PD13-10 – Impact of Proton Pump Inhibitors on Palbociclib Outcomes in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer: Exploratory Analysis of the PARSIFAL Trial

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BACKGROUND

- The use of proton pump inhibitors (PPI) among cancer patients (pts) is quite frequent [1,2].
- Palbociclib (PAL) is an oral, cyclin-dependent kinase 4 and 6 inhibitor recommended under fed conditions [3]. PAL showed a reduced solubility when gastric pH is > 4.5, a level commonly achieved by PPI [3].
- Observational retrospective studies on concomitant PPI with PAL or ribociblib demonstrated a shorter progression-free survival (PFS) among PPI users than nonusers [4].
- In the randomized, phase 2 PARSIFAL trial, PAL plus fulvestrant demonstrated no improvement in PFS and overall survival (OS) *versus* PAL plus letrozole as frontline treatment in hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer (ABC) pts [5].

OBJECTIVE

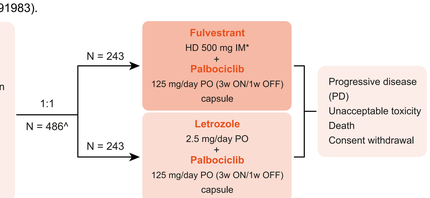
- To assess the impact of PPI on PAL efficacy and safety in pts included in the PARSIFAL study.

STUDY DESIGN

Post-hoc exploratory analysis including **all pts** in the **intention-to-treat** (ITT) set of the **PARSIFAL study** (ClinicalTrials.gov identifier: NCT02491983).

Key elegibility criteria

- HR[+]/HER2[-] ABC
- Postmenopausal or premenopausal women
- No prior therapy for advanced disease
- Endocrine-sensitive criteria:
  - Relapse >12 months from the end of endocrine therapy; or
  - *de novo* metastatic disease



*: Days 1, 15, 29 and once monthly thereafter; ^Randomization: type of disease (*de novo*, metastatic or recurrent) and presence or absence of visceral involvement

Abbreviations: HD, high dose; IM, intramuscular; mg, milligrams; N, number; PO, orally; w, weeks

METHODS

Data Source

- Review of concomitant medication records to identify pts with PPI prescription. Pts were divided based on PPI coadministration:

PPI naïve (N-PPI): no PPI administration over the whole study treatment

PPI users: pts with ≥1 PPI received over the entire PAL-based regimen

- **Early PPI users (E-PPI)**: Pts receiving PPI since the PAL-based treatment initiation
- **Long-term PPI users (LT-PPI)**: Pts who received PPI over the entire or ≥ 2/3 of the treatment with PAL
- **Other PPI users**: PPI users defined as neither E-PPI nor LT-PPI

Outcomes

- **Use of PPI** was evaluated with respect to:

i. **Pts baseline characteristics**;
ii. **Investigator-assessed progression-free survival (PFS)**;
iii. **Investigator-assessed overall survival (OS)**; and
iv. **Safety and tolerability of PAL plus endocrine therapy** by using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistics

- The differences in Investigator-assessed PFS and OS between PPI users and N-PPI were evaluated by Cox regression with age, Eastern Cooperative Oncology Group (ECOG) performance status, type of disease, visceral involvement, and number of metastatic sites as factors. The immortal time bias and misclassification for the analysis of ITT were addressed by landmark analyses.
- The differences in adverse events (AEs) between PPI users and N-PPI were assessed with adjusted logistic regression models. For all endpoints two-sided P values with an alpha ≤0.05 level of significance were used.

RESULTS

1. Study Development

- Enrollment for PARSIFAL study was carried out from July 30, 2015, to January 8, 2018, at 47 sites in 7 countries.
- The median follow-up was 32 months.
- Data cutoff was January 31, 2020, when the target number of PFS events (n = 256) was met.
- H2-antagonists were recommended as an alternative of PPIs.

2. Patient Characteristics at Baseline

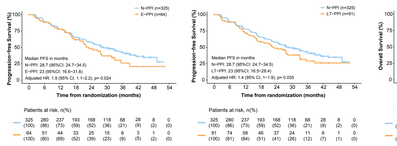
Characteristic	All patients (n=486)	PPI naïve (n=325)	PPI users (n=161)	Early PPI users (n=64)	Long-term PPI users (n=91)	Other PPI users (n=56)
Age, years, median (range)	63 (25–90)	60 (25–90)	66 (34–88)	67.5 (34–88)	68 (34–88)	62 (41–85)
P value	-	ref.	**<0.001**	**<0.001**	**<0.001**	0.211
Race						
White	461 (94.9)	306 (94.2)	155 (96.3)	64 (100)	91 (100)	50 (89.3)
Others	25 (5.1)	19 (5.8)	6 (3.7)	0	0	6 (10.7)
P value	-	ref.	0.273	0.269	0.134	**0.016**
ECOG performance status						
0	275 (56.6)	195 (60.0)	80 (49.7)	22 (34.4)	39 (42.9)	35 (62.5)
1	187 (38.5)	120 (36.9)	67 (41.6)	36 (56.2)	42 (46.2)	17 (30.4)
2	24 (4.9)	10 (3.1)	14 (8.7)	6 (9.4)	10 (11.0)	4 (7.1)
P value	-	ref.	**0.009**	**<0.001**	**<0.001**	0.35
Menopausal status						
Premenopausal	37 (7.6)	29 (8.9)	8 (5.0)	3 (4.7)	3 (3.3)	5 (8.9)
Postmenopausal	449 (92.4)	296 (91.1)	153 (95.0)	61 (95.3)	88 (96.7)	51 (91.1)
P value	-	ref.	0.172	0.38	0.119	0.899
Duration of palbociclib treatment, months, median (IQR)	25.1 (12.1–33.9)	25.5 (12.2–34.6)	24.6 (11.8–33.8)	20.4 (9–28.6)	20 (9.5–31.2)	31.4 (24.4–40.4)
P value	-	ref.	0.654	**0.015**	**0.014**	**0.002**
Hormone therapy administered in combination with palbociclib						
Fulvestrant	243 (50.0)	153 (47.1)	90 (55.9)	35 (54.7)	53 (58.2)	30 (53.6)
Letrozole	243 (50.0)	172 (52.9)	71 (44.1)	29 (45.3)	38 (41.8)	26 (46.4)
P value	-	ref.	0.083	0.329	0.078	0.67
Relative dose intensity of palbociclib						
%, median (IQR)	93.7 (85.6–98.4)	93.6 (85.1–98.3)	93.7 (86.9–98.7)	93.5 (83.7–98.4)	94.2 (87.3–99)	94.3 (87–98.5)
P value	-	ref.	0.39	0.815	0.212	0.212
Relative dose intensity of fulvestrant, n	243	153	90	35	53	30
%, median (IQR)	99.2 (97.3–100)	99.2 (96.8–100)	99.2 (98.3–100)	99 (98.1–100)	99.8 (98.5–100)	98.8 (98.3–99.8)
P value	-	ref.	0.185	0.401	0.316	0.243
Relative dose intensity of letrozole, n	243	172	71	29	38	26
%, median (IQR)	98.8 (96.3–99.9)	98.7 (96.2–99.9)	98.9 (97.2–99.8)	98.5 (97.1–99.5)	99 (97.2–100)	98.8 (97.4–99.5)
P value	-	ref.	0.709	0.948	0.271	0.271
Type of disease						
De novo	198 (40.7)	130 (40.0)	68 (42.2)	25 (39.1)	36 (39.6)	27 (48.2)
Recurrent	288 (59.3)	195 (60.0)	93 (57.8)	39 (60.9)	55 (60.4)	29 (51.8)
P value	-	ref.	0.708	1	1	0.287
Disease site						
Visceral	233 (47.9)	161 (49.5)	72 (44.7)	30 (46.9)	47 (51.6)	21 (37.5)
Nonvisceral	253 (52.1)	164 (50.5)	89 (55.3)	34 (53.1)	44 (48.4)	35 (62.5)
P value	-	ref.	0.366	0.8	0.813	0.128
Number of disease sites						
<3	274 (56.4)	189 (58.2)	85 (52.8)	30 (46.9)	43 (47.3)	34 (60.7)
≥3	212 (43.6)	136 (41.8)	76 (47.2)	34 (53.1)	48 (52.7)	22 (39.3)
P value	-	ref.	0.306	0.127	0.083	0.581
Previous treatment with PPI						
No	407 (83.7)	320 (98.5)	87 (54)	5 (7.8)	33 (36.3)	52 (92.9)
Yes	79 (16.3)	5 (1.5)	74 (46)	59 (92.2)	58 (63.7)	4 (7.1)
P value	-	ref.	**<0.001**	**<0.001**	**<0.001**	0.076
Duration of previous therapy, n	79	5	74	59	58	4
Months, median (IQR)	8.5 (1.4–46.9)	2.1 (1.1–2.4)	8.8 (1.6–49.7)	9.1 (1.6–53.9)	9.2 (1.4–58.2)	5.4 (3.8–17.5)
P value	-	ref.	0.255	0.271	0.258	0.286
Type of concomitant PPI						
Omeprazole	130 (26.7)	0	130 (80.7)	54 (84.4)	74 (81.3)	44 (78.6)
Pantoprazole	33 (6.8)	0	33 (20.5)	6 (9.4)	19 (20.9)	13 (23.2)
Esomeprazole	24 (4.9)	0	24 (14.9)	4 (6.2)	14 (15.4)	9 (16.1)
Lansoprazole	11 (2.3)	0	11 (6.8)	3 (4.7)	6 (6.6)	4 (7.1)
Rabeprazole	3 (0.6)	0	3 (1.9)	2 (3.1)	3 (3.3)	0
Treatment duration with concomitant PPI, n	161	0	161	64	91	56
Months, median (IQR)	11 (0.9–52.2)	0	11 (0.9–52.2)	15.4 (2.4–52.2)	18.1 (9.1–52.2)	1.4 (0.3–27.3)
Time to PPI treatment start since randomization, n	161	0	161	64	91	56
Months, median (IQR)	1 (0–13.5)	0	1 (0–13.5)	0	0 (0–2.7)	16.5 (5.2–29.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range, defined as percentile 25 and percentile 75; n, number; ref, reference category; PPI, proton pump inhibitors

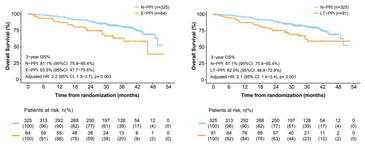
NOTE: Data presented as No. (%) unless otherwise noted

3. Effect of concomitant PPI on efficacy

Kaplan-Meier curves of PFS between N-PPI and E-PPI or LT-PPI



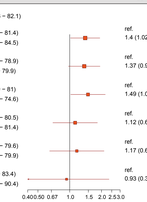
Kaplan-Meier curves of OS between N-PPI and E-PPI or LT-PPI



Abbreviations: 95% CI, 95% of confidence interval; E-PPI, early PPI users; HR, hazard ratio; LT-PPI, long-term PPI users; n, number of patients; N-PPI, PPI nave; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitors

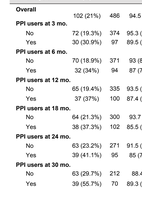
Landmark analysis of PFS at 3, 6, 12, 18, 24, and 30 months in N-PPI and PPI users

Landmark analysis	PFS events (%)	n	1–year PFS rate (%) 95% CI	Adjusted HR 95% CI	p
Overall	256 (52.7%)	486	78.7% (74.6 – 82.1)		
PPI users at 3 mo.					
No	188 (50.9%)	369	77.4 (72.7 – 81.4)	ref. 1.4 (1.02–1.93)	0.039
Yes	47 (58%)	81	76.6 (65.4 – 84.5)		
PPI users at 6 mo.					
No	164 (48.5%)	338	74.5 (69.4 – 78.9)	ref. 1.37 (0.97–1.94)	0.071
Yes	43 (55.1%)	78	71 (59.4 – 79.9)		
PPI users at 12 mo.					
No	120 (42.9%)	280	76.4 (70.9 – 81)	ref. 1.49 (1.02–2.17)	0.038
Yes	37 (48.7%)	76	64.9 (52.8 – 74.6)		
PPI users at 18 mo.					
No	80 (35.6%)	225	75.3 (68.9 – 80.5)	ref. 1.12 (0.69–1.83)	0.635
Yes	21 (31.3%)	67	71.6 (58.1 – 81.4)		
PPI users at 24 mo.					
No	51 (27%)	189	73.2 (65.2 – 79.6)	ref. 1.17 (0.64–2.11)	0.61
Yes	15 (23.8%)	63	67.7 (50.7 – 79.9)		
PPI users at 30 mo.					
No	25 (18.8%)	133	75.6 (65 – 83.4)	ref. 0.93 (0.37–2.36)	0.883
Yes	6 (13.3%)	45	79.5 (59.2 – 90.4)		



Landmark analysis of OS at 3, 6, 12, 18, 24 and 30 months in N-PPI and PPI users

Landmark analysis	Deaths (%)	n	1–year OS rate (%) 95% CI	Adjusted HR 95% CI	P
Overall	102 (21%)	486	94.5 (92 – 96.2)		
PPI users at 3 mo.					
No	72 (19.3%)	374	95.3 (92.6 – 97.1)	ref. 2.12 (1.34–3.33)	0.001
Yes	30 (30.9%)	97	89.5 (81.4 – 94.2)		
PPI users at 6 mo.					
No	70 (18.9%)	371	93 (89.9 – 95.2)	ref. 2.02 (1.28–3.19)	0.002
Yes	32 (34%)	94	87 (78.3 – 92.4)		
PPI users at 12 mo.					
No	65 (19.4%)	335	93.5 (90.2 – 95.7)	ref. 2.06 (1.26–3.38)	0.004
Yes	37 (37%)	100	87.4 (78.8 – 92.6)		
PPI users at 18 mo.					
No	64 (21.3%)	300	93.7 (90.1 – 96)	ref. 1.87 (1.06–3.31)	0.03
Yes	38 (37.3%)	102	85.5 (75.6 – 91.5)		
PPI users at 24 mo.					
No	63 (23.2%)	271	91.5 (86.9 – 94.5)	ref. 1.66 (0.85–3.22)	0.135
Yes	39 (41.1%)	95	85 (73.3 – 91.8)		
PPI users at 30 mo.					
No	63 (29.7%)	212	88.4 (81 – 93)	ref. 1.1 (0.44–2.75)	0.844
Yes	39 (55.7%)	70	89.3 (75.9 – 95.4)		

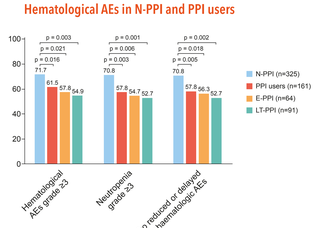


Abbreviations: 95% CI, 95% of confidence interval; HR, hazard ratio; n, number of patients; N-PPI, PPI naïve; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitors ; ref, reference category.

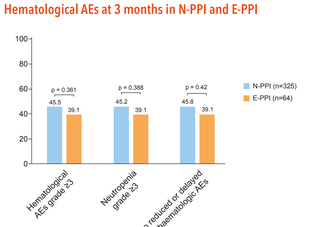
4. Safety of PAL plus endocrine therapy according to PPI coadministration

- Grade ≥3 hematological AEs occurred in 71.7% (233 of 325 pts) of N-PPI compared with 57.8% (37 of 64 pts; P=0.021) of E-PPI and 54.9% (50 of 91 pts; P=0.003) of LT-PPI.
- Dose reductions and delays due to hematological AEs were reported in 70.8% (230 of 325 pts) of N-PPI compared with 56.3% (36 of 64 pts; P=0.018) of E-PPI and 52.7% (48 of 91 pts; P=0.002) of LT-PPI.
- At 3 months, 45.8% (149 of 325 pts) of N-PPI required a dose reduction or delay due to hematological AEs compared with 39.1% (25 of 64 pts; P=0.42) of E-PPI.

Hematological AEs in N-PPI and PPI users



Hematological AEs at 3 months in N-PPI and E-PPI



Abbreviations: AEs, adverse events; E-PPI, early PPI users; LT-PPI, long-term PPI users; N-PPI, PPI nave; PPI, proton pump inhibitors

STUDY LIMITATIONS

1. This is a non pre-planned analysis form PARSIFAL study.
2. Although the protocol specified the administration of PAL with food, PAL intake was not monitored.
3. The indication for PPI use may have influenced the results of our study, particularly regarding the OS (elderly patients and worst PS at baseline).
4. The lack of pharmacokinetic data prevented us from fully confirm the interaction between PAL and PPIs by a reduced absorption.

CONCLUSIONS

1. Early and sustained coadministration of PPI with PAL and endocrine therapy were associated with lower efficacy, hematological toxicities, and dose modifications. Despite the post-hoc nature of the study, these findings suggest pharmacokinetic interactions between PPI and PAL capsules.
2. Further confirmatory studies including the tablet formulation of PAL, which is expected to assure its optimal absorption, are needed.

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