Health economic properties of *palbociclib* in breast cancer patients with high risk of relapse following neoadjuvant therapy – results from the Penelope-B trial

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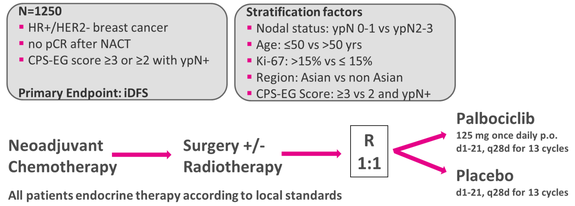
Background

Patients with hormone receptor-positive, HER2-negative breast cancer who have residual invasive disease after neoadjuvant chemotherapy (NACT) are at high risk of relapse. PENELOPE-B was a double-blind, placebo-controlled phase III study that investigated adding *palbociclib* (PAL) to adjuvant endocrine therapy (ET) in these high-risk patients. Clinical results showed no improvement in invasive disease-free survival with ET+PAL compared to ET alone[1]. Of note, PAL use in early breast cancer is not approved. Here we evaluated the cost-effectiveness of ET+PAL in PENELOPE-B.

Patients and Methods

A total of 1250 patients were recruited from 221 centres in 10 countries according to the eligibility criteria shown in Figure 1. Health and medical resource use were assessed before, during, and after treatment for up to 72 months. The EQ-5D instrument was used to score health-related quality of life[2]. Patient diaries and questionnaires were used to collect information on healthcare utilization.

Figure 1. Trial design



Medical costs were assessed from the German health system perspective using publicly available 2020 price weights[3-6]. Costs and effects were discounted at 3%. Main results are shown at four year follow-up (FU), estimates for years five and six were adjusted for administrative censoring with inverse probability weighting[7]. The incremental impacts of PAL on costs and quality-adjusted life years (QALYs) were modelled with seemingly unrelated regressions (SUR) controlling for patient characteristics and healthcare utilization at baseline. Missing outcome values were imputed with multiple imputation using chained equations (MICE) via predictive mean matching (PMM). Scenario and sensitivity analyses explored uncertainty in patient pathways and costs. Subgroup analyses were performed for key prognostic risk factors.

Results

Table 1. Sample characteristics

	ET + PAL N[a]=633 % (N)	ET N=611 % (N)
First diagnosis ≤ age 50 vs > 50	56 (356)	57 (347)
ypN 0-1 vs ypN 2-3	49 (313)	50 (304)
Ki-67 status > 15% vs ≤ 15%	28 (178)	29 (177)
CPS-EG score ≥ 3 vs 2 and ypN+	60 (380)	59 (361)
Tumour grade 1 or 2 vs 3	53 (337)	52 (315)
Hysterectomy (yes/no)	4 (25)	2 (13)
Breast reconstruction surgery (yes/no)	16 (104)	20 (120)
Germany (yes/no)	34 (218)	35 (213)

[a] 3 patients in PAL +ET and 3 patients in ET arm who never started study treatment were excluded.
Key: ET = Endocrine Therapy; PAL = Palbociclib; N = Number of patients; SD = Standard Deviation; CPS-EG = Clinical Pathological Stage-Estrogen Receptor;

- Table 1 shows patient characteristics were balanced between the arms, further details on the sample are available from Loibl et al[1].

Table 2. Clinical events, costs and QALYs

	ET + PAL Mean (SD)	ET Mean (SD)	P-value
Clinical events N = 1244			
FU to event (years)	2.14 (1.27)	1.77 (1.24)	0.009*
Relapse	0.23 (0.42)	0.23 (0.42)	0.891
Number of relapses	1.63 (1.06)	1.69 (1.23)	0.688
Secondary malignancy	0.02 (0.13)	0.02 (0.13)	0.763
Death	0.10 (0.30)	0.11 (0.31)	0.560
Quality of life N = 1104			
FU (years)	3.10 (1.32)	3.06 (1.34)	0.683
Baseline utility	0.90 (0.13)	0.89 (0.14)	0.179
Total QALYs	2.55 (1.13)	2.44 (1.10)	0.099*
Total discounted QALYs	2.39 (1.03)	2.29 (1.00)	0.101
Total cost (Euros, 2020) N = 1145			
FU (years)	3.20 (1.00)	3.16 (1.01)	0.443
Targeted therapy	35519 (8035)	989 (3893)	0***
Total costs	43050 (13383)	7685 (9690)	0***
Total discounted costs	41490 (12606)	7212 (9004)	0***

Key: QALY = Quality-Adjusted Life Years; ET = Endocrine Therapy; PAL = Palbociclib; SD = Standard Deviation; N = Number of patients; FU = Follow-Up. *** - statistically significant at 1%; ** - statistically significant at 5%; * - statistically significant at 10%.

- Table 2 shows no significant differences in clinical events or QALYs.
- Differences in costs between arms were dominated by the cost of PAL.
- Number of patients varied by outcome due to item-missingness, loss to follow-up, and censoring.

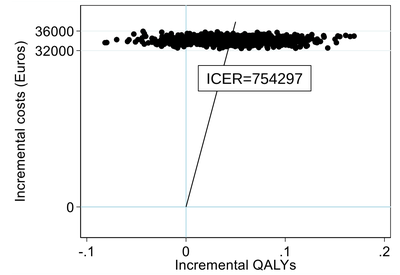
Table 3. Incremental costs, QALYs and ICERs at four years of FU

Adjustment for missing values/ baseline characteristics	None/None N costs = 1145 N QALYs = 1104 Mean (SE)	CC/SUR N = 1007 ß(SE)	MICE/SUR N = 1244 ß (SE)
	I	II	III
Incremental costs	32138 (735)***	34942 (362)***	34114 (695)***
Incremental QALYs	.048 (.065)	-.0136 (.028)	.045 (.055)
ICER	664837	PAL dominated	754297

Key: QALY = Quality-Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio; FU = Follow-Up; CC = Complete Case analysis; SUR = Seemingly Unrelated Regressions; MICE = Multiple Imputation by Chained Equations; N = Number of patients; SD = Standard Deviation; SE = Standard Error; ; *** - statistically significant at 1%; ** - statistically significant at 5%; * - statistically significant at 10%.
SUR control for stratification factors, baseline healthcare use, and country; QALY equation also controls for baseline utility

- Table 3 compares raw differences (column I) in costs and effects between the arms to impact estimates adjusted for stratification and baseline characteristics in complete case (CC) analysis (column II) and following imputation of missing values using MICE (column III). Across specifications costs were consistently higher in the ET+PAL arm (by approximately the cost of PAL) while impact on QALYs was highly variable tending toward marginal improvement in patients with relatively worse health status.
- After the first year, differences in costs and QALYs were marginal and increasing over time to favour PAL; however, the absolute magnitude of cost savings was highly uncertain due to the large fraction of administratively censored observations (53% in year five, 84% in year six).
- Bootstrapped (1000 replications) incremental impacts (dots) and the resulting ICER (black line) shown in Figure 2 for MICE/SUR specification highlight that the variation in ICER was driven primarily by the variation in the impact of PAL on QALYs.
- For Germany sub-sample ICER was estimated at 787198 Euros per QALY gained; ICERs were above 600000 Euros in all other scenarios tested.

Figure 2. Cost-effectiveness plane ET + PAL vs ET: MICE/SUR



Key: ET = Endocrine therapy; PAL = Palbociclib; MICE = Multiple Imputation by Chained Equations; SUR = Seemingly Unrelated Regressions; QALY = Quality-Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio.

Conclusions

One year of PAL added to ET is not likely to be cost-effective in women with residual invasive disease after NACT. We found limited evidence suggesting PAL enabled additional marginal improvement in health and some cost savings in later years, however, these did not offset the initial cost of PAL therapy through year six. The analysis is subject to self-report bias and limitations of the data collection instruments. Administrative censoring further limited power to estimate impacts beyond year four.

References

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