354P Synergistic preclinical efficacy through combination of the CDK4 and CDK2 selective inhibitors, PF-07220060 and PF-07104091, respectively, in HR+ HER2- breast cancer

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Background: PF-07220060 (CDK4i) is a first-in-class CDK4 selective inhibitor, with superior efficacy and improved safety profile when compared to dual CDK4/6 inhibitors. PF-07220060 is currently being evaluated in a Phase 3 clinical trial in HR+/HER2- breast cancer. PF-07220060 provides the flexibility to increase its exposure and thus realize near complete target coverage of the CDK4 oncogene in HR+/HER2- breast cancer. PF-07104091 (CDK2i) is a first-in-class CDK2-selective inhibitor, also under clinical investigation in patients with HR+/HER2- breast cancer.

Methods: We interrogated the mechanisms of resistance to PF-07220060 in an in vivo model of HR+/HER2- breast cancer. Unbiased molecular analysis of the resistant tumors was conducted and in vitro as well as in vivo follow-up studies performed. Various dosing regimens with the combination of CDK4i (PF-07220060) and CDK2i (PF-07104091), were tested in naïve and palbociclib resistant in vivo models to identify minimum doses that could still achieve significant tumor growth inhibition (TGI).

Results: Molecular analysis of PF-07220060 resistant tumors showed upregulation of numerous candidate resistance mediators, including cyclin E1. Expression of CDK6 remained undetectable. Co-treatment of PF-07220060 with the selective CDK2i, PF-07104091, inhibited RB1 phosphorylation and sensitized HR+/HER2- breast tumors to PF-07220060. Combinatorial benefit was characterized by tumor regression rather than tumor stasis. Despite lowering one or both inhibitor concentrations, there were no differences in TGI observed between the different dosing regimens. At clinically relevant dosing, the anti-tumor efficacy of PF-07104091 in combination with PF-07220060 was superior to PF-07104091 plus palbociclib.

Conclusions: Combining the highly selective CDK2i (PF-07104091) and CDK4i (PF-07220060) for HR+/HER2- breast cancer circumvents inhibition of CDK6, resulting in less hematologic toxicity. Further, increased anti-tumor efficacy and tumor regression seen with this combination (unlike with the single agents, or the combination of CDK2i and palbociclib) provide the rationale for the current clinical trial NCT05262400.

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355P EVERolimus effectiveness after proGREssion on CDK4/6 inhibitors for ENdocrine receptor-positive/HER2-negative, advanced breast cancer: EVERGREEN quasi-experimental study

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Background: Optimal sequence of endocrine therapy (ET) for ER+/HER2- advanced breast cancer (ABC) after progression on CDK4/6 inhibitors (CDK4/6i) remains uncertain. We aimed to compare the effectiveness and safety of everolimus-based ET (EVE) with ET alone (ETa) in this setting.

Methods: Multicentre, international, retrospective, quasi-experimental study of female patients (pts) with ER+/HER2- ABC who started next line of therapy after progression on CDK4/6i until 31/12/2022 with EVE (EVE-cohort, 9 sites) or ETa in sites where EVE is not standard of care in this setting (ETa-cohort, 5 sites), in Belgium and Portugal. We excluded pts receiving alpelisib as immediate next line. Primary endpoint was real-world progression-free survival (rwPFS); secondary endpoints were time to EVE failure, time to chemotherapy, overall survival (OS) and safety. We compared baseline characteristics and assessed their prognostic/predictive value in univariate/sub-group analyses. Time-to-event endpoints were assessed from start of EVE/ETa and measures of association were determined with 95% confidence interval (CI).

Results: We included 207 pts (EVE-cohort: 150; ETa-cohort: 57). Baseline characteristics were well balanced, except for visceral disease and number of prior lines (Table). ET was mostly exemestane in EVE-cohort (77%) and fulvestrant in ETa-cohort (61%). Median rwPFS was 5.0 for EVE vs. 4.3 m for ETa (HR 0.75, 95%CI 0.55-1.02), with a numerically higher magnitude of benefit in pts with *PIK3CA-AKT1-PTEN* pathway alterations (HR 0.56, 0.20-1.61, *N*=20 EVE: 15, ETa: 5). Secondary efficacy endpoints in the table. Multivariate analysis will be presented at the meeting. No notable safety issues emerged.

Table: 355P Main baseline characteristics and secondary time-to-event endpoints

	EVE (*N*=150)	ETa (*N*=57)	*p*-value
Characteristics			
Age, median (IQR)	61.0 (53.0, 71.0)	63.0 (50.0, 72.0)	0.61
ECOG, 0-1 (%)	132 (88)	53 (93)	0.68
Charlson Comorbidity Index, 6 (%)	116 (77)	43 (75)	0.63
PR-positive (%)	107 (71)	36 (63)	0.26
Recurrent (%)	108 (72)	38 (68)	0.45
Visceral (%)	97 (65)	43 (75)	*0.02*
One prior line (%)	86 (57)	45 (79)	*<0.01*
CDK4/6i $\geq$ 12 m (%)	97 (65)	33 (58)	0.51
Endpoints			
Time to EVE failure (m)	4.2		
Time to chemotherapy (m)	5.8	6.3	HR 1.02, 0.75-1.41
mOS (m)	24.2	20.6	HR 0.81, 0.54-1.20

Conclusions: We found a non-statistically significant trend for superiority of EVE compared to ETa for unadjusted rwPFS. Pts with *PIK3CA-AKT-PTEN* pathway alterations, may particularly benefit from the combination.

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356P Real-world effectiveness in subgroups of palbociclib + endocrine therapy in HR+/HER2- ABC patients: Interim results of the PERFORM study

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Background: Endocrine-therapy (ET) + CDK4/6i is 1L standard of care for HR+/HER2- ABC patients (pts) based upon demonstrated efficacy and tolerability in pivotal trials. As pts with low ECOG accrued to clinical trials may not represent a real-world cancer population, prospectively collected real-world data on effectiveness, tolerability and treatment patterns is of high medical interest.

Methods: Overall, 1.900 pts receiving 1L palbociclib + ET will be enrolled in the prospective NIS PERFORM at 320 sites across Germany and Austria. Primary endpoint is PFS. Secondary objectives include treatment patterns, effectiveness, and PROs. Three years after first patient-in the IA 3 was conducted, focusing on patient- and disease-characteristics, PROs and effectiveness in all pts and in corresponding subgroups. Here we focus on ECOG subgroups.

Results: Between 10/2020 and 09/2023, 1211 pts were enrolled. Of those, 990 pts were evaluable. Median age was 68.5 years and 91.4% of the primarily female population (99.2%) were postmenopausal. 391 (39.5%) pts presented with *de novo* ABC and 599 (60.5%) had relapsed from EBC. 11.7% of pts had an ECOG $\geq$2 at inclusion. ECOG $\geq$2 pts were older (median age 74.8 years) and presented more often with *de novo* ABC (48.3 vs 38.1%) and visceral disease (52.6 vs 44.6%) compared to ECOG $<$2 pts. Median PFS in the total population was 29.6 months. 12- and 24-month PFS rates were 71.0% and 52.1%, respectively. Across ECOG subgroups, 12-month PFS rate was 58.3% for ECOG $\geq$2 and 72.9% for $<$2. ORR and CBR were higher in pts with ECOG $<$2 vs ECOG $\geq$2, respectively (27.6 vs 34.8% and 50.0 vs 65.2%). Therapy was modified for 72.0% of pts in the total cohort and was comparable for ECOG subgroups with 73.3% for ECOG $\geq$2 and 71.8% for $<$2.

Conclusions: The IA3 of the PERFORM study gives further insights into effectiveness of 1L palbociclib + ET in a real-world setting. ECOG $\geq$2 pts were older and presented more often with *de novo* ABC and visceral metastases. 12-months PFS rate, ORR and CBR were higher in pts with ECOG $<$2. Therapy modification numbers were comparable. The results show that palbociclib + ET is tolerable and effective in this unfavorable subgroup with high therapeutical need.

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357P Bridging the gap between real-world studies (RWSs) and randomized controlled trials (RCTs) of 1st-line palbociclib+aromatase inhibitors (P+AI) in hormone receptor-positive (HR+)/HER2-negative(-) metastatic breast cancer (mBC)

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Background: RCTs remain the gold standard to assess the efficacy of a treatment seeking regulatory approval. However, RWSs provide insights into patients (pts)' outcomes in routine clinical practice. We assessed the real-world (RW) efficacy of 1st-line P+AI and compared it to RCTs' results.

Methods: A systematic review was performed to identify RWSs published from 2019 to 2023 including pts with HR+/HER2- mBC treated with 1st-line P+AI, with available median progression-free survival (mPFS) and/or overall survival (mOS). A meta-analysis was performed to estimate the pooled mPFS/OS using the median of the medians (MM) and weighted median of medians (WM). The RW estimates were deemed comparable to PALOMA1/2 RCTs' mPFS/OS, if MMPFS/OS or WMPFS/OS were in RCTs' mPFS/OS 95% confidence intervals (CI). Similar criteria applied to pooled hazard ratios (HR) of PFS/OS for P+AI vs. AI in visceral/non-visceral subgroups.

Results: Among 8 included RWSs (n=4624 pts) a MMPFS of 22.5 months (95%CI: 19.5-31.8) and WMPFS of 20.0 (95%CI: 19.3-31.8) were observed with 1st-line P+AI. The MMPFS was comparable to those of PALOMA1 (20.2, 95%CI: 13.8-27.5) and PALOMA2 (27.6 months, 95%CI: 22.4-30.3). The WMPFS was inferior to that of PALOMA2. A RW MMOS of 51.2 months (95%CI: 49.1-53.3) and WMOS of 49.1 (95%CI: 49.1-53.3) were observed, outperforming the PALOMA1 mOS of 37.5 months (95%CI: 37.5-47.8) and being comparable to PALOMA2 mOS of 53.8 (95%CI: 49.8-59.2). P+AI vs. AI in RW in visceral disease had superior PFS (HR: 0.56, 95%CI: 0.46-0.68) and OS (HR: 0.61, 95%CI: 0.49-0.77), similarly to the PALOMA2 PFS (HR: 0.62, 95%CI: 0.47-0.81) and better than PALOMA1 (HR: 1.13, 95%CI: 0.68-1.88) and PALOMA2 (HR: 0.86, 95%CI: 0.65-1.13) OS. In RW non-visceral disease, P+AI vs. AI had lower PFS benefit (HR: 0.76, 95%CI: 0.65-0.88) than PALOMA2 (HR: 0.50, 95%CI: 0.37-0.67). RW OS (HR: 0.82, 95%CI: 0.69-0.99) was similar than that of PALOMA2 (HR: 0.98, 95%CI: 0.74-1.31).

Conclusions: Our findings add to the understanding of the generalisability of RCTs results to RW and confirm the benefit of palbociclib+AI vs. AI alone.