Virtual Kick-off Discussion Guide

Flatiron Real-World Palbociclib + Aromatase Inhibitor (AI) vs AI Alone: Extended Follow-up of Overall Survival

Purpose of Virtual Kick-off Call	• To introduce authors to agency/Pfizer personnel assigned to this manuscript • To ensure all authors are aware of the Pfizer guidelines/processes and ICMJE requirements (**Table S1**) • To discuss how to position the paper • To discuss and agree on the general scope, content, figures and tables, to be included in the publication • To review and agree upon a timeline for developing the manuscript • To answer any questions/concerns authors may have regarding publication development
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Author Responsibilities	Per ICMJE authorship guidelines: Authors must meet all 4 criteria, including providing substantive input on one or more drafts and approval of the final version of the manuscript (**Table S1**). **The authors are kindly reminded that approving or making minor/editorial changes to the manuscript draft does not meet the 2nd element of the ICMJE authorship criteria which is also Pfizer policy and was stated in the Author Letter provided to all external authors before this manuscript started.**
Datavision	Development of the manuscript will be conducted in the Pfizer publication software platform (Datavision). All author comments will be documented in Datavision. Please see the instructions at the end of the Discussion Guide regarding resetting your Datavision password (if applicable).

<table>
<tr><td>Proposed Title</td><td>Overall Survival with Palbociclib Plus Aromatase Inhibitor Versus Aromatase Inhibitor Alone in Postmenopausal Women and in Men With HR+/HER2– Metastatic Breast Cancer: Extended Follow-Up in Real-World US Clinical Practice</td></tr>
<tr><td>Proposed Authors and Order</td><td>Hope S. Rugo, MD; Adam Brufsky, MD, PhD; Xianchen Liu, MD, PhD; Benjamin Li, PhD; Lynn McRoy, MD; Connie Chen, PharmD; Rachel M. Layman, MD; Massimo Cristofanilli, MD; Giuseppe Curigliano, MD; PhD; Angela DeMichele, MD</td></tr>
<tr><td>Timeline</td><td>Tentative timeline for manuscript development:
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<tr><th>Stage</th><th>Date</th></tr>
<tr><td>ICON to send Discussion Guide to authors (virtual kick-off)</td><td></td></tr>
<tr><td>ICON to send First Draft to authors</td><td></td></tr>
<tr><td>ICON to send Second Draft to authors</td><td></td></tr>
<tr><td>ICON to send Final Draft for Approval</td><td></td></tr>
<tr><td>Pfizer Internal Compliance Steps</td><td></td></tr>
<tr><td>Submission to NPJ Breast Cancer</td><td></td></tr>
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Authors, please advise of any conflicts during the above dates.

Timeline assumes all data are available and provided to ICON prior to initiation of Draft 1 development and is dependent upon timely reviews by Pfizer and authors</td></tr>
<tr><td>Proposed journal</td><td>NPJ Breast Cancer

Authors, please see the target journal table for journal information.</td></tr>
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	• t7_post_m_rwpfs_subgroup_kims2393.xlsx • t8_post_m_os_subgroup_kims2393.xlsx • t9_post_m_second_line_treatments_kims2393.xlsx
Objectives	• To compare overall survival (OS) of first-line palbociclib plus aromatase inhibitor (AI) versus AI alone in postmenopausal women or in men with hormone receptor–positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) • To compare real-world progression-free survival (rwPFS) of first-line palbociclib plus AI versus AI alone in postmenopausal women or in men with HR+/HER2– MBC • To describe treatment patterns of palbociclib, including subsequent second-line treatments
Introduction	Suggested key points: • State epidemiology of breast cancer in the United States ○ In 2021, it was estimated 281,550 new case of female breast cancer would be diagnosed and there would be 43,600 deaths.[1] ○ In 6% of breast cancers cases, the breast cancer has spread to distant tissues (ie, metastatic breast cancer [MBC]); the 5-year survival rate for MBC is 29.0%. ○ The majority of breast cancer cases are HR+/HER2– (68%). • Describe treatment recommendations for women and men with first-line HR+/HER2– MBC. ○ A cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in combination with endocrine therapy is recommended by the National Comprehensive Cancer Network treatment

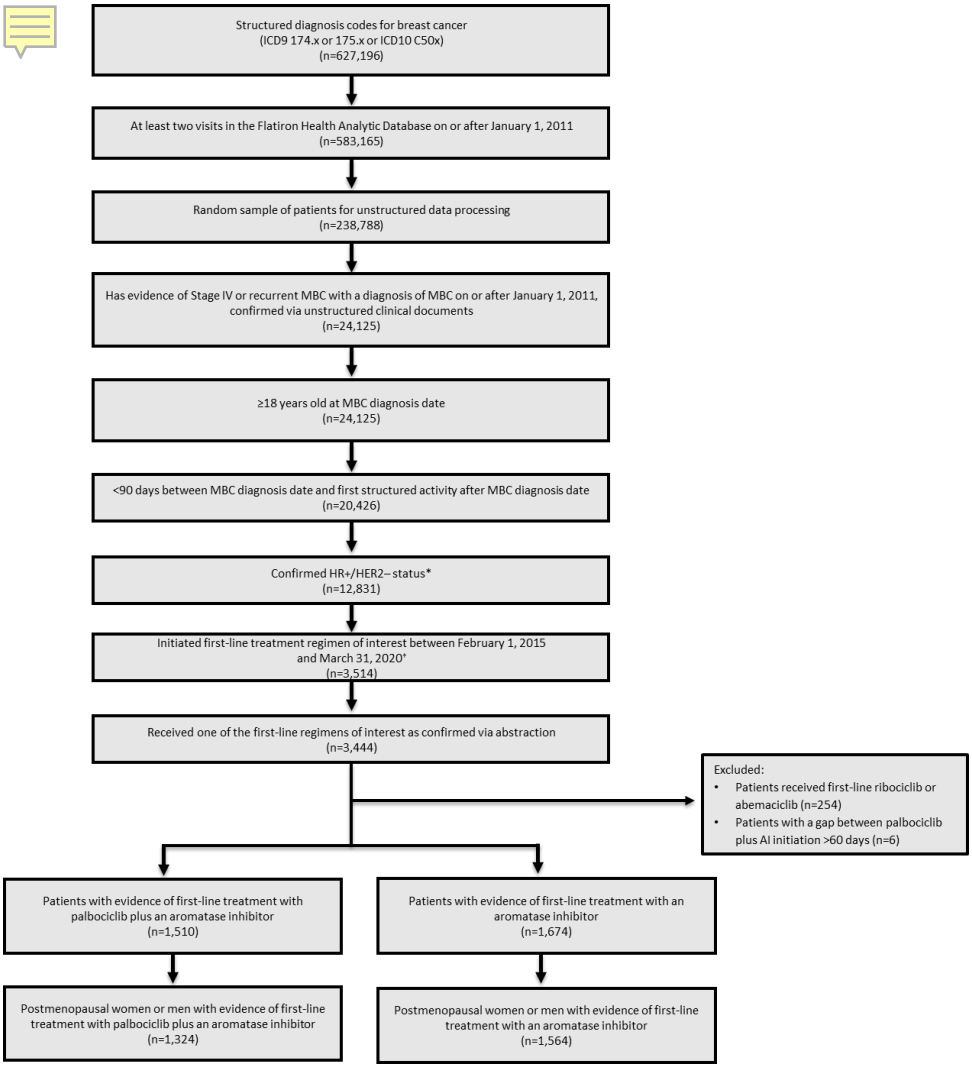
guidelines for the treatment of pre- and postmenopausal women and for men with HR+/HER2– MBC.[2]

- Describe palbociclib and PALOMA-2 trial results[3,4]
  - The CDK4/6 inhibitor, palbociclib, was approved in February 2015 as first-line treatment for HR+/HER2– MBC in combination with an aromatase inhibitor, and approved in February 2016 in combination with fulvestrant for patients who progressed while on prior endocrine therapy.
  - In the phase 3 PALOMA-2 trial, first-line palbociclib plus letrozole versus letrozole plus placebo significantly prolonged median PFS in patients with estrogen receptor–positive/HER2– MBC.[3,4]
  - OS data for PALOMA-2 are not yet mature.
- Describe the importance of real-world evidence
  - Real-world evidence is used to validate the efficacy and safety of a drug in routine clinical practice.[5]
  - Real-world studies also allow for the inclusion of patients underrepresented in clinical trials and help reinforce treatment recommendations.[6]
- Briefly summarize real-world evidence of palbociclib
  - Emerging real-world data have demonstrated the safety and effectiveness of a CDK4/6 inhibitor plus endocrine therapy for HR+/HER2– MBC.
    - Using the Flatiron Database Health Analytic Database, a comparative effectiveness real-world study demonstrated longer real-world progression-free survival (rwPFS) and overall survival (OS) among

	patients treated with palbociclib plus letrozole versus letrozole alone.[7] ▪ Another real-world comparative study in the Flatiron Database showed a higher chance of tumor response with palbociclib plus letrozole versus letrozole alone as well as a significant improvement in median rwPFS and OS with combination therapy.[8] o However, real-world data on OS in patients treated with palbociclib plus endocrine therapy versus endocrine therapy alone are limited by small sample sizes and short follow-up time. ▪ In both studies mentioned above, patients had potential follow-up for ≥3 months from the index date to data cutoff date. • Describe purpose of this study o This real-world analysis used the Flatiron Health Analytic Database to evaluate OS and rwPFS of palbociclib plus AI versus AI alone in postmenopausal women and in men with HR+/HER– MBC in routine clinical practice in the United States. ▪ As palbociclib has been available as treatment for HR+/HER2– MBC for 7 years, the current study has the longest index period from palbociclib approval. ▪ Moreover, this study includes an extended follow-up time of ≥6 months from the index date to data cutoff date.

	Authors: *Do you agree with including the above points? Are there other key points that should be included?*
Methods	Suggested key points: **Study Design/Data Source** • This was a retrospective analysis of electronic health records (EHRs) from the Flatiron Health Analysis Database ○ Flatiron is a longitudinal database that contains de-identified patient data from structured and unstructured EHRs from >280 cancer clinics (~800 sites of care) representing >2.4 million actively treated US patients with cancer. • Patient attrition diagram is presented in **Figure 1**

Figure 1: Patient Attrition Diagram



- Inclusion criteria included women aged ≥18 years at MBC diagnosis with confirmed HR+/HER2– MBC at any point in patient history. Patients also had a date of first prescription (index date) for palbociclib plus AI or AI alone as first-line therapy for MBC between February 3, 2015 and March 31, 2020 and a potential follow-up for ≥6 months from the index date to the study cutoff date of September 30, 2020.

- Exclusion criteria included evidence of prior treatment with CDK4/6 inhibitors, tamoxifen, raloxifene, toremifene, fulvestrant, or chemotherapy in the metastatic setting; first structured activity >90 days after MBC diagnostic date; and lacks relevant unstructured documents in the Flatiron Health database for review by the abstraction team.

Outcomes

- The primary outcome was OS
  - OS was defined as the time in months from start of palbociclib plus AI or AI alone (February 1, 2015) to death.
  - Date of death was derived from a recent mortality data set generated by combining multiple data sources and benchmarked against the National Death Index.[5]
  - If patients did not die, they were censored at the study cutoff date of September 30, 2020.
- The secondary outcome was rwPFS
  - rwPFS was defined as the number of months from start of palbociclib plus AI or AI alone to the date of the first documentation of a real-world progressive disease or death due to any cause, whichever occured first.
  - Patients last known to be alive and progression-free within the follow up cut-off date were censored at the date of the last clinic note.
  - Disease progression was concluded by the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment.

- Duration of follow-up was defined as the number of months from start of palbociclib plus AI or AI alone to death due to any cause or the data cutoff date of September 30, 2020.

Statistical Analyses

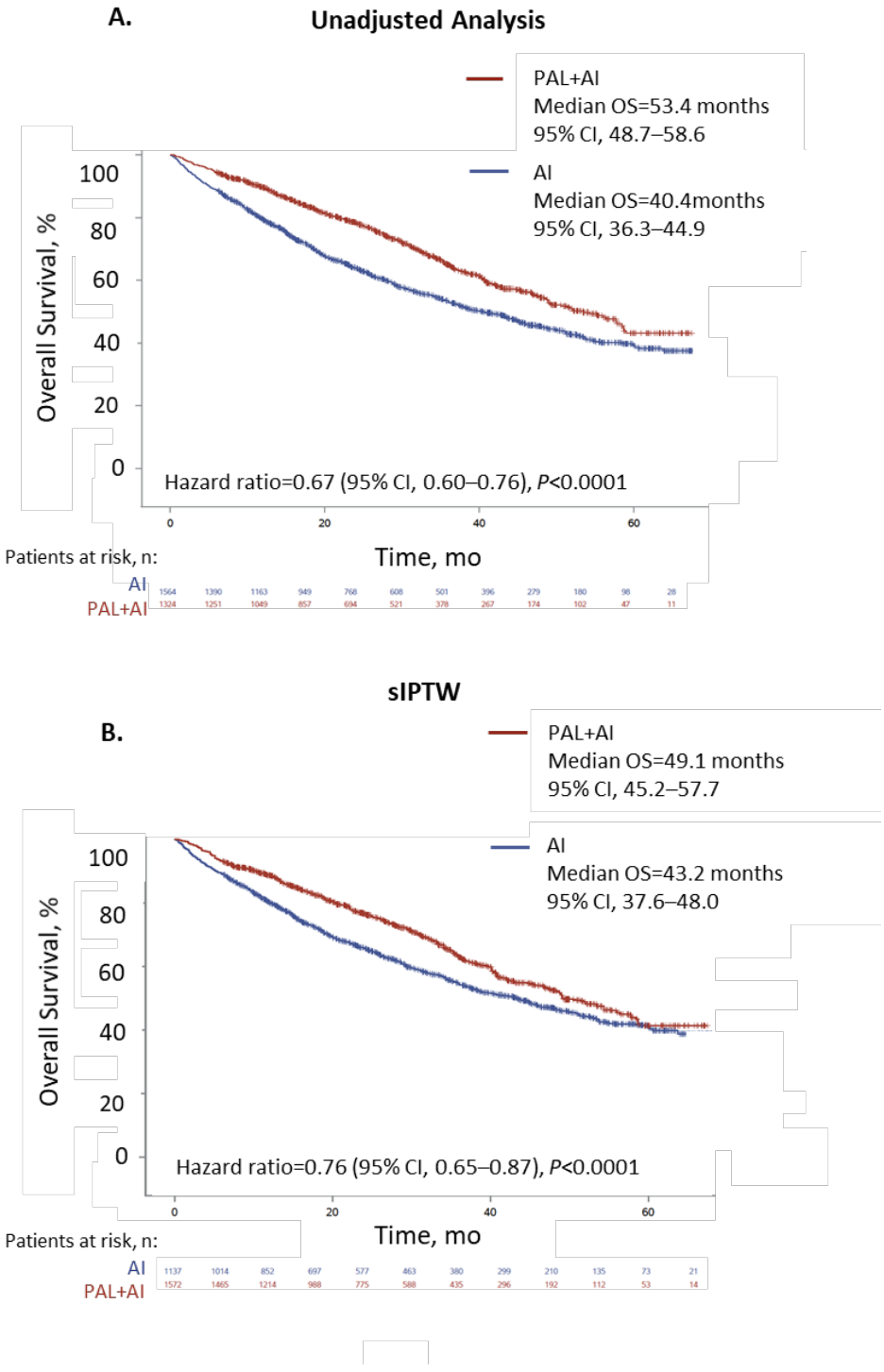
- Approximately 3000 patients will be included with about a 1:1 ratio between palbociclib plus AI and AI alone cohorts.
- The median OS for AI alone is assumed to be 40 months. An improvement of 25% to a median OS of 50 months (corresponding to a hazard ratio of 0.80) would be considered clinically meaningful. Therefore, 750 OS events will be required to have at least 80% power to detect a hazard ratio of 0.80 using a two-sided log-rank test at a significance level of 0.05 based on the exponential distribution assumptions of OS for both cohorts.
- Stabilized inverse probability treatment weighting (sIPTW) will be the primary analysis used to balance baseline demographic and clinical characteristics between palbociclib plus AI and AI alone groups.
    - The weighted Cox proportional hazards model will be used to compute the hazard ratio and the corresponding 95% CI.
- Propensity score matching (PSM) was conducted as a sensitivity analysis to balance baseline demographic and clinical characteristics and to adjust for differences in observed potential confounders between the two cohorts; matches will be made using 1:1 nearest neighbor matching without replacement.
    - A stratified Cox proportional hazards model will be used to compute the hazard ratio and the corresponding 95%CI.

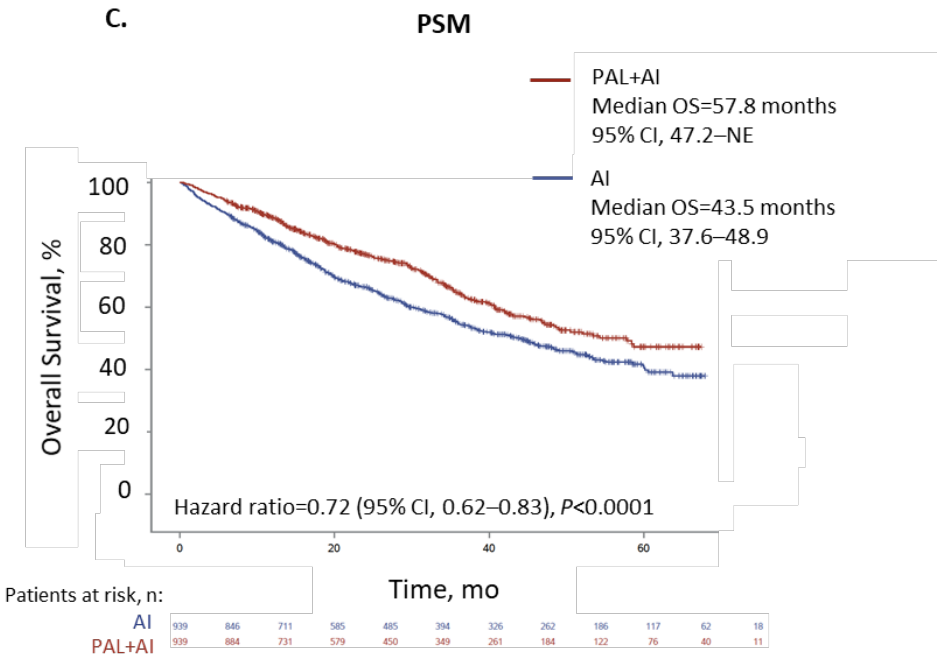
	• OS and rwPFS will be summarized using the weighted Kaplan-Meier method. • All analyses will be performed by using SAS® Version 9.1.4 or higher. ***Authors:*** *Are there any other methods that should be included?*

Results	Suggested key points and suggested figures/tables:
	
	Patients
	
	• From February 3, 2015 to March 31, 2020, in the Flatiron Database a total of 2888 postmenopausal women or men with HR+/HER2– MBC started palbociclib plus AI (n=1324) or AI alone (n=1564) as first-line therapy.
	• A total of 10 men were included in the palbociclib group and 19 men in the AI alone group.
	• Patient characteristics were generally balanced after sIPTW adjustment (**Table 1**), and between propensity score–matched groups (**Supplementary Table 1**).
	  ○ After sIPTW adjustment, the median age was 70 years in both treatment groups.
	  ○ The majority of patients (~68%) were white in each treatment group.
	  ○ Other baseline characteristics will be summarized
	• After sIPTW adjustment, the median duration of follow-up was 23.9 months (IQR, 12.8–38.0) in the palbociclib plus AI group and 24.5 months (IQR, 12.0–42.9) in the AI alone group.

	Overall Survival • In the unadjusted analysis of the full cohort (n=2888), median OS was significantly longer among patients in the palbociclib group versus the AI group (*P*<0.0001; **Figure 2A**). • After sIPTW adjustment, OS (95% CI) was 49.1 months (45.2–57.7) in the palbociclib group (n=1572) and 43.2 months (37.6–48.0) in the AI group (n=1137; hazard ratio, 0.76 [95% CI, 0.65–0.87]; *P*<0.0001; **Figure 2B**). o The OS rate at 24, 36, and 48 months were 76.6%, 62.9%, and 52.4% in the palbociclib plus AI group, and 65.6%, 54.4%, and 46.8% in the AI alone group. • Using PSM (sensitivity analysis), OS (95% CI) was 57.8 months (47.2–not estimable) in the palbociclib group (n=939) and 43.5 months (37.6–48.9) in the AI group (n=939; hazard ratio, 0.72 [95% CI, 0.62–0.83]; *P*<0.0001; **Figure 2C**).

Figure 2. Kaplan-Meier Curves of Overall Survival

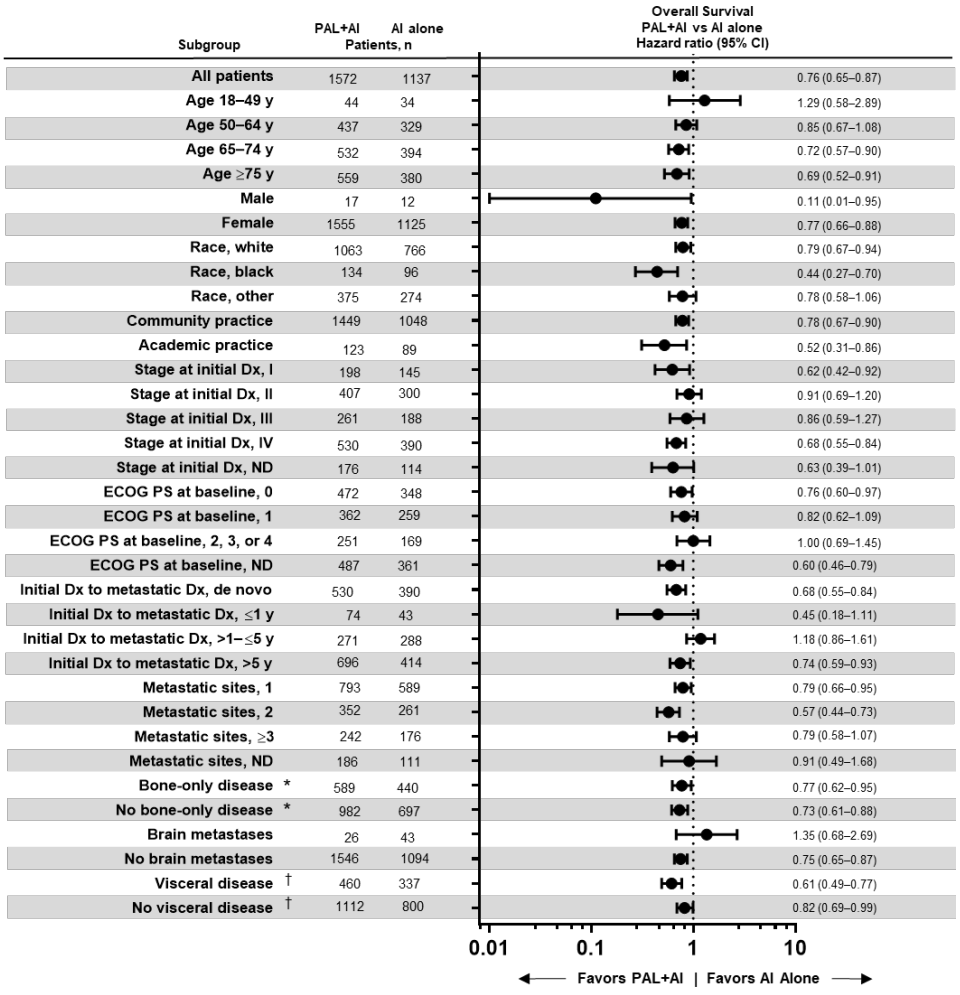




AI=aromatase inhibitor; NE=not estimable; OS=overall survival; PAL=palbociclib; PSM=propensity score matching; sIPTW=stabilized inverse probability of treatment weighting.

- A consistent OS benefit with palbociclib plus AI versus AI alone was observed generally across most subgroups examined after sIPTW (**Figure 3**).
- Similar OS subgroup results were observed in the PSM-adjusted sensitivity analysis (**Supplementary Figure 1**).

Figure 3. Forest Plot of OS by Subgroup after sIPTW



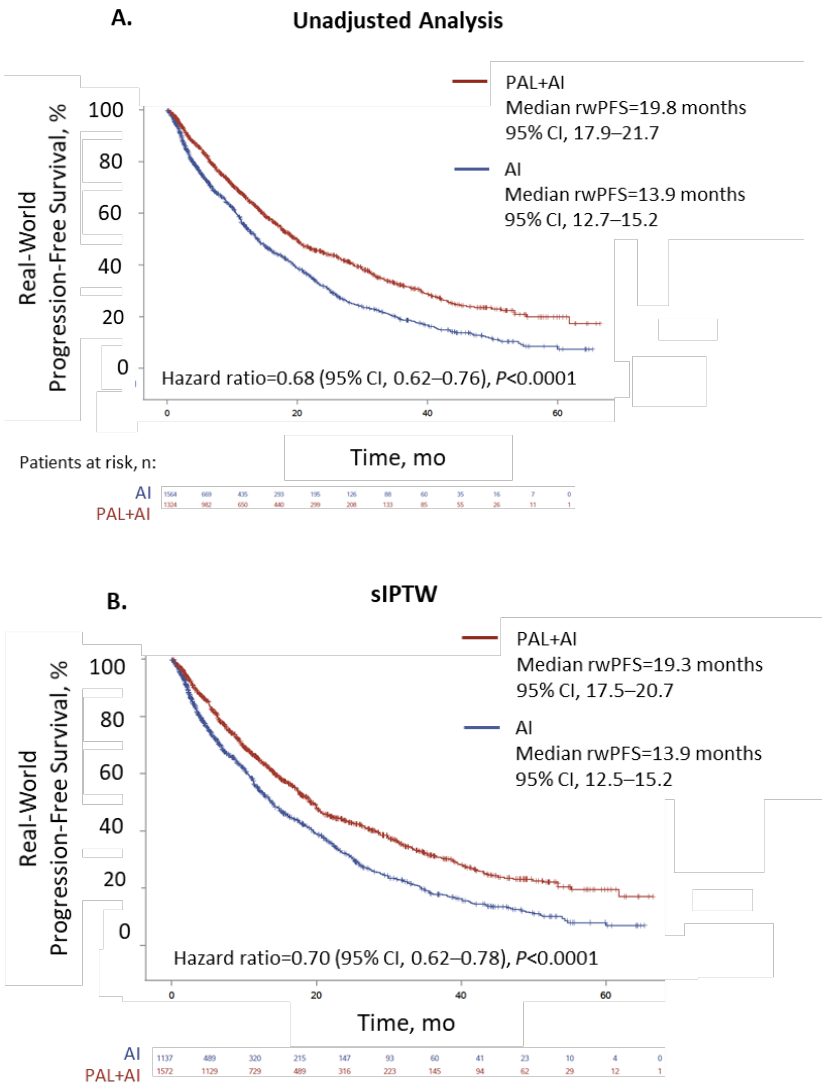
AI=aromatase inhibitor; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; ND=not documented; PAL=palbociclib; sIPTW=stabilized inverse probability of treatment weighting.
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.
‡Bone-only disease was defined as metastatic disease in the bone only.

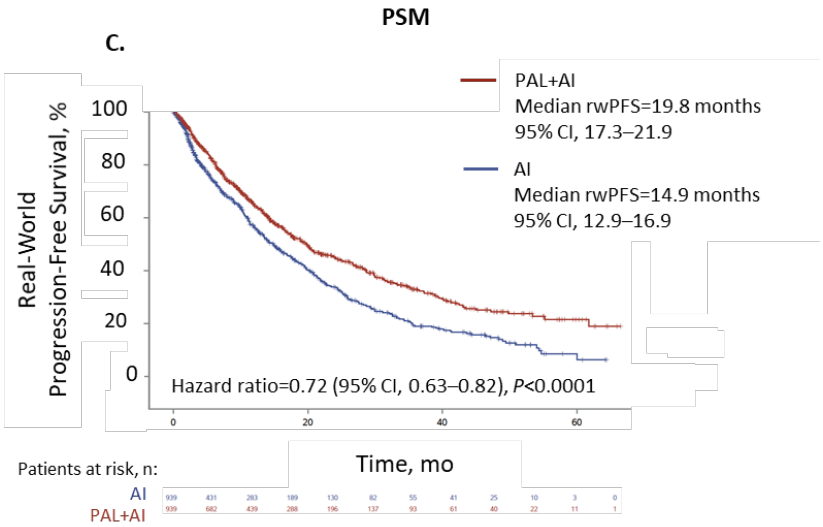
Real-World Progression-Free Survival

- In the unadjusted analysis of the full cohort, median rwPFS was significantly longer among patients in the palbociclib group versus the AI group (*P*<0.0001; **Figure 4A**).

- After sIPTW adjustment, rwPFS (95% CI) was 19.3 months (17.5–20.7) in the palbociclib group and 13.9 months (12.5–15.2) in the AI group (hazard ratio, 0.70 [95% CI, 0.62–0.78]; *P*<0.0001; **Figure 4B**).
- Using PSM, rwPFS (95% CI) was 19.8 months (17.3–21.9) in the palbociclib group and 14.9 months (12.9–16.9) in the AI group (hazard ratio, 0.72 [95% CI, 0.63–0.82]; *P*<0.0001; **Figure 4C**).

Figure 4. Kaplan-Meier Curves of Real-World Progression-Free Survival

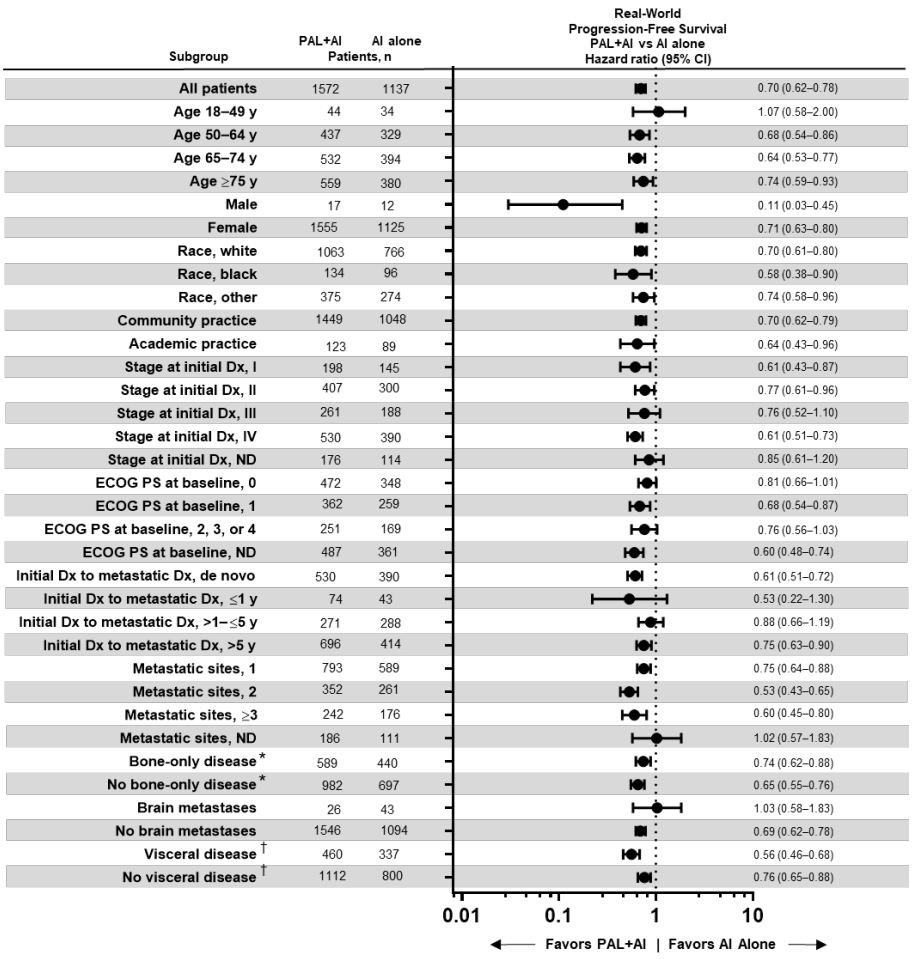




AI=aromatase inhibitor; PAL=palbociclib; rwPFS=real-world progression-free survival; PSM=propensity score matching; sIPTW=stabilized inverse probability of treatment weighting.

- A consistent rwPFS benefit with palbociclib plus AI versus AI alone was observed generally across most subgroups examined after sIPTW (**Figure 5**).
- Similar rwPFS subgroup results were observed in the PSM-adjusted sensitivity analysis (**Supplementary Figure 2**).

Figure 5. Forest Plot of rwPFS by Subgroup after sIPTW



AI=aromatase inhibitor; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; ND=not documented; PAL=palbociclib; sIPTW=stabilized inverse probability of treatment weighting.
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.
‡Bone-only disease was defined as metastatic disease in the bone only.

- Subsequent second-line treatments following first-line palbociclib plus AI or AI alone after sIPTW analysis are presented in **Table 2**.
    - About 50% of patients in the palbociclib group and 65% of patients in the AI alone group had data available on any second-line treatment.

	▪ Among these patients, about 21% and 33% of patients in the palbociclib group and AI group, respectively, received a CDK4/6 inhibitor as second-line treatment. ***Authors:*** *Are there other results that may be important to include?*
Discussion	Suggested key points: • Summarize study results (ie, OS, rwPFS, subgroup analyses, second-line treatments). • Briefly discuss the effectiveness of palbociclib plus aromatase inhibitors in the context of PALOMA-2. • Discuss findings in context with other real-world palbociclib studies conducted using the Flatiron database. ○ The sample size in the current study was larger than previous Flatiron studies (n=2888 vs n=1430 in DeMichele et al and n=1383 in Brufsky et al).[7,8] ○ Previous studies had potential follow-up for ≥3 months from the index date to data cutoff date while the current study had potential follow-up for ≥6 months from the index date to data cutoff date. ○ In DeMichele et al, median duration of follow-up was 24.2 months and 23.3 months in the palbociclib and letrozole groups, respectively.[7] ▪ Median rwPFS was 20.0 versus 11.9 months, respectively; median OS was 43.1 months in the letrozole group and not reached in the palbociclib group.

	○ In Brufsky et al, median duration of follow-up of 20.6 months in the palbociclib plus letrozole group and 22.3 months in the letrozole alone group.[8] ▪ Among patients with at least one tumor response assessment, median rwPFS was longer with palbociclib combination therapy; OS was 43.4 months with letrozole alone and not reach with palbociclib plus letrozole • Discuss findings in context with other real-world palbociclib studies. • Highlight that the findings presented herein support the use of palbociclib plus AI as first-line treatment in postmenopausal women and in men with HR+/HER2– MBC. • Discuss study limitations ○ Retrospective database analysis ○ Findings from the Flatiron Database may not be generalized to other patient populations ○ Some subgroups may have insufficient sample size ***Authors:*** *Are there any other discussion points you would like to include?*
Conclusions	Suggested key points: • This is the largest real-world comparative effectiveness study to date. • Treatment with palbociclib plus AI significantly prolonged OS and rwPFS versus AI alone in a heterogeneous population of postmenopausal women and men with HR+/HER2– MBC.

	○ These results were observed across most subgroups. • These results support first-line palbociclib plus AI as a standard of care for patients with HR+/HER2– MBC. ***Authors:*** *Are there any other important concluding points?*
Acknowledgments	Editorial support was provided by Jill Shults, PhD, of ICON plc (Blue Bell, PA, USA), and was funded by Pfizer Inc. ***Authors:*** *Are there any other people who should be acknowledged?*

Potential References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER) cancer stat facts: female breast cancer. Available at: https://seer.cancer.gov/statfacts/html/breast.html. Accessed May 19, 2021.
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6. Cottu P, et al. *Breast*. 2021;61:118-122.
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8. Brufsky A, et al. *Target Oncol*. 2021;16(5):601-611.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Unadjusted Total Cohort			Cohort After sIPTW		
	Palbociclib + AI (n=772)	AI Alone (n=658)	Standardized Difference	Palbociclib + AI (n=839)	AI Alone (n=698)	Standardized Difference
Age, y						
Mean (SD)	67.1 (9.6)	70.9 (9.7)	–0.3949	69.4 (10.8)	69.5 (8.2)	–0.0161
Median (IQR)	67 (61–74)	72 (64–80)		70.0 (63–78)	70.0 (63–79)	
Age group,* n (%), y						
18–49	48 (3.6)	41 (2.6)	0.0577	44 (2.8)	34 (3.0)	–0.0134
50–64	468 (35.4)	375 (24.0)	0.2509	437 (27.8)	329 (28.9)	–0.0238
65–74	495 (37.4)	500 (32.0)	0.1140	532 (33.8)	394 (34.7)	–0.0172
≥75	313 (23.6	648 (41.4)	–0.3868	559 (35.6)	380 (33.5)	0.0445
Gender						
Male	10 (0.76)	19 (1.2)	–0.0465	17 (1.1)	12 (1.0)	
Female	1314 (99.2)	1,545 (98.8)		1,555 (98.9)	1125 (99.0)	
Race/ethnicity,* n (%)						
White	900 (68.0)	1059 (67.7)	0.0057	1063 (67.6)	766 (67.4)	0.0044
Black	107 (8.1)	136 (8.7)	–0.0222	134 (8.5)	96 (8.5)	0.0019
Other	317 (23.9)	369 (23.6)	0.0082	375 (23.9)	274 (24.1)	–0.0060
Practice type,* n (%)						
Community	1208 (91.2)	1449 (92.7)	–0.0518	1449 (92.2)	1,048 (92.1)	0.0016
Academic	116 (8.8)	115 (7.4)		123 (7.8)	89 (7.9)	
Disease stage at initial diagnosis,* n (%)						
I	147 (11.1)	216 (13.8)	–0.0821	198 (12.6)	145 (12.8)	–0.0060
II	345 (26.1)	418 (26.7)	–0.0152	407 (25.9)	300 (26.4)	–0.0118
III	181 (13.7)	297 (19.0)	–0.1443	261 (16.6)	188 (16.6)	0.0011
IV	541 (40.9)	464 (29.7)	0.2359	530 (33.7)	390 (34.3)	–0.0110
Not documented	354 (26.7)	169 (10.8)	–0.0850	176 (11.2)	114 (10.0)	0.0389
ECOG PS,* n (%)						
0	499 (37.7)	397 (25.4)	0.2672	472 (30.1)	348 (30.6)	–0.0126
1	318 (24.0)	334 (21.4)	0.0636	362 (23.0)	259 (22.8)	0.0066
2, 3, or 4	153 (11.6)	271 (17.3)	–0.1647	251 (15.9)	169 (14.9)	0.0290

Not documented	354 (26.7)	562 (35.9)	–0.1992	487 (31.0)	361 (31.7)	–0.0160
Visceral disease,*† n (%)						
No	880 (66.5)	1,160 (74.2)	–0.1692	1112 (70.7)	800 (70.3)	0.0085
Yes	444 (33.5)	404 (25.8)		460 (29.3)	337 (29.7)	
Bone-only disease,‡ n (%)						
No	805 (60.8)	965 (61.7)	–0.0185	982 (62.5)	697 (61.3)	0.0253
Yes	519 (39.2)	599 (38.3)		589 (37.5)	440 (38.7)	
Brain metastases, n (%)						
No	1298 (98.0)	1,514 (96.8)	0.0778	1546 (98.3)	1094 (96.2)	0.1310
Yes	26 (2.0)	50 (3.2)		26 (1.7)	43 (3.8)	
Disease-free interval, n (%), y						
De novo	541 (40.9)	464 (29.7)	0.2359	530 (33.7)	390 (34.3)	–0.0110
≤1	40 (3.0)	66 (4.2)	–0.0642	74 (4.7)	43 (3.8)	0.0442
>1–5	191 (14.4)	429 (27.4)	–0.3238	271 (17.2)	288 (25.4)	–0.1992
>5	551 (41.6)	601 (38.4)	0.0651	696 (44.3)	414 (36.4)	0.1612
Not documented	1 (0.08)	4 (0.3)	–0.0443	1 (0.05)	2 (0.2)	–0.0388
Number of metastatic sites,*§ n (%)						
1	654 (49.4)	843 (53.9)	–0.0902	793 (50.4)	589 (51.8)	–0.0273
2	367 (27.7)	291 (18.6)	0.2173	352 (22.4)	261 (22.9)	–0.0136
3	178 (13.4)	133 (8.5)	0.1586	158 (10.1)	129 (11.3)	–0.0413
4	56 (4.2)	31 (2.0)	0.1298	51 (3.3)	27 (2.4)	0.0501
≥5	33 (2.5)	22 (1.4)	0.0786	33 (2.1)	20 (1.7)	0.0256
Not documented	36 (2.7)	244 (15.6)	–0.4581	186 (11.8)	111 (9.8)	0.0654
First-line AI						
Letrozole	1,140 (86.1)	659 (42.1)	1.0314	1,321	491 (43.2)	0.9368
Anastrozole	143 (10.8)	735 (47.0)	–0.8709	197	522 (45.9)	–0.7893
Exemestane	41 (3.1)	170 (10.9)	–0.3086	55	124 (10.9)	–0.2906

AI=aromatase inhibitor; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; IQR=interquartile range; sIPTW= stabilized inverse probability treatment weighting.

*Variable used in propensity score matching model.

[†]Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.
[‡]Bone-only disease was defined as metastatic disease in the bone only.
[§]Multiple metastases at the same site were counted as 1 site (eg, if a patient had 3 bone metastases in the spine, it was considered only 1 site).
The balance in important prognostic baseline characteristics was assessed using a standardized differences approach, with a standardized difference of ≥0.10 considered indicative of practical significance [24].
The total patient population for different subgroups varied due to the application of sIPTW. Therefore, the total n number for each subgroup may not have always equaled the N number of the treatment arm (due to rounding error and categorization differences). Calculated percentages were based on the number of patients reported within each subgroup.

Table 2. Subsequent Second-Line Anticancer Treatments After sIPTW Analysis

Treatments, n (%)	Palbociclib + AI (n=1572)	AI Alone (n=1137)
First-line treatment only*		
Any second-line treatment received†	768 (48.9)	741 (65.1)
CDK4/6 inhibitor	331 (43.1)	374 (50.5)
Chemotherapy	162 (21.1)	112 (15.1)
Endocrine therapy alone	154 (20.1)	225 (30.4)
Other anticancer treatment	164 (21.4)	94 (12.7)

AI=aromatase inhibitor; CDK4/6=cyclin-dependent kinase 4/6; sIPTW=stabilized inverse probability of treatment weighting.
*Includes patients who continued treatment, died, or were censored in the first-line setting.
†Patients could have received >1 category of second-line treatment.

Authorship credit is to be given only if all four of the following criteria are met:

ICMJE CRITERIA	
1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND	"A substantial contribution is an important intellectual contribution, rather than technical assistance, without which the work, or an important part of the work, could not have been completed or the manuscript could not have been written and submitted for publication."* General supervision of the research group that is conducting or supervising a project is not sufficient for authorship. Similarly, participation solely in the acquisition of funding or collection of data does not justify authorship.
2) Drafting the work or revising it critically for important intellectual content; AND	This criterion refers to revisions beyond minor corrections for grammar, language, formatting, or layout. The key is sustained intellectual contribution, the provision of substantial comments, and approval of the final version. Although preferred, it is not always feasible or necessary for authors to comment on every stage of manuscript development.
3) Final approval of the version to be published; AND	To give final approval, it is necessary to have carefully read the entire manuscript from start to finish.
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved	Each author is accountable for the work and should have confidence in the integrity of the other authors' contributions. Each author should be able to identify who wrote each section.

Table S2. Target Journal

Journal	Circ.	IF	Issues, per y	Reject Rate, %	Sub to Acc, wk	Acc to O/L Pub, wk	Acc to Pub, wk	Notes	Supplementary Material
NPJ Breast Cancer	NA	6.923	NA	NA	6-27	NA	NA	• Abstract: 150 words • Length: 4,500 words • Tables|figures: 10 • References: 60	• Supplemental material may include tables, figures, video, audio, notes, data, discussion or equations

Abbreviations: Acc=acceptance; Circ=circulation; IF=impact factor; Sub=submission; n/a=not available; O/L=online; Pub=publication; Reject=rejection.

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