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Authors

Sedrak, Mina S
Lee, Minji K
Ji, Jingran
et al.

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Palbociclib in adults aged 70 years and older with advanced breast cancer: A phase 2 multicenter Ttrial (Alliance A171601)

Mina S. Sedrak, MD, MS[1], **Minji K. Lee, PhD, MS**[2], **Jingran Ji, MD**[3], **Daniel V. Satele, MS**[2], **Rachel A. Freedman, MD, MPH**[4], **Philip D. Poorvu, MD**[4], **Tracey O'Connor, MD**[5], **Grant R. Williams, MD, MSPH**[6], **Judith O. Hopkins, MD**[7], **Hyman B. Muss, MD**[8], **Harvey Jay Cohen, MD**[9], **Ann H. Partridge, MD**[4], **Lisa A. Carey, MD**[8], **Selina L. Chow, MD**[10], **Niveditha Subbiah, LLM, MA**[10], **Jennifer Le-Rademacher, PhD**[2], **Aminah Jatoi, MD**[11]

[1]Department of Medicine, UCLA David Geffen School of Medicine, Los Angeles, CA

[2]Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN

[3]Department of Medical Oncology & Therapeutics Research, City of Hope, Duarte, CA

[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

[5]Department of Breast Oncology, Moffitt Cancer Center, Tampa, Florida, USA.

[6]Department of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL

[7]SCOR/NCORP/Novant Health Cancer Institute, Winston-Salem, NC

[8]Department of Medicine, University of North Carolina, Chapel Hill, NC

[9]Department of Medicine, Duke University School Medical Center, Durham, NC

[10]Alliance Protocol Operations Office, Chicago, IL

[11]Department of Oncology, Mayo Clinic, Rochester, MN

Abstract

Introduction: Palbociclib is a widely used treatment for advanced breast cancer in older adults. However, the existing evidence regarding its safety and tolerability in this age group is inconsistent and limited to retrospective subgroup or pooled analyses.

Materials and Methods: We conducted a prospective single-arm multicenter phase 2 study to evaluate the safety and tolerability of palbociclib in participants aged 70 years or older

Corresponding Author: Mina S. Sedrak, MD, MS, UCLA David Geffen School of Medicine, 650 Charles Young Drive South, Room A2-125 CHS, Los Angeles, CA 90095-6900, msedrak@mednet.ucla.edu.

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with advanced hormone receptor-positive breast cancer. Participants were given palbociclib in combination with their physician's choice of endocrine therapy (letrozole or fulvestrant). The primary endpoint was the incidence of grade 3+ adverse events (AEs) by six months. Secondary endpoints included AE-related dose delays, dose reductions, early discontinuations, and hospitalizations. Additionally, we compared these endpoints by age groups (70-74 and ≥75 years).

Results: Of the 90 participants (median age 74 years [70-87]) enrolled, 75.6% (95% confidence interval [CI], 65.4-84.0) had grade 3+ AEs by six months. The most frequent grade 3+ AEs were neutropenia (61%), fatigue (4%), and nausea (3%). Febrile neutropenia was uncommon (1.1%). Due to AEs, 36% had dose delays, 34% had dose reductions, 10% had early discontinuations, and 10% had hospitalizations. Compared to those aged 70-74 years, participants aged ≥75 years had higher rates of early discontinuations (5.9% vs 15.9%, a difference of 9.5% [95% CI 3.5% – 22.5%]).

Discussion: Palbociclib has an overall favorable safety profile in adults aged ≥70 with advanced breast cancer. However, adults ≥75 years had a trend toward higher rates of AE-related early discontinuations compared to those 70-74 years. Further research is needed to evaluate tolerability and improve the delivery of palbociclib in older adults.

Keywords

breast cancer; older adults; palbociclib; endocrine therapy

Introduction

Palbociclib is indicated for treating hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer in combination with endocrine therapy due to the dramatic improvement in progression-free survival (PFS) compared to endocrine therapy alone.[1-5] In registration trials, patients receiving palbociclib with endocrine therapy reported grade 3+ adverse event (AE) rates of 75.7% (PALOMA-2) and 69.3% (PALOMA-3).[1,2,5] The most common toxicities were neutropenia, fatigue, and nausea. However, our understanding of the safety of palbociclib in older adults, the largest and fastest-growing population with breast cancer, remains limited.

Most of what we know about the toxicity profile of palbociclib in older adults primarily stems from subgroup or pooled analyses and retrospective evaluations of real-world data. Subgroup analyses comparing the toxicity of palbociclib in older adults (aged ≥65) to younger adults (aged <65) revealed similar rates of grade 3+ AEs and dose reductions between age subgroups.[6] However, fewer than 10% of participants in the registration trials were 70 years or older, and therefore, these analyses do not represent a substantial proportion of patients in clinical practice.

In contrast, a pooled analysis of Food and Drug Administration (FDA) registration trials involving multiple CDK4/6 inhibitors, including palbociclib, reported that over half of patients aged 70 years and older required multiple dose reductions and interruptions due to severe toxicities.[7] Similarly, retrospective analyses of real-world data have shown varying

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results, with some demonstrating the safety and tolerability of palbociclib in older adults[8-11] and others not.[12] These inconsistencies are due to limitations with pooling different study designs and populations and the absence of prospective data.

Here, we conducted a prospective, multicenter, phase 2 clinical trial to evaluate the safety and tolerability of palbociclib with endocrine therapy in women aged 70 years and older with HR+/HER2− advanced breast cancer.

Methods

Study Design

Alliance for Clinical Trials in Oncology (Alliance) A171601 was a prospective multicenter, open-label, single-arm, phase 2 trial conducted across 57 centers in the United States, comprising of both academic and community sites. This study was designed by the Cancer in the Older Adult Committee of the Alliance National Cancer Institute (NCI) Community Oncology Program (NCORP) Research Base and approved by the NCI Division of Cancer Prevention. The study was also approved by the NCI Central Institutional Review Board, and written informed consent was obtained.

Study Participants

Eligible participants were aged ≥70 years with measurable or non-measurable HR+, HER2− advanced breast cancer and no prior history of treatment with a CDK4/6 inhibitor. One prior line of endocrine therapy or chemotherapy was allowed. Participants with brain metastases were excluded. Proficiency in English or Spanish was required.

Study Agents

Palbociclib was administered orally at a daily dose of 125 mg, with a 28-day cycle (21 days of treatment followed by seven days off) in conjunction with endocrine therapy. Endocrine therapy options included letrozole or fulvestrant, determined by the treating clinician. Letrozole was administered orally at a daily dose of 2.5 mg as a continuous therapy, while fulvestrant was injected intramuscularly at a dose of 500 mg on days 1 and 15 during the first cycle, followed by 500 mg every 28 days on subsequent cycles. Dose reductions of palbociclib and endocrine therapy were allowed and are detailed in the protocol to match the FDA package insert.

Baseline Assessments

At baseline, participants completed sociodemographic questionnaires, including age, sex, race, and ethnicity. Participants also completed a section of the geriatric assessment (GA), which consists of a healthcare provider portion (physician-rated performance status [Eastern Cooperative Oncology Group score][13,14]; physical function [Timed Up and Go Test][15]; cognitive screening [Blessed Orientation Memory Concentration Test][16]; body composition measurements [weight, height, body mass index (BMI), unintentional weight loss]) and a participant portion of self-reported functional status (fall history; activities of daily living [ADL][17]; instrumental ADLs[18]), comorbidity[19,20], medications, psychological state[17,21,22], and social support[17,23] (see Protocol). Then, using individual GA items, we calculated the

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frailty index at baseline, a measure of health status calculated from the GA as a score from 0 to 1, with 0 representing robust health ('fit') and 1 representing frail health.[24-26]

In addition to the GA, health-related quality of life was assessed at baseline by patient self-report using EQ-5D-3L, an instrument that consists of two parts: the descriptive system and the EQ visual analog scale (EQ VAS)[27]. The EQ-5D-3L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has three levels: 1, no problems; 2, some or moderate problems; and 3, extreme problems. The scores for the five dimensions can be combined into an index (EQ-5D-3L index), a score between 0 and 1, with 1 representing an overall good health state.[28] The EQ-VAS records the participant's self-rated health on a vertical, visual analog scale where the endpoints are classified as follows: 'best imaginable health state' =100 and 'worst imaginable health state' =0.[28]

Primary Endpoint

The primary endpoint was the proportion of participants experiencing grade 3-5 toxicity, as per NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0)[29]. AEs were assessed and graded by treating physicians during each cycle, and the highest grade observed from treatment initiation to the six-month mark was recorded and used in the final analysis.

Secondary Endpoints

Secondary endpoints included grade 2 and higher AEs (captured using the CTCAE v5.0), AE-related dose delays (proportion of participants who experienced at least one dose interruption due to AEs), AE-related dose reductions (proportion of participants who experienced at least one dose reduction due to AEs), AE-related early discontinuations (proportion of participants who prematurely discontinued treatment due to AEs), and AE-related hospitalizations (proportion of participants with at least one hospitalization due to AEs). Adherence to the planned dose was defined as the proportion of participants who took 90% of the planned dose of palbociclib during a 28-day cycle and was assessed for cycles 1-3.

Health-related quality of life was measured as the change in the mean EQ-5D-3L index and EQ-VAS scores from baseline to the end of treatment (all participants were asked to complete these quality of life questionnaires at baseline and when going off treatment for any reason). Participants also completed 46 Patient-Reported Outcomes (PRO)-CTCAEs items measuring 24 symptomatic AEs (fatigue, decreased appetite, nausea, vomiting, heartburn, taste changes, diarrhea, constipation, insomnia, joint pain, muscle aches, headaches, rash, dry skin, alopecia, neuropathy, pain, anxiety, sadness, sexual interest, sweating, hot flashes, dry mouth, mouth/throat sore) at baseline and during treatment (at the beginning of each cycle and every cycle thereafter until cycle 6).

Participant satisfaction with trial participation was measured at the end of treatment using the Was It Worth It (WIWI) questionnaire.[30,31] The WIWI included three items: (1) Was it worthwhile for you to receive the cancer treatment given in this study?; (2) If you had to do it over again, would you choose to have this cancer treatment?; and (3) Would you

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recommend this cancer treatment to others? The response options for each of these three items were ‘yes,’ ‘uncertain,’ and ‘no.’ We also asked two additional questions to capture participant perceptions: (4) Overall, did your quality of life change by participating in this research study? (responses: ‘it improved,’ ‘it stayed the same,’ or ‘it got worse’); and (5) Overall, how was your experience participating in this research study? (responses: ‘better than I expected,’ ‘the same as I expected,’ or ‘worse than I expected’).

PFS was defined as the time from start of treatment to the first of the following disease events: local/regional/distant recurrence, invasive contralateral breast disease, second primary, or death due to any cause. Overall survival (OS) was defined as start of treatment to death due to any cause. Time to treatment failure (TTF) was defined as the time from start of treatment to one of the following events: grade 3+ AE, disease progression, or participant refusal.[32]

Statistical Analysis

A sample size of 88 participants was targeted, accounting for accrual feasibility and potential dropout rates. Based on prior literature estimating a grade 3-5 AE rate of 70% for palbociclib and endocrine therapy, a sample size of 88 allowed for 95% confidence interval (CI) of 60% to 80% estimates of grade 3+ AEs. Furthermore, to ensure sufficient participants who were aged ≥75 years to assess the severe toxicity rate and safety of palbociclib, participant accrual continued until 40 participants aged ≥75 years were enrolled.

Descriptive statistics were used to summarize baseline participant characteristics and the primary endpoint. The proportion of grade 3+ AEs was compared between participants aged 70-74 years and those ≥75 years using chi-square test. Additionally, univariate associations were assessed between baseline participant characteristics and the primary endpoint, using chi-square test or Fisher’s exact test. This was followed by multivariate logistic regression modeling. The strengths of the associations were expressed in terms of odds ratios (ORs) and their associated 95% CIs. In separate logistic regression models, we then explored factors as identified by a cancer-specific GA that may be predictive of grade 3+ AEs. Age group and BMI were entered in each model.

For secondary endpoints, we conducted descriptive analyses to characterize grade 2+ AEs; AE-related outcomes (dose delays, dose reductions, early discontinuations, hospitalizations); adherence to the planned dose of palbociclib; and the change in the mean EQ-5D-3L index and EQ-VAS score. For the AE-related outcomes, we compared the proportions between participants aged 70-74 years and those ≥75 years, along with 95% CIs to examine the widths of the intervals and the position of the null value in relation to the intervals.

We assessed the feasibility of using PRO-CTCAE to measure self-reported symptomatic AEs in our patient population. Feasibility was defined as 75% of the participants completing 75% (i.e., 35 out of 46 items) of the questionnaires. The 75% completion threshold was achieved through cycle 4 and dropped to 74% in cycle 5 and 61% in cycle 6 (Supplemental Table 1). We computed the percentage of participants reporting severe (moderate, severe, very severe); interfering (somewhat, quite a bit, very much); and frequent (occasionally, frequently, almost constantly) symptoms on PRO-CTCAE. PRO-CTCAE was further

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analyzed to assess the agreement rate between PRO-CTCAE CTCAE by determining the proportion of participants having at least some symptoms or no symptoms at all according to both sets of criteria throughout the 6 cycles.

For the WIWI, analysis was conducted considering each WIWI item as a categorical variable with three response options: yes, uncertain, and no (for items 1-3) and related three responses (for items 4-5). Kaplan-Meier survival analysis was used to describe PFS, OS, and TTF, and the log-rank test was used to compare outcomes between participants aged 70-74 and those ≥75. For these analyses, we used data frozen on March 14, 2022. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided, and statistical significance was defined as a p-value <0.05. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Management Center. Data quality was ensured by review of data by the Alliance Statistics and Data Management Center and by the study chairperson following Alliance policies.

Results

From August 15, 2018 to March 3, 2020, 93 participants were registered for the trial. Of these, three participants were excluded from the analysis: one withdrew before therapy, one was found to be ineligible after commencing treatment, and one was unevaluable due to the treating physician's divergence from the protocol (Figure 1).

Baseline Characteristics

Table 1 outlines the demographic data, disease characteristics, and GA scores of the participants. The median age of participants was 74 years (range: 70-87), with 39 (43.3%) aged at or over 75 years. A majority (80.9%) received palbociclib as first-line therapy, and about half had bone-only, non-measurable disease. In GA, 75% noted impairments in ADL, 44% in instrumental ADL, and 39% in walking one block. The baseline sociodemographic, disease, and GA impairments were similar across the 70-74 and ≥75-year age groups.

Grade 3+ AEs by Six Months

Among the 90 evaluable participants, 68 (75.6%) experienced a grade 3+ AE (95% CI, 65.4-84.0) by six months (Table 2). The most frequent grade 3+ AEs were neutropenia (61%), leukopenia (24%), fatigue (4%), and nausea (3%). Febrile neutropenia was uncommon (1.1%). There was no significant difference in the rate of grade 3+ AE between participants aged 70-75 and those aged ≥75 (p=0.47) (Table 2).

Univariate analysis revealed that participants with a baseline BMI>30 had a decreased likelihood of experiencing grade 3+ AEs (OR 0.15, 95% CI 0.03-0.73, p=0.019) (Table 3). No other baseline sociodemographic, GA, or disease/treatment variables were significantly correlated with toxicity.

Secondary Endpoints

Grade 2+ AEs included 87.8% neutropenia, 21.1% anemia, and 7.8% thrombocytopenia. Grade 2+ fatigue was reported in 26.7% of participants.

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Due to AEs, 36% participants had dose delays, 34% had dose reductions, 10% had early discontinuations, and 10% had hospitalizations (Table 4). The proportion of participants with AE-related dose reductions did not differ by age group (33.3% vs. 35.3%, a difference in rates of 2.0% [95% CI, −17.8% – 21.7%]). However, compared to those aged 70-74 years, participants aged ≥75 years had higher (although not statistically significant) rates of AE-related dose delays (41.0% vs. 31.4%, a difference of 9.7% [95% CI −10.4% – 29.7%]), AE-related early discontinuations (5.9% vs 15.4%, a difference of 9.5% [95% CI −3.5% – 22.5%]), and AE-related hospitalizations (5.9% vs. 15.4%, a difference of 9.5% [95% CI −3.5% – 22.5%]). Of note, although the rates of participants with early discontinuations and hospitalizations were identical in the overall sample and across the two age groups, when examined further, we found that these outcomes did not occur in the same participants (i.e., not all hospitalized participants had early discontinuation and vice versa; see footnote in Table 4 for further details).

Adherence to the planned dose of palbociclib was 76.7% for cycle 1, 64.0% for cycle 2, and 69.1% for cycle 3. Health-related quality of life measured using EQ-5D-3L and EQ-VAS scores indicated participants reporting stable health-related quality of life (HRQOL) throughout the six cycles of treatment (Supplemental Table 2). More than 40% of participants reported pain, aching muscles/joints, and fatigue on PRO-CTCAEs (Supplemental Table 3), and this trend was more pronounced in participants aged ≥ 75 years (Supplemental Table 5) than those aged 70-74 years (Supplemental Table 4). The agreement rate with CTCAE across PRO-CTCAE items ranged from 24.4% to 88.9%, averaging 62.7%. At the end of the study, the WIWI questionnaire revealed that most participants felt it was worthwhile to participate (90.9%), would do it again (90.9%), and would recommend the study to others (90.2%) (Supplemental Table 6).

With a median follow-up of 24.8 months, the median PFS for the entire cohort was 29.4 months (95% CI, 24.9-not estimable [NE]). No significant difference in median PFS was observed between participants aged 70-74 years and those aged 75 years or older (hazard ratio [HR]=1.20, 95% CI, 0.63-2.28, p=0.58) (Figure 2A, 2B). The median OS for the entire cohort was 35.6 months (95% CI, 35.6-NE), with no significant difference in median OS between the two age groups (HR=0.54, 95% CI, 0.22-1.30, p=0.16) (Figure 2C, 2D). The median TTF for the entire cohort was 14.8 months (95% CI, 11.3-20.1), with no significant difference between the age groups (HR=0.77, 95% CI, 0.48-1.26, p=0.3) (Figure 2E, 2F).

Discussion

In this study, we found that palbociclib has an overall favorable safety profile in adults aged ≥70 years with advanced breast cancer. Although the absolute rate of grade 3+ adverse events (AEs) by six months was high, most of these events were asymptomatic, lab-based hematologic toxicities (e.g., neutropenia), and symptomatic toxicities (e.g., neutropenic fever) were uncommon.

To date, other than this trial, only one prospective study, the PALOMAGE study, focusing on older adults with HR+/HER2− advanced breast cancer receiving palbociclib and endocrine therapy, has been preliminarily reported.[33] Our findings align with data

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from the PALOMAGE study, FDA registration trials,[1,2] and pooled analyses[6] showing that palbociclib has similar toxicity in older adults with breast cancer compared to younger adults. Additionally, our efficacy results align with those of registration trials,[1,2] retrospective analyses,[34,35] and the recent PALMOAGE study,[33] which underscores the benefits of palbociclib in older adults.

Our study implies that palbociclib is a safe option for older adults with advanced breast cancer. There were no unexpected toxicities and rates of grade 3+ AEs were comparable to that seen in younger adults. Of the observed grade 3+ AEs, the majority were lab-based hematologic toxicities and did not translate to severe clinical manifestations (e.g., grade 3+ fever or infection from neutropenia, fatigue or dyspnea from anemia, or bleeding from thrombocytopenia). The incidence of grade 3+ gastrointestinal toxicity was also low with only three participants reporting grade 3 nausea and one reporting grade 3 vomiting. No participants had grade 3+ diarrhea. Additionally, this study confirms the potential benefits of palbociclib treatment for older patients in the recurrent or metastatic breast cancer setting, provided that dosing and toxicities are effectively managed.

We did observe that participants ≥75 years of age had a trend toward higher rates of AE-related dose interruptions, early discontinuations, and hospitalizations compared to those aged 70-74 years, suggesting lesser tolerability in the very old adults. However, the rate of grade 3+ AEs was not greater in the those aged ≥75 years compared to those aged 70-74 years. Thus, the increased rates of dose interruptions and early discontinuations may also reflect less willingness of physicians to risk continuation of treatment for the very old adults who experience AEs or AE-related hospitalization. Further research is needed to evaluate tolerability in the ≥75 years age group and identify optimal dosing strategies for this high-risk population.

Consistent with previous data, there was an association between higher baseline BMI (>30) and a reduced likelihood of grade 3+ AEs.[36,37] The correlation between BMI and neutropenia is likely due to reduced pharmacodynamic impact of palbociclib in individuals affected by obesity. Aside from BMI, we did not observe any correlation between other baseline characteristics, including GA variables, with grade 3+ AEs. We hypothesize that the lack of correlation between baseline measures of function and grade 3+ AEs is due to the fact that the majority of grade 3+ AEs consisted of neutropenia, a direct result of bone marrow progenitor cell quiescence from CDK 4/6 inhibition that may not be dependent on age or its associated vulnerabilities to toxicity.[38]

Finally, this study serves as a model for therapeutic trials tailored to older adults, conducted through the National Clinical Trials Network and NCORP. It underscores the feasibility of executing such older adult-specific trials, which will help us fill in the missing evidence base for older adults with cancer.[39-42]

There are limitations to this study. First, the generalizability of this trial is limited because of the small sample size and the small number of participants from each participating site. Second, there was no comparator arm with other age groups or standard-of-care therapies. Therefore, we cannot directly compare the toxicity profile between older and younger adults.

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Third, we cannot make any conclusions on the toxicity profile of palbociclib compared to other agents, such as other CDK4/6 inhibitors. Finally, we did not study any potential interventions to improve the toxicity profile and tolerability of palbociclib in older adults, such as early planned dose reductions, which would be an important area of investigation for future trials.

Conclusion

Our findings reveal that palbociclib has an overall favorable safety profile in adults aged ≥70 years with advanced breast cancer. However, participants ≥75 years had a trend toward higher rates of AE-related complications compared to those 70-74 years. Further research is needed to improve the delivery of palbociclib in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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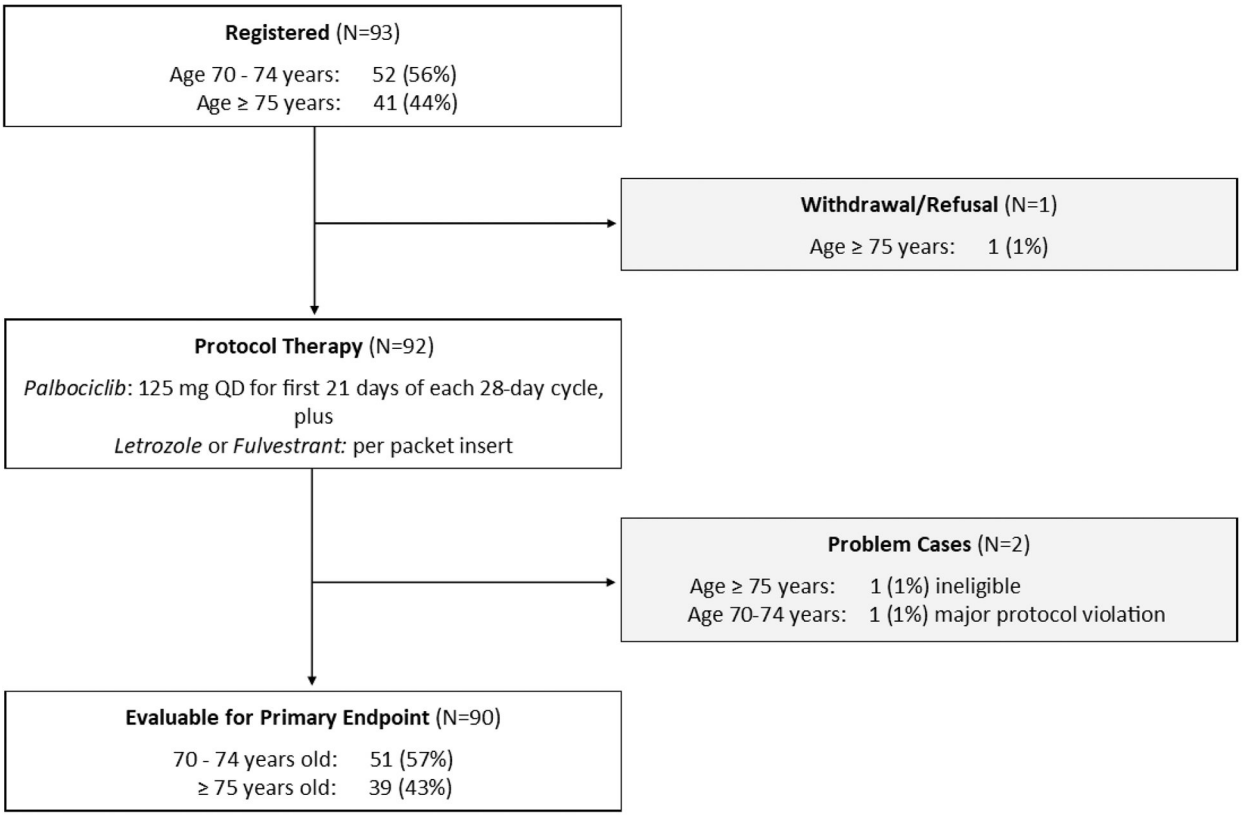

Figure 1.

Consort Diagram.

*We allowed continued enrollment over the target sample size of 88, and by the end of the study, we had a total of 93 participants registered (52 participants age <75 and 41 participants age ≥75).

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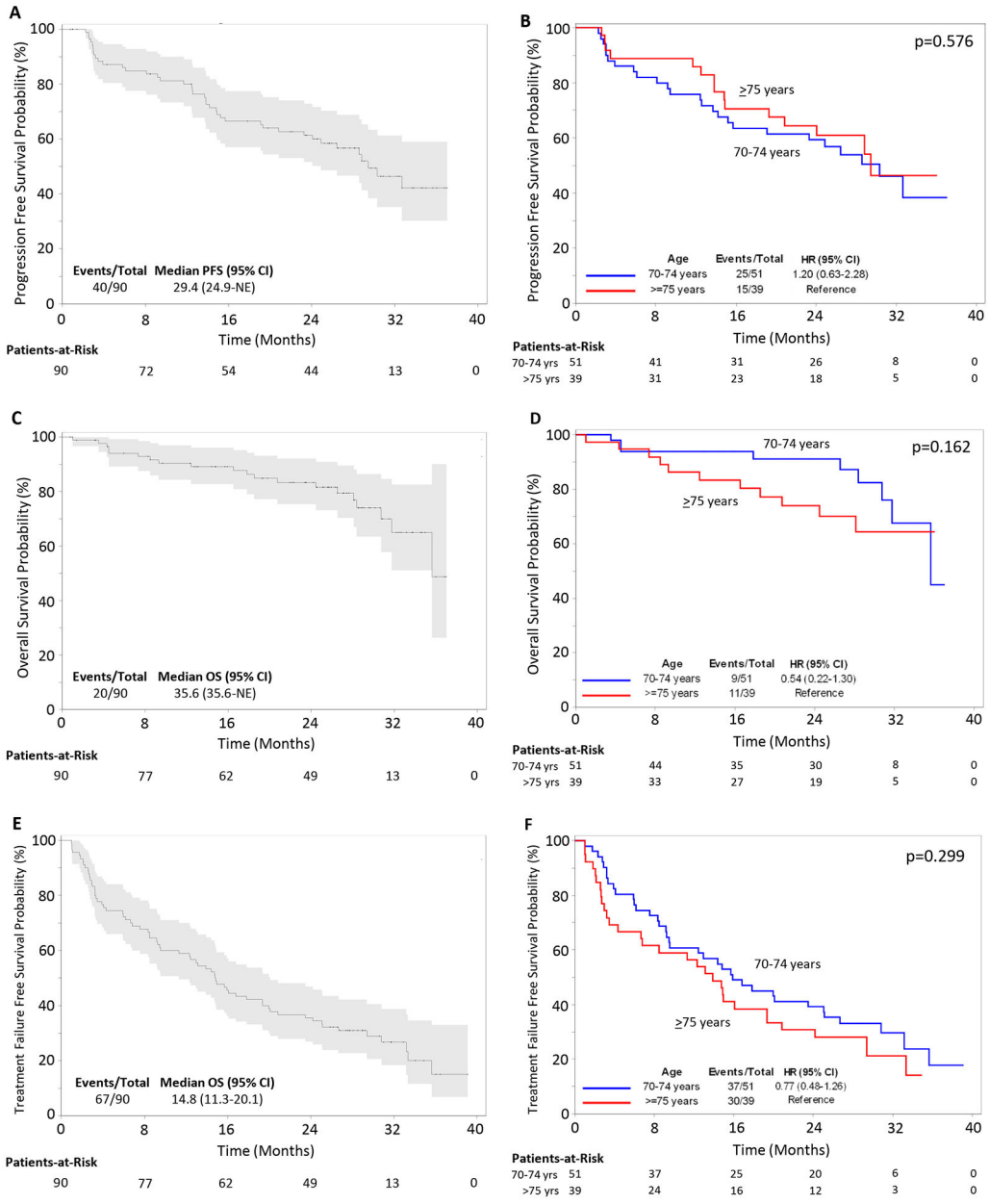

Figure 2.
Progression-free survival, overall survival, and time to treatment failure.

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Table 1.

Baseline characteristics.

	Overall (N=90)	Age 70-74 years (n=51)	Age ≥75 years (n=39)
Sociodemographic			
Age, years, Median (range)	74 (70-87)	72 (70-74)	78 (75-87)
Female, No. (%)	89 (98.9)	51 (100)	39 (97.4)
Race, No. (%)			
White	82 (91.1)	45 (88.2)	37 (94.9)
Black or African American	4 (4.4)	3 (5.9)	1 (2.6)
Asian	1 (1.1)	1 (2.0)	0 (0)
Not reported	1 (1.1)	1 (2.0)	0 (0)
Ethnicity, No. (%)			
Not Hispanic or Latino	85 (94.4)	47 (92.2)	38 (97.4)
Hispanic or Latino	3 (3.3)	3 (5.9)	0 (0)
Disease & Treatment			
Metastatic Status, No. (%)			
Recurrent disease	64 (71.1)	36 (70.6)	28 (71.8)
Metastatic de novo	26 (28.9)	15 (29.4)	11 (28.2)
First line of treatment, No. (%)	72 (80.9)	43 (86.0)	29 (74.4)
Metastatic site, No. (%)			
Bone only	43 (47.8)	24. (47.1)	19 (48.7)
Both bone and lung	24 (26.7)	13 (25.5)	11 (28.2)
Lung only	14 (15.6)	10 (19.6)	4 (10.3)
Neither bone nor lung	9 (10.0)	4 (7.8)	5 (12.8)
Measurable disease, No. (%)	46 (51.1)	29 (56.9)	17 (43.6)
Prior adjuvant endocrine therapy, No. (%)	59 (65.5)	29 (56.9)	30 (76.9)
Prior systemic therapy for metastatic breast, No. (%)	72 (80.9)	33 (84.6)	30 (76.9)
Geriatric Assessment and HRQOL			
Impaired (≥2) ECOG performance status, No. (%)	3 (3.3)	3 (5.9)	0 (0.0)
Frailty index			
Median (range)	0.2 (0.0-0.5)	0.1 (0.0-0.5)	0.2 (0.0-0.4)
Reported limitations in walking one block, n (%)	30 (36.1)	17 (35.4)	13 (37.1)
≥ 1 falls, No. (%)	12 (15.2)	6 (12.8)	6 (18.8)
≥ 1 item of IADL impaired, No. (%)	33 (39.8)	17 (35.4)	16 (45.7)
≥ 1 item of ADL impaired, No. (%)	59 (71.1)	33 (68.8)	26 (74.3)
EQ-5D-3L Index, median (range)	0.8 (0.3-1.0)	0.8 (0.3-1.0)	0.8 (0.3-1.0)
EQ-VAS, median (range)	75 (5-100)	70 (5-100)	75 (10-100)
BMI, No. (%)			
Normal/underweight (<25)	23 (27.7)	13 (27.1)	10 (28.6)
Overweight (25-30)	27 (32.5)	17 (35.4)	10 (28.6)
Obesity (>30)	33 (39.8)	18 (37.5)	15 (42.9)

Abbreviations: No. = number, HRQOL= health-related quality of life, ECOG = Eastern Cooperative Oncology Group, Frailty index = deficit accumulation index, ADL-MOS = Activities of Daily Living – Medical Outcome Study, IADL = Instrumental Activities of Daily Living, MHI-17 = Mental Health Inventory -17, EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level, EQ-VAS = EuroQol-Visual Analogue Scale, BMI = body mass index

Some numbers may not add to 100 due to rounding, including: 2 missing race/ethnicity, 1 missing prior adjuvant chemotherapy, and 1 missing prior systemic therapy for metastatic breast cancer.

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Table 2.

The proportion of older participants with adverse events on palbociclib and endocrine therapy.

Observed Adverse Events	% of participants who experienced AE					
	Overall (N=90)		Age 70-74 (n=51)		Age ≥75 (n=39)	
	Grade		Grade		Grade	
	Any	≥3	Any	≥3	Any	≥3
All Observed Adverse Events	100	75.6	100	78.4	100	71.8
Hematologic						
Neutropenia	91	61	92	62.7	90	59
Leukopenia	86	24	90	19.6	79	30.8
Anemia	73	2	67	0	79	3.9
Thrombocytopenia	53	0	57	0	49	0
Non-hematologic						
Fatigue	79	4	80	8	77	0
Diarrhea	40	0	43	0	36	0
Nausea	38	3	45	6	28	0
Neuropathy	36	0	29	0	44	0
Anorexia	28	0	24	0	33	0
Mucositis	28	0	27	0	28	0
Vomiting	14	1	18	2	10	0
Upper respiratory infection	9	1	12	2	5	0
Thromboembolism	3	1	4	2	3	0

*When looking at any grade AEs, participants aged 70-74 years reported leukopenia, thrombocytopenia, diarrhea, nausea, and vomiting more than those aged ≥75 years. In contrast, participants ≥75 years reported anemia, neuropathy, and anorexia more than those in the 70-74 years group.

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Table 3.

Risk factors associated with toxicity.

	n	OR (95% CI)	p-value	Overall p-value
Age, years				0.469
70-74	51	1 (Reference)		
≥75	39	0.70 (0.27 - 1.84)		
Race/Ethnicity				0.337
Not Hispanic or Latino, White	80	1 (Reference)		
Hispanic or Latino, non-White	9	2.85 (0.34 – 24.1)		
ECOG Performance Status				0.631
0	41	1 (Reference)		
1-2	49	1.27 (0.48 - 3.32)		
BMI				0.058
Normal weight/Underweight (<25)	23	1 (Reference)		
Overweight (25-30)	27	0.27 (0.05 - 1.47)	0.130	
Obese (>30)	**33**	**0.15 (0.03 - 0.73)**	**0.019**	
Number of Comorbidities				0.532
0	5	1 (Reference)		
1-2	34	2.57 (0.36 - 18.5)	0.348	
>3	44	1.59 (0.24 – 10.7)	0.633	
Endocrine Therapy Agent				1.000
Letrozole	45	1 (Reference)		
Fulvestrant	45	1.00 (0.38 - 2.62)		
Baseline GA Predictors				
Reported limitations in walking one block (vs. not)		0.99 (0.36 - 2.72)		0.980
≥ 1 falls (vs. no falls)		1.98 (0.40 - 9.89)	0.406	
≥ 1 item of IADL impaired, n (%)		0.73 (0.27 - 1.95)	0.525	
≥ 1 item of ADL impaired, n (%)		0.46 (0.14 - 1.52)	0.202	
Frailty Index Score * (for every 0.10 increase in score)		0.98 (0.63-1.53)	0.923	

Abbreviations: OR = odds ratio, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, BMI = body mass index, GA = geriatric assessment, IADL = instrumental activities of daily living, ADL = activities of daily living

* The OR for frailty index is based upon every 0.1 increase in score. All analyses in this table are univariable analyses.

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Table 4.

Palbociclib dose interruptions, reductions, early discontinuations, and hospitalizations due to adverse events.

AE-related treatment disruptions	% of participants receiving palbociclib + endocrine therapy who experienced one or more of these outcomes due to AE			
	Overall (N=90) %	Age 70-74 years (n=51) %	Age ≥75 years (n=39) %	Difference in proportion between two age groups (95% CI)
Dose interruptions/delays	35.6	31.4	41.0*	9.7 (−10.4 – 29.7)
Dose reductions	34.4	35.3	33.3	2.0 (−17.8 – 21.7)
Early discontinuations	10.0	5.9	15.4*	9.5 (−3.5 – 22.5)
Hospitalizations	10.0	5.9	15.4*	9.5 (−3.5 – 22.5)

Abbreviations: AE – adverse event, CI = confidence interval

*Participants ≥75 years had higher rates of dose interruptions/delays, early discontinuations, and hospitalizations due to AEs (although these differences were not statistically significant).

Additionally, although the proportion of participants with early discontinuations and hospitalizations was the same overall and across the two age groups, when examined further, we found that these outcomes did not occur in the same participants (i.e., not all hospitalized participants had early discontinuation and vice versa).

In the age 70-74 group, there were 3 (5.9%) participants who discontinued treatment early due to AEs; 2 of them had AE-related hospitalizations, and 1 did not.

In the age 75+ group, there were 6 (15.4%) participants who discontinued treatment early due to AEs; 1 of them had an AE-related hospitalization, and 5 did not.