1. Patient demographics and characteristics

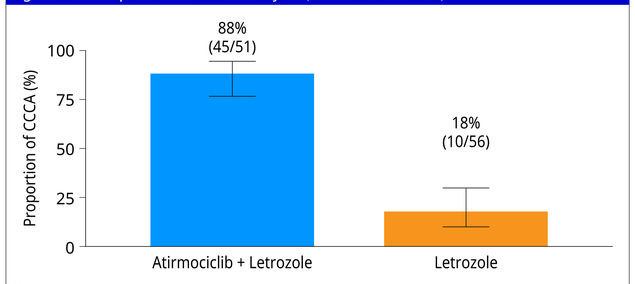
Characteristics	Atirmociclib + Letrozole (n = 59)	Letrozole (n = 62)	Total (N = 121)
Age, years			
Median (range)	66 (51–82)	63 (52–82)	65 (51–82)
<65, n (%)	25 (42.4)	34 (54.8)	59 (48.8)
≥65, n (%)	34 (57.6)	28 (45.2)	62 (51.2)
Race, n (%)			
White	49 (83.1)	41 (66.1)	90 (74.4)
Asian	2 (3.4)	3 (4.8)	5 (4.1)
Black or African American	0	2 (3.2)	2 (1.7)
American Indian/Alaska Native	1 (1.7)	0	1 (0.8)
Unknown	2 (3.4)	4 (6.5)	6 (5.0)
Not reported	5 (8.5)	12 (19.4)	17 (14.0)
ECOG PS, n (%)			
0	49 (83.1)	58 (93.5)	107 (88.4)
1	10 (16.9)	4 (6.5)	14 (11.6)
Ki-67 absolute value (central)			
<10%	5 (8.5)	5 (8.1)	10 (8.3)
≥10% to <20%	7 (11.9)	11 (17.7)	18 (14.9)
≥20%	44 (74.6)	43 (69.4)	87 (71.9)
Non evaluable	3 (5.1)	3 (4.8)	6 (5.0)
Histologic classification			
Invasive ductal carcinoma	39 (66.1)	45 (72.6)	84 (69.4)
Invasive lobular carcinoma	12 (20.3)	9 (14.5)	21 (17.4)
Other	8 (13.6)	8 (12.9)	16 (13.2)
Tumor histology grade			
Grade 1	9 (15.3)	8 (12.9)	17 (14.0)
Grade 2	35 (59.3)	42 (67.7)	77 (63.6)
Grade 3	12 (20.3)	12 (19.4)	24 (19.8)
Grade X	3 (5.1)	0	3 (2.5)
TNM stage			
Stage I	16 (27.1)	22 (35.5)	38 (31.4)
Stage II	37 (62.7)	35 (56.5)	72 (59.5)
Stage III	6 (10.2)	5 (8.1)	11 (9.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor, nodes, metastasis.

Ki-67 RESULTS

- A total of 51 patients in the atirmociclib + letrozole arm and 56 patients in the letrozole arm were included in the Ki-67 evaluable analysis set; of these, 77% and 70% had Ki-67 ≥20% at baseline (centrally assessed).
- At day 14, the proportion of patients who achieved CCCA was 88.2% (95% CI, 76.6–94.5) in the atirmociclib + letrozole arm, which was substantially higher than 17.9% (95% CI, 10.0–29.8) in the letrozole arm (**Figure 2**).
- At day 14, the median absolute change from baseline for Ki-67 was -30.1% (range, -96.8, 14.7) for the atirmociclib + letrozole arm and -17.3% (range, -56.7, 14.1) for the letrozole alone arm (**Figure 3**).
- At day 14, the median relative change from baseline for Ki-67 was -97.3% (range, -99.8, 34.0) for the atirmociclib + letrozole arm and -72.4% (range, -98.3, 139.9) for the letrozole alone arm.
- Proportion of patients with CCCA at day 14 in each subgroup was consistently higher in the atirmociclib + letrozole arm than in the letrozole arm (**Table 2**).

Figure 2. Participants with CCCA at day 14 (Ki-67 evaluable set)



CCCA, complete cell cycle arrest.

Figure 3. Absolute Ki-67 value at baseline and day 14 (Ki-67 evaluable set)

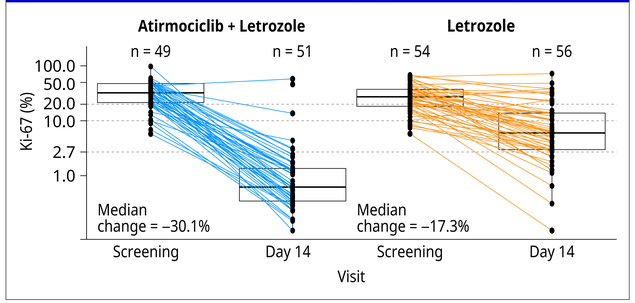


Table 2. Frequency of CCCA by subgroup (Ki-67 evaluable set)

	Atirmociclib + Letrozole (n = 51)		Letrozole (n = 56)	
	N	n (%)	N	n (%)
Tumor grade				
1/2	36	32 (88.9)	45	9 (20.0)
3/X	15	13 (86.7)	11	1 (9.1)
Histological classification				
Invasive ductal carcinoma	33	30 (90.9)	42	8 (19.0)
Other	18	15 (83.3)	14	2 (14.3)
TNM stage				
Stage I	14	11 (78.6)	20	3 (15.0)
Stage II	31	29 (93.5)	32	6 (18.8)
Stage III	6	5 (83.3)	4	1 (25.0)
Primary tumor stage				
T1c	15	12 (80.0)	19	2 (10.5)
T2	30	28 (93.3)	32	7 (21.9)
T3/T4	6	5 (83.3)	5	1 (20.0)
Regional lymph nodes stage				
N0	36	30 (83.3)	43	8 (18.6)
N1/N2/N3	15	15 (100)	13	2 (15.4)
Progesterone receptor				
Positive (≥1%)	49	43 (87.8)	51	9 (17.6)
Negative (<1%)	2	2 (100)	5	1 (20.0)
Baseline Ki-67 (central)				
<20%	10	9 (90.0)	15	4 (26.7)
≥20%	39	35 (89.7)	39	6 (15.4)

CCCA, complete cell cycle arrest; TNM, tumor, nodes, metastasis.

SAFETY

- The most common TEAEs were diarrhea (18.6%), fatigue (15.3%), and nausea (13.6%) in the atirmociclib + letrozole arm and headache (11.3%), fatigue (9.7%), and hot flush (9.7%) in the letrozole alone arm.
- Most TEAEs were grade 1/2 in severity; no grade 3/4 treatment-related TEAEs were reported.
- No treatment discontinuations due to TEAEs were reported.

Table 3. TEAEs in ≥5% of patients

	Atirmociclib + Letrozole (n = 59)			Letrozole (n = 62)		
TEAE, n (%)	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any	22 (37.3)	0	0	16 (25.8)	0	0
Diarrhea	11 (18.6)	0	0	1 (1.6)	0	0
Fatigue	9 (15.3)	0	0	6 (9.7)	0	0
Nausea	8 (13.6)	0	0	3 (4.8)	0	0
Arthralgia	4 (6.8)	0	0	4 (6.5)	0	0
Leukopenia	3 (5.1)	0	0	0	0	0
Headache	2 (3.4)	0	0	7 (11.3)	0	0
Hot flush	2 (3.4)	0	0	6 (9.7)	0	0

TEAE, treatment-emergent adverse event.

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