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Survival outcomes after neoadjuvant Letrozole and palbociclib versus third generation chemotherapy for high risk Oestrogen Receptor- positive HER2-negative breast cancer patients

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Keywords

CDK4/6 inhibitor, neoadjuvant, luminal breast cancer, chemotherapy, survival

These data were presented orally at the 2021 ESMO Breast meeting

Highlights

- First CDK4/6 neoadjuvant randomised trial to report survival outcomes
- NEOPAL trial compared neoadjuvant Letrozole Palbociclib versus chemotherapy
- Pathological complete response rates were identically low (3.8% and 5.9% respectively)
- PFS (HR = 1.01; [95%CI 0.36-2.90], p=0.98) did not differ between both arms.
- Invasive DFS (HR= 0.83; [95%CI 0.31-2.23], p=0.71) did not differ between both arms.

Abstract:

Background: Beside their development as additional adjuvant treatments, CDK4/6 inhibitors combined to endocrine therapy could represent less toxic alternatives to chemotherapy in postmenopausal women with high-risk oestrogen receptor-positive, HER2-negative breast cancer currently candidate for chemotherapy. The multicentre, international, randomised phase 2 NEOPAL trial showed that letrozole-palbociclib combination led to clinical and pathological responses equivalent to a sequential anthracycline-taxanes chemotherapy. Secondary objectives included survival outcomes.

Methods Secondary endpoints of NEOPAL included progression-free survival (PFS) and invasive-disease free survival (iDFS) in the intent-to-treat population. Exploratory endpoints were overall survival (OS) and breast cancer specific survival (BCSS) in the intent-to-treat population, as well as iDFS, OS and BCSS according to the administration of chemotherapy.

Results A hundred and six patients were randomized. Pathological complete response rates were 3.8% and 5.9%. Twenty-three of the 53 patients in the letrozole-palbociclib arm received postoperative adjuvant chemotherapy. At median follow-up of 40.4 months [0-56.6], 11 progressions have been observed, of which three were in the letrozole-palbociclib and 8 in the control arm. PFS (HR = 1.01; [95%CI 0.36-2.90], p=0.98) and iDFS (HR= 0.83; [95%CI 0.31-2.23], p=0.71) did not differ between both arms. The 40 months PFS rate was 86.7% [95%CI 78.0-96.4] and 89.9% [95%CI 81.8-98.7] in letrozole-palbociclib and control arms respectively. Outcomes of patients who did not receive chemotherapy were not statistically different from those who received it.

Conclusions NEOPAL suggests that a neoadjuvant letrozole-palbociclib strategy may allow sparing chemotherapy in some patients with luminal breast cancer while allowing good long-term outcomes. Larger confirmatory studies are needed.

Introduction

Breast cancer is the leading incident cancer worldwide, and oestrogen receptor (ER)-positive, HER2-negative breast cancer is the most frequent breast cancer subtype [1]. Beyond local treatments, the cornerstones of curative therapies proposed to these patients are endocrine therapy and chemotherapy [2,3]. The current approach to systemic treatment decisions in this setting, in order to allow the best possible cure chances, together with minimized long-term harms, is first to assess for long-term individual risk of relapse. To this end, several genomic tests have been developed and are currently used together with clinical risk assessment, thus refining individual prediction and informing systemic treatment decisions, mostly regarding chemotherapy decisions [4–7]. In postmenopausal women, the indications of adjuvant chemotherapy have recently been refined based on the results of the MINDACT and RxPONDER trials, which demonstrated that patients with low or intermediate genomic risk scores and up to 3 positive nodes do not derive benefit from chemotherapy [7,8]. More light has been shed in the meantime on medium and long term adverse events of chemotherapy, including underexplored problems such as fatigue and cognitive symptoms [9,10].

CDK4/6 inhibitors have revolutionized the treatment of patients with advanced ER-positive HER2-negative breast cancer, allowing a doubling of progression-free survival and clinically meaningful overall survival benefits as first line treatment or beyond [11]. However, strategies attempting at assessing their role as an addition to standard treatment in early breast cancer have yet led to mixed results. The addition of palbociclib to standard adjuvant chemotherapy and endocrine therapy did not improve invasive disease-free survival compared with adjuvant endocrine therapy alone in patients with high risk, localized breast cancer in the PALLAS and PENELOPE-B trials [12,13]. However, addition of abemaciclib in very high risk patients led to an early small but subsequently sustained improvement of invasive disease-free survival [14,15].

A major and still unaddressed question is whether CDK4/6 inhibitors combined to neo/adjuvant aromatase inhibitors could allow replacing neo/adjuvant chemotherapy in selected patients with high-risk early ER-positive HER2-negative breast cancer who retain indications of chemotherapy, instead of being added on top of it. The NEOPAL trial showed that letrozole-palbociclib combination and standard chemotherapy led to equivalent pathological and identical clinical responses, while letrozole-palbociclib combination led to encouraging biomarker responses in Prosigna[®]-defined luminal high-risk breast cancer patients [16]. The CORALLEEN trial using the letrozole-ribociclib combination had a similar design and led to similar results [17]. We report here the survival outcomes of patients included in NEOPAL.

Methods

Study design and patients

The NEOPAL trial (NCT02400567) has been previously detailed [16]. Briefly, postmenopausal women aged 18 years or older were accrued in this prospective, international, multicentre, randomised, parallel, non-comparative phase II clinical trial, if they had an ER-positive (Allred score ≥ 4), HER2-negative stage II-IIIa invasive Prosigna[®]-defined luminal B (irrespective of nodal status) or node-positive luminal A breast carcinoma, not candidate for upfront breast conservative surgery. The study, which received the approval of the regulatory authorities on December 12th, 2014, was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Two written informed consents were obtained from all randomised patients (one before enrolment, and the second prior to randomisation after results of the Prosigna[®] test and axillary lymph node characterisation). The study obtained full approval by a national French ethic committee (CPP Ile de France III, Paris, France) and by local IRB (UCL Saint-Luc) in Belgium.

Randomisation and treatment

Eligible patients were randomised in a 1:1 ratio to either arm A (letrozole + palbociclib) or arm B (standard chemotherapy). Randomisation was stratified based on tumour size (T3 vs T1/T2) and Prosigna[®]-defined luminal subtype (Luminal A vs Luminal B) [18].

Patients randomised in arm A were to receive 28-day cycles of continuous daily letrozole, 2.5 mg per day, and palbociclib, 125 mg per day, according to a 3 weeks on/1 week off schedule, for a total duration of 19 weeks. Patients randomised in the standard chemotherapy arm were to receive six conventional third-generation 21-day cycles of sequential chemotherapy: a combination of 5 fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 500 mg/m² (FEC100) during cycles 1 to 3, and docetaxel 100 mg/m² (D100) during cycles 4 to 6. Breast surgery was performed at day 1 of week 20, i.e. at day 21 of the fifth cycle of letrozole and palbociclib, and four weeks after the last chemotherapy infusion. Patients discontinuing palbociclib treatment due to treatment-related toxicity could continue on the active treatment phase of the study receiving letrozole monotherapy as per the investigator's discretion. Residual Cancer Burden (RCB) and Preoperative Endocrine Prognostic Index (PEPI) scores were assessed as previously described [16,19,20]. Patients who received letrozole-palbociclib who did not achieve an RCB0-1 pathological response were proposed adjuvant chemotherapy.

If among the first 30 patients included in the letrozole-palbociclib arm, five or less than five local RCB 0-1 were observed (16.7%), the trial was to be stopped for futility. Between February 14, 2014, and November 15, 2016, 186 patients were screened in 22 centres in France and Belgium, and 106

patients (out of 120 planned) had been randomised (intent-to-treat and safety population) when the trial was stopped for futility.

Outcomes

The primary endpoint was RCB and has been described previously [16,20]. Secondary endpoints included locally assessed clinical response (clinical examination and US measurements), PEPI scores[19], safety (CTC-AE V4.0), as well as progression-free survival (since patients' accrual occurred at primary diagnosis with local tumour in place) and invasive disease-free survival at 3 years. Progression-free survival (PFS) is the interval between the date of randomisation and the date of tumour progression, relapse (local, regional or distant) or death from any cause, whichever occurs first. Invasive disease-free survival (iDFS) is the interval between the date of randomisation and the date of invasive breast cancer relapse (local, regional or distant) or the date of invasive contralateral breast cancer or second invasive cancer or death from any cause, whichever occurs first. Overall survival (OS), defined as time from randomisation to death from any cause), and breast cancer specific survival (BCSS), defined as time from randomisation to death from breast cancer) are exploratory endpoints.

Statistical analyses

This study was a prospective, randomised, parallel, non-comparative phase II trial based on a Fleming's two-step statistical design. The main objective was evaluated on the intent-to-treat population of patients. Secondary endpoints were assessed using classical descriptive statistical methods and results are given with their 95% confidence intervals. Predefined outcome assessments (3-year PFS and iDFS) as well as exploratory OS and BCSS were conducted in an intent-to-treat basis. Additional exploratory analyses among patients who received chemotherapy were conducted in post-hoc-defined populations. Data cut-off for the survival outcomes evaluation was May 25, 2020. Safety was analysed on the safety population defined as all patients who received at least one treatment dose after randomisation, regardless of their eligibility for the study. All analyses were performed using R software (version 3.2.2) (<http://cran.r-project.org>).

Role of the Funding sources

The NEOPAL study is an academic study led by the French Breast Cancer InterGroup-UNICANCER (UCBG). UNICANCER, as sponsor, had full responsibility for the design and conduct of the study, and publications of the results. Pfizer provided financial support for the management of the trial and palbociclib. The Prosigna® tests were provided by Nanostring Technologies. All authors, but not the funders, had access to all of the study's data and had final responsibility to submit for publication.

Results

Patients' characteristics, treatments received, pathological responses

Hundred-six patients were randomised in NEOPAL, of whom 53 had been assigned the letrozole-palbociclib arm, and 53 the chemotherapy arm (Figure 1). Patients' characteristics are described in Table 1. Overall, 55% of the patients accrued had stage II, and 45% stage III breast cancer. Most patients (88.7% in each arm) had Luminal B breast cancer, while 11.7% had node-positive luminal A tumour. The median risk of recurrence (ROR) score was 70 (range 22-93), and 73 (25-91) in arms A and B respectively.

RCB 0-I was observed in four and eight patients in the letrozole-palbociclib [7.7% (95% CI 0.4-14.9)] and chemotherapy [15.7% (95% CI 5.7-25.7)] arms, and pathological complete response rates in 3.8% and 5.9%, respectively. Clinical response (75%) and breast-conserving surgery rates (69%) were similar in both arms.

Among 106 patients randomised, 3 stopped the trial treatment before surgery, 2 in the chemotherapy and one in the letrozole-palbociclib arm (1 consent withdrawal, 1 loss to follow-up, 1 suicide). Detailed treatments received in both arms are presented in Table 1.

Four out of 52 patients who underwent surgery in the letrozole-palbociclib arm (7.7%, [95% CI 0.4-14.9]) and eight of 51 in the chemotherapy arm (15.7%, [95% CI 5.7-25.7]) achieved a locally assessed RCB 0-I tumour response. Out of 48 patients in the letrozole-palbociclib arm who did not achieve an RCB0-1, 23 received an adjuvant chemotherapy (43% of the intent-to-treat population).

3-year survival outcomes

Median follow-up is 40.4 months [Min = 0 - Max = 56.6]. Eleven progressions have been observed, of which three were in the letrozole-palbociclib and eight in the control arm. Ten were metastatic events, while one was a regional progression. Two additional iDFS events were observed in the letrozole-palbociclib arm (secondary malignancies). Intent-to-treat PFS (HR = 1.01; [95%CI 0.36-2.90], p=0.98) and iDFS (HR= 0.83; [95%CI 0.31-2.23], p=0.71) did not differ between both arms (Figure 2). The 3-years PFS and iDFS rates were identical at 86.7% [95%CI 78.0-96.4] and 89.9% [95%CI 81.8-98.7] in the letrozole-palbociclib and chemotherapy arms respectively.

Seven deaths have occurred until data cutoff; six in the letrozole-palbociclib arm (two from breast cancer and four unrelated: 1 from endometrial cancer, 1 from septic shock due to a pyelonephritis, 1 from suicide and 1 from alcoholic cirrhosis) and one in the control arm (breast cancer). Overall survival in the intent to treat populations appeared numerically higher in the chemotherapy arm

(LogRank p value = 0.047) but was driven by non-breast cancer deaths in the letrozole-palbociclib arm. Breast cancer specific survival was identical in both arms (LogRank p value = 0.474) (Figure 2). Exploratory analyses among merged women who received (N=76) or did not receive (N=30) chemotherapy showed no difference in terms of breast cancer specific survival (3-year BCSS in letrozole-palbociclib only patients: 96.2% [95%CI 89.0-100]; versus 98.6% [95%CI 95.9-100] in chemotherapy patients; p=0.177). Invasive disease-free survival was numerically lower but was not significantly different according to the receipt of chemotherapy (3-year iDFS in letrozole-palbociclib only patients 83.1% [95%CI 70.6-97.8]; versus 91.8% [95%CI 85.7-98.3] in chemotherapy patients; p=0.56). Overall survival was again numerically higher in patients who received chemotherapy, but this difference was driven by non-breast cancer deaths in the letrozole-palbociclib arm (3 years OS: 86.4% [95%CI 74.9-100]; versus 97.3% [95%CI 93.6-100] in those who received chemotherapy; p=0.014) (supplementary Fig 1).

Multivariable analysis of outcome

Treatment arm, PEPI scores (PEPI II/III vs I: HR 0.80, [95%CI 0.18-3.67]) as well as RCB scores (RCB II/III vs 0/I: HR 1.36; [95%CI 0.17-10.6]) did not appear as independent predictors of PFS or iDFS (Table 2).

Discussion

In this high risk population of early Luminal A and node-positive, or Luminal B breast cancer patients (median ROR score 70-73), neoadjuvant letrozole-palbociclib combination produced encouraging results. As previously published, it led to pathological response rates that did not significantly differ from those obtained with chemotherapy (7.6% RCB 0-I versus 15.7% for chemotherapy; but 40.4% RCBIII versus 47.1 for chemotherapy), and equivalent clinical responses and breast conserving surgery rates. The present preplanned 3-year survival outcomes evaluation shows equivalent 3-years PFS (HR = 1.01; [95%CI 0.36-2.90], p=0.98) and iDFS (HR= 0.83; [95%CI 0.31- 2.23], p=0.71) results. Overall survival appeared numerically inferior but this observation is linked to non-breast cancer (and non-protocol)-related deaths in this small population. For 43% of the intent-to-treat population in the letrozole-palbociclib arm received an adjuvant chemotherapy, we evaluated in an additional exploratory analysis, whether the patients who did not receive any chemotherapy trended to do worse than their counterparts did. No significant difference was observed, although a numerical trend appeared to favor chemotherapy.

Recent results of two major international randomized studies, MINDACT and RxPONDER, have led to limit the indications of adjuvant chemotherapy among postmenopausal women with low or intermediate genomic risk breast cancer, who consistently appear not to derive benefit from this treatment [7,8]. However, the postmenopausal population accrued in NEOPAL would currently retain chemotherapy indication for most of them, in view of their aggressive tumor burden and biology (more than 88% had luminal B tumors and their ROR risk class was high in 84% of the cases) [16]. The benefits driven from chemotherapy by patients with genomic high risk tumors remain uncontested, although probably lower than initially expected [5]. In parallel, the short-, median-, and long-term toxicity burden associated with these treatment has now been better recognized [9].

In the metastatic setting, the progression-free and overall survival results of first-line combination of endocrine therapy and aromatase inhibitors reached unprecedented levels [11,21]. Based on these excellent results, CDK4/6 inhibitors first appeared as very good candidates to improve outcomes of high-risk early ER-positive, HER2-negative breast cancer patients, as an adjunctive treatment on top of already existing strategies, including chemotherapy. As mentioned, this strategy has revealed to be rather disappointing, with two negative versus one positive trial, MonarchE, although longer follow-up of the latter confirms the early observed benefit [12,13,15].

Whether CDK4/6 inhibitors in combination with endocrine therapy could also be moved to adjuvant or neoadjuvant settings in replacement of multiagent chemotherapy in selected patients in the early setting is yet unknown. Direct comparisons of such combination to chemotherapy in the advanced setting has been addressed in two trials: the young PEARL (KCSG-BR15-10) phase 2 trial randomly assigned 184 premenopausal patients to palbociclib plus endocrine therapy versus capecitabine and showed that the chemotherapy-free strategy was superior in terms of progression-free survival (median 20,1 months vs 14,4 months) [21]. Furthermore, the larger phase III Pearl trial, which randomized postmenopausal patients in first or second line treatment between exemestane or fulvestrant combined to palbociclib versus capecitabine, showed equivalent progression-free survival between both groups [22].

Based on our results and those of the parallel CORALLEEN trial, which obtained identical response results [17], CDK4/6 inhibition combined to aromatase inhibitors proposed instead of chemotherapy thus appears as a promising avenue. The neoadjuvant approach seems the most appropriate, since it allows the adjunction of chemotherapy in cases where a degree of resistance to the endocrine-CDK inhibition combination was observed. Of note, the 86.7 % [95%CI 78.0 – 96.4] in letrozole-palbociclib arm and 89.9 % [95%CI 81.8 – 98.7] in the chemotherapy arm 3-year invasive disease free survival of the high-risk patients treated in both arms in NEOPAL compare well with that observed at the same timeline in MonarchE and PALLAS [12,15].

Unfortunately, outcome data from NEOPAL do however not allow to identify which patients should receive chemotherapy after surgery, since the choice of giving adjuvant chemotherapy in the LETPAL arm patients was investigator- and patient- based upon the absence of RCBO or 1 at surgery. Ongoing translational research on NEOPAL and CORALLEEN as well as larger strategic running trials such as the German ADAPT (NCT01779206) or others in preparation, should help answer this question. Still, the early introduction of the CDK4/6 inhibition appears as a seducing approach, which could avoid the emergence of endocrine resistant or chemo-resistant subclones [23].

The strengths of our study are a randomized design, well-defined high-risk population, good compliance to study protocol and more than 3 years follow-up data. Our study also has some clear limitations. Due to an early ending of the trial because of futility at interim analysis, it is noticeably underpowered to draw any definitive conclusions regarding the ability of a non-chemotherapy protocol to allow outcomes equivalent to those obtained by sequential chemotherapy-endocrine therapy strategies. The follow-up is still limited, while more than 60% of luminal-like HER2-negative tumors relapse after 3 years [24]. The present pre-planned 3-year outcome assessments were designed as rather exploratory evaluations to allow or not for the further development of such chemotherapy-free strategies.

In conclusion, this study is underpowered for definitive conclusions but strongly suggests that such pre-operative non-chemotherapy CDK4/6 inhibitor-endocrine therapy combination approach may spare some postmenopausal high-risk patients chemotherapy, and deserves further exploration.

Contributors

PC, SDE, AVS, CC, and JL, conceived and designed the study. PC, VD, FL, ID, PEH, FD, CL, MAMR, FD, JSF, CJ, LVB, SN, JMF, JLC, JG, and SDe collected the data. SDe, PC, SDu, CC, FD, AR, JL, AVS, analysed and interpreted the data. SDe and PC wrote the manuscript. All authors reviewed and approved the final version of the submitted report.

Declaration of Interest

SDe, PC and JL report institutional funding for the present trial from Pfizer and Nanostring technologies.

SDe reports institutional consulting fees from AstraZeneca, Besins, Sanofi, Rappta; institutional honoraria from AstraZeneca, Seagen, MSD, Pfizer; institutional investigating fees from Taiho, AstraZeneca, Pfizer, MSD, Novartis, Sanofi, G1 therapeutics, BMS, Pfizer, Roche; and personal support for attending US conference from AstraZeneca and Pfizer

FL reports honoraria from AstraZeneca, Eisai, Lilly, Novartis, P Fabre, Roche ; support for attending meetings from AstraZeneca, Eisai, Lilly, Novartis, P Fabre, Pfizer, Roche; participation on IDMC or advisory boards from AstraZeneca, Eisai, Lilly, Pierre Fabre, Roche

JSF reports personal consulting fees from ROCHE, ASTRA ZENECA, NOVARTIS, DAIICHI, LILLY, PFIZER, CLOVIS, GSK, MSD; honoraria from ASTRA ZENECA, NOVARTIS, DAIICHI, LILLY, PFIZER, CLOVIS, MSD, AMGEN; support for attending meetings from ASTRA ZENECA, NOVARTIS, DAIICHI, LILLY, PFIZER, CLOVIS, MSD; participation on IDMC or advisory board from ASTRA ZENECA, NOVARTIS, DAIICHI, LILLY, PFIZER, CLOVIS, MSD, PIERRE FABRE

PEH reports consulting fees from Novartis, Pfizer, Lilly; and support from Mylan, Eisai, Roche, Novartis

VDH reports support for attending meetings from Roche, Novartis Pfizer

CJ reports personal honoraria from Daiichi, AstraZeneca, Pfizer

FD reports consulting fees from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi, Pierre Fabre, Seagen; and support for attending meetings from Roche and Pfizer

PC reports personal consulting fees from Pfizer, Roche, Lilly, Novartis, Daiichi and Seagen, honoraria from Pfizer and Novartis

The others did not report disclosures

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Table 1 Patients and tumours characteristics, treatments received, pathological responses

	Arm A Letrozole-Palbociclib N=53			Arm B Chemotherapy N=53 N(%)
	Total N= 53 N(%)	Received adjuvant chemo N = 23 N(%)	Did not receive adjuvant chemo N = 30 N(%)	
Mean age (sd)	65 (7)	62 (8.)	63 (7)	62 (8)
Tumour size (ultrasound)				
T0-1	10 (19.2)	4 (17.4)	6 (20.7)	13 (26.0)
T2	38 (73.1)	17 (73.9)	21 (72.4)	36 (72.0)
T3	4 (7.7)	2 (8.7)	2 (6.9)	1 (2.0)
Lymph node status				
N0	22 (43.1)	7 (33.3)	15 (50.0)	25 (47.2)
N1	29 (56.9)	14 (66.7)	15 (50.0)	28 (52.8)
Baseline tumour stage				
IIA	29 (55.8)	10 (43.5)	19 (65.5)	29 (58.0)
IIB	19 (36.5)	11 (47.8)	8 (27.6)	20 (40.0)
IIIA	4 (7.7)	2 (8.7)	2 (6.9)	1 (2.0)
Histological type				
Invasive NOS	44 (83.0)	20 (87.0)	24 (80.0)	41 (77.4)
Lobular	7 (13.2)	2 (8.7)	5 (16.7)	10 (18.8)
Other	2 (3.8)	1 (4.3)	1 (3.3)	2 (3.8)
Histological grade				
1	6 (11.3)	0 (0)	6 (20.0)	3 (5.6)
2	35 (66.1)	16 (69.6)	19 (63.3)	33 (62.3)
3	12 (23.6)	7 (30.4)	5 (16.7)	17 (32.1)
Ki67 expression				
<14%	5 (11.6)	1 (6.3)	4 (14.8)	5 (12.5)
≥14%	38 (88.4)	15 (93.7)	23 (85.2)	35 (87.5)
ER expression > 10%	53 (100)	23 (100)	30 (100)	53 (100)
Allred score 7-8	51 (96.2)	23 (100)	28 (93.3)	51 (96.2)
PR expression > 10%	38 (71.7)	17 (73.9)	21 (72.4)	50 (94.3)
Allred score 7-8	20 (53.3)	9 (39.1)	11 (36.7)	24 (47.7)
Prosigna®-Intrinsic subtype				
Luminal A	6 (11.3)	2 (8.7)	4 (13.3)	6 (11.3)
Luminal B	47 (88.7)	21 (91.3)	26 (86.7)	47 (88.7)
Median ROR score (sd)	67 (15)	64 (13)	69 (15)	70 (14)
ROR risk class				
Low	0			0
Intermediate	7 (13.2)	4 (17.4)	3 (10.0)	9 (16.9)
High	46 (86.8)	19 (82.6)	27 (90.0)	44 (83.1)

Treatments received				
Completed treatment per protocol	43 (81.1)	20 (87.0)	23 (76.7)	48 (90.5)
Treatment discontinuation	7 (13.2)	3 (13.0)	4 (13.3)	3 (5.7)
Treatment dose level decrease	3 (5.7)	0 (0)	3 (10.0)	2 (3.8)
RCB				
0	2 (3.8%)	0 (0)	2 (6.9)	3 (5.9%)
1	2 (3.8%)	0 (0)	2 (6.9)	5 (9.8%)
2	27 (51.9%)	10 (43.5)	17 (58.6)	19 (37.3%)
3	21 (40.4%)	13 (56.5)	8 (27.6)	24 (47.1%)
Breast conserving surgery	36 (69.2%)	15 (65.2)	21 (70.0)	35 (68.6%)

NOS: no specific subtype; ER: oestrogen receptor; PR: progesterone receptor; ROR: risk of recurrence according to the Prosigna® score [19]; RCB: residual cancer burden [22]; chemo: chemotherapy

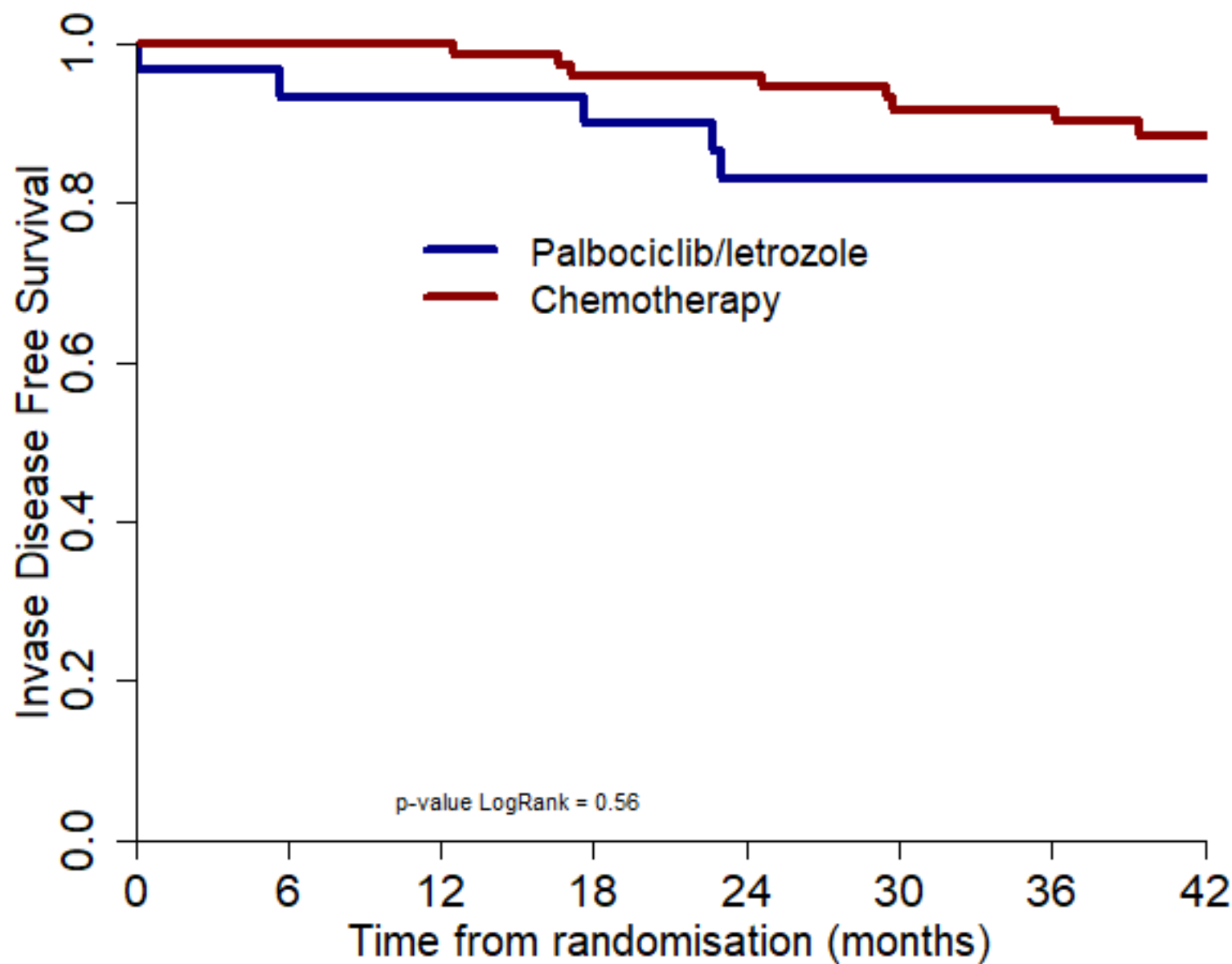
Table 2: Multivariable predictors of outcomes

PFS	Hazard Ratio (CI95%)	p-value
Arm of treatment		0,54
Control Arm	1	
Palbociclib-Letrozole Arm	0,60 [0,12 - 2,97]	
RCB		0,74
0/I	1	
II/III	1,43 [0,18 - 11,2]	
Chemotherapy		0,60
No chemotherapy during the study	1	
Chemotherapy	0,63 [0,11 - 3,48]	
iDFS	Hazard Ratio (CI95%)	p-value
Arm of treatment		0,88
Control Arm	1	
Palbociclib-Letrozole Arm	0,90 [0,23 - 3,53]	
RCB		0,72
0/I	1	
II/III	1,47 [0,19 - 11,4]	
Chemotherapy		0,78
No chemotherapy during the study	1	
Chemotherapy	0,81 [0,19 - 3,44]	

RCB: residual cancer burden [22]

Figure 1 Flow chart

Figure 2 (a,b,c,d): Progression-free survival (a), invasive disease-free survival (b), breast cancer specific survival (c) and overall survival (d) in letrozole-palbociclib and chemotherapy arms (intent-to-treat population)



Number at risk

30
76

28
74

28
74

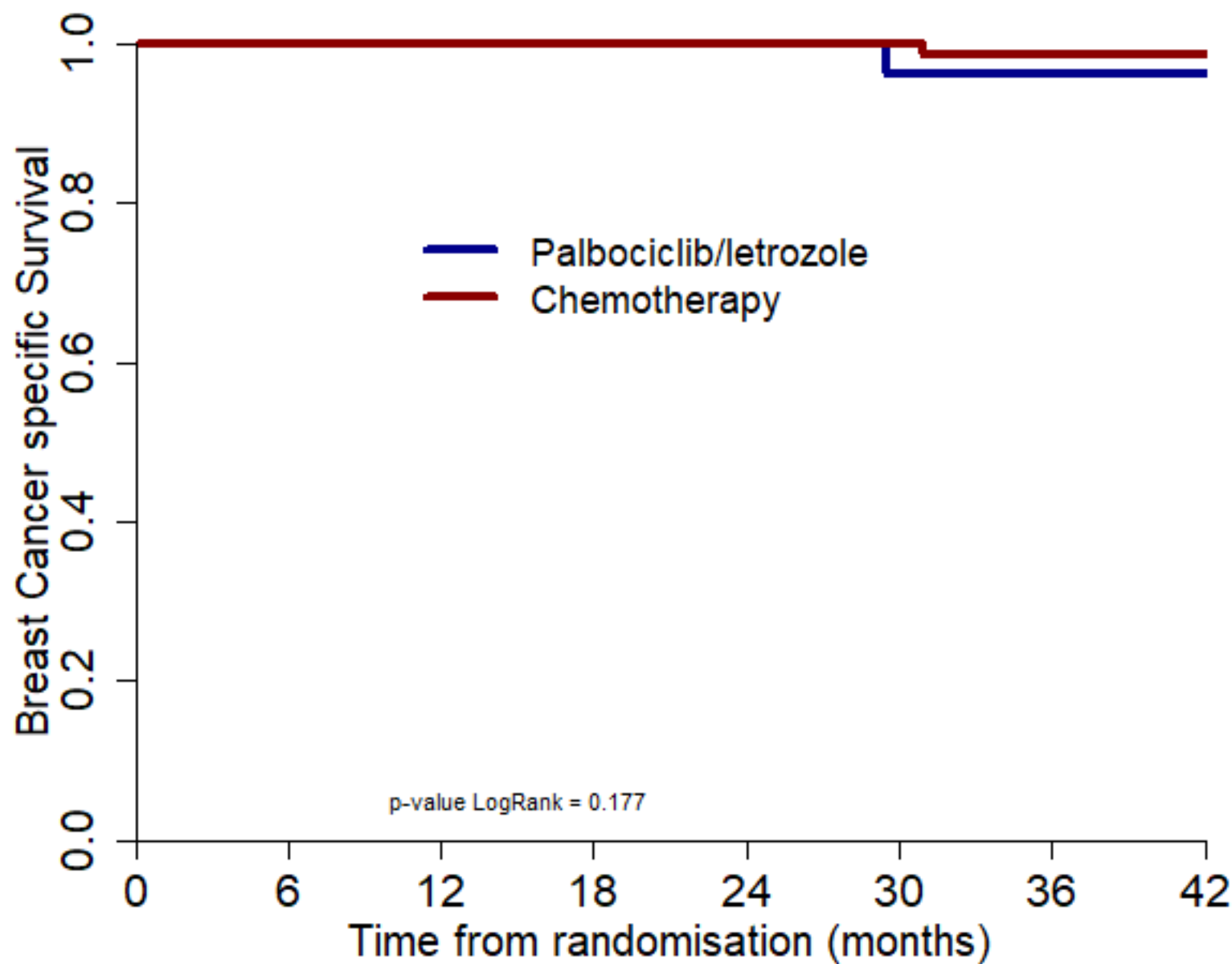
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71

24
70

24
66

24
63

10
14



Number at risk

30
76

29
74

29
74

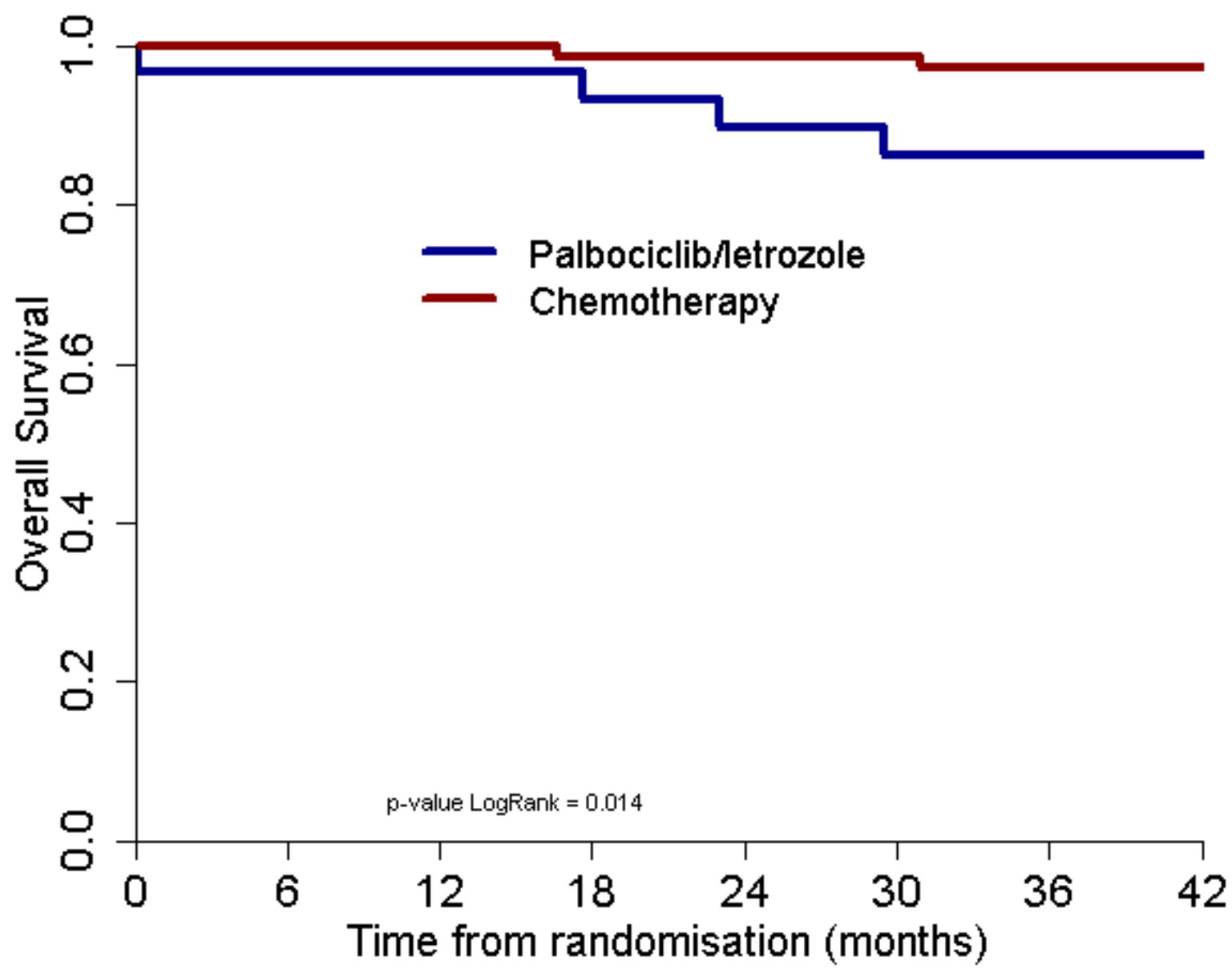
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26
72

25
71

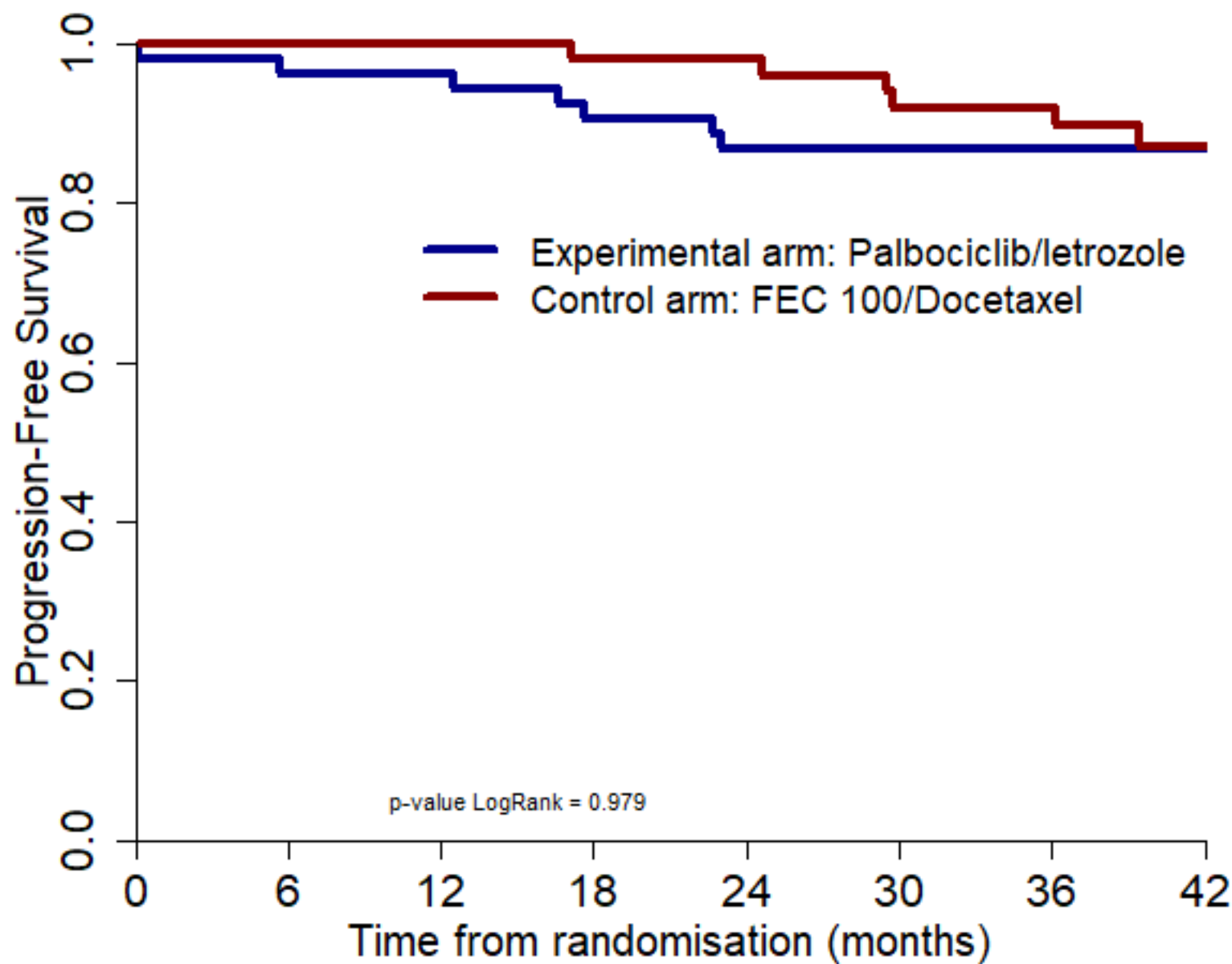
25
67

10
16



Number at risk

30	29	29	28	26	25	25	10
76	74	74	73	72	71	67	16



Number at risk

53
53

51
51

51
51

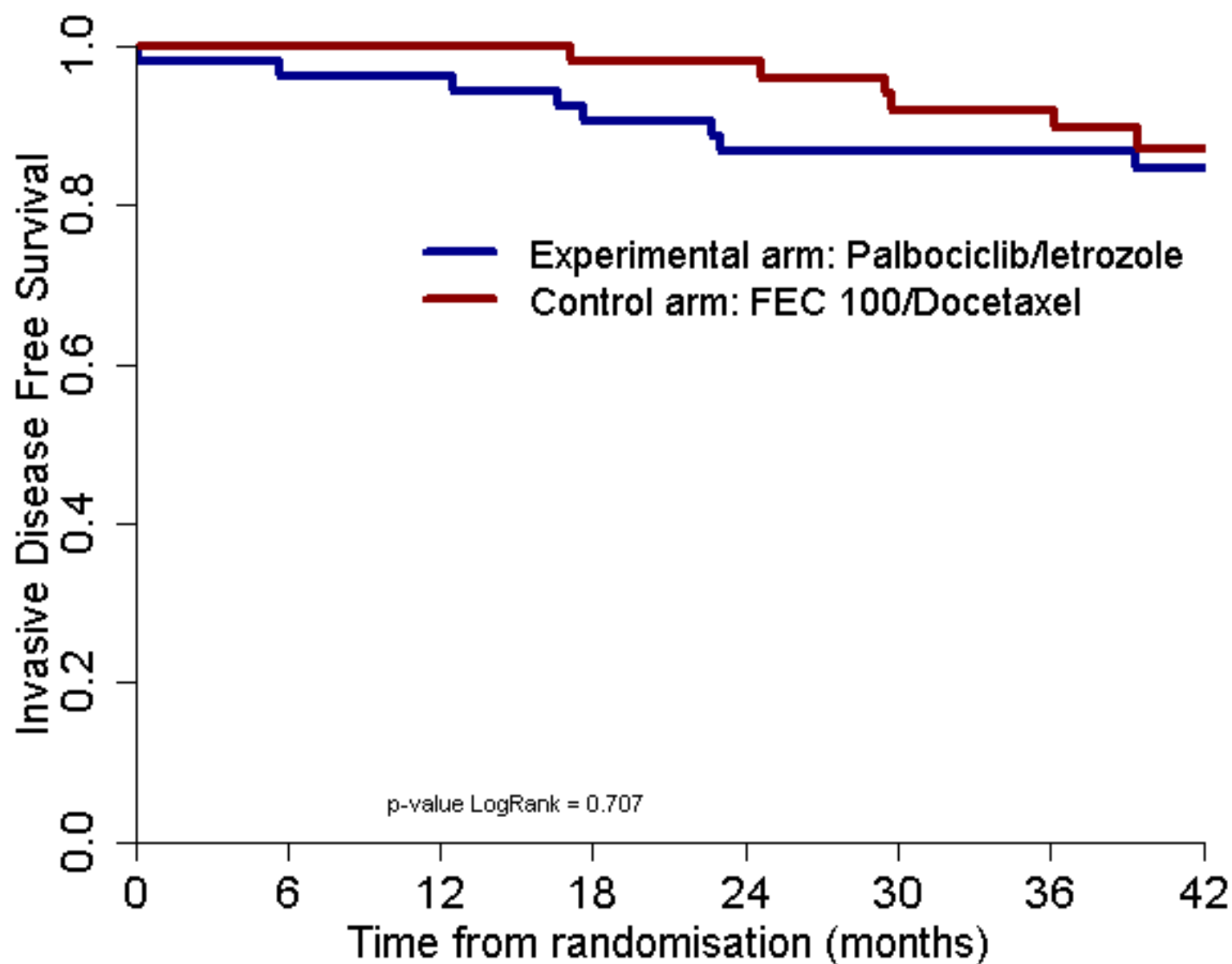
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45
49

45
45

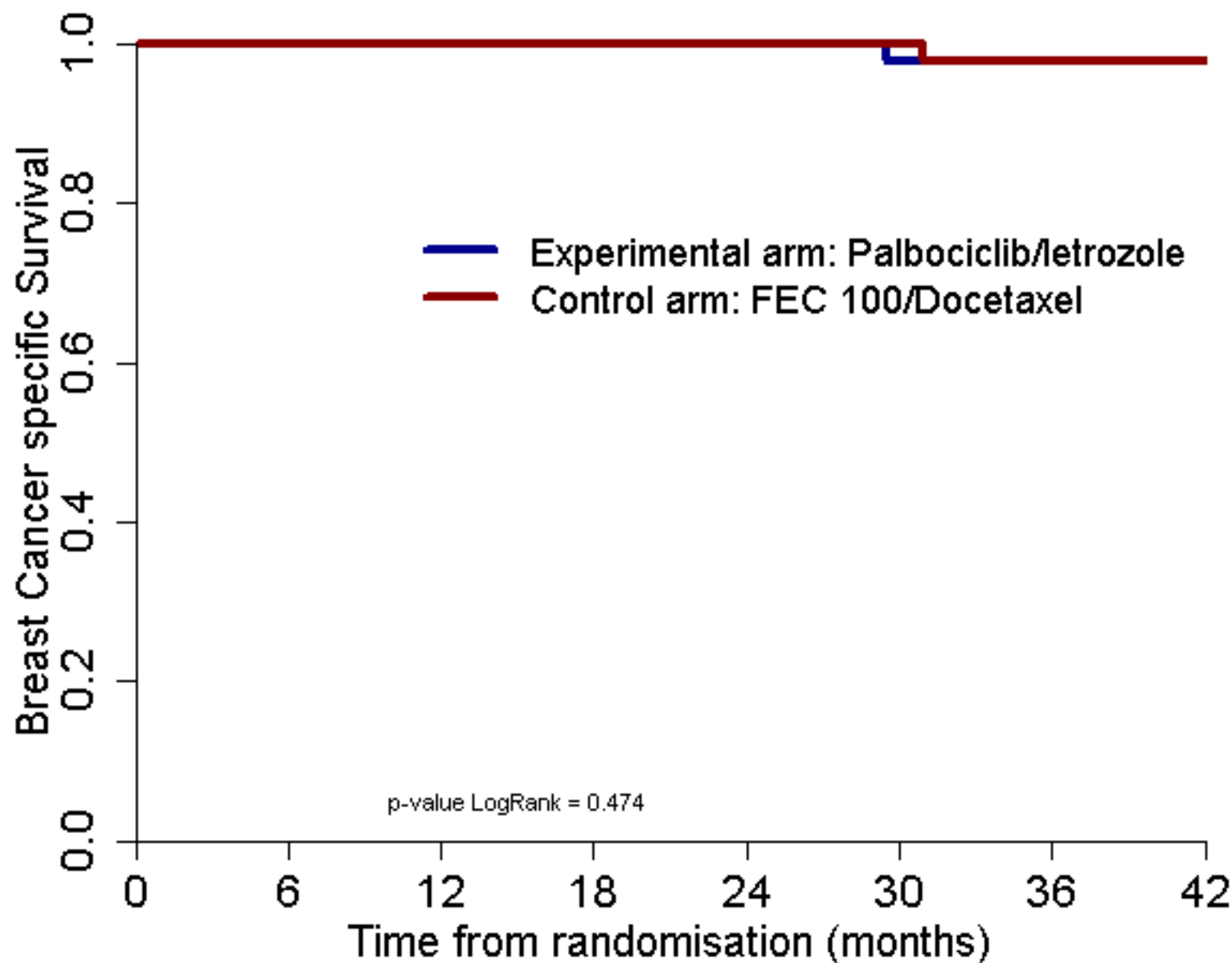
43
44

14
9



Number at risk

53	51	51	48	45	45	43	15
53	51	51	50	49	45	44	9



Number at risk

53
53

52
51

52
51

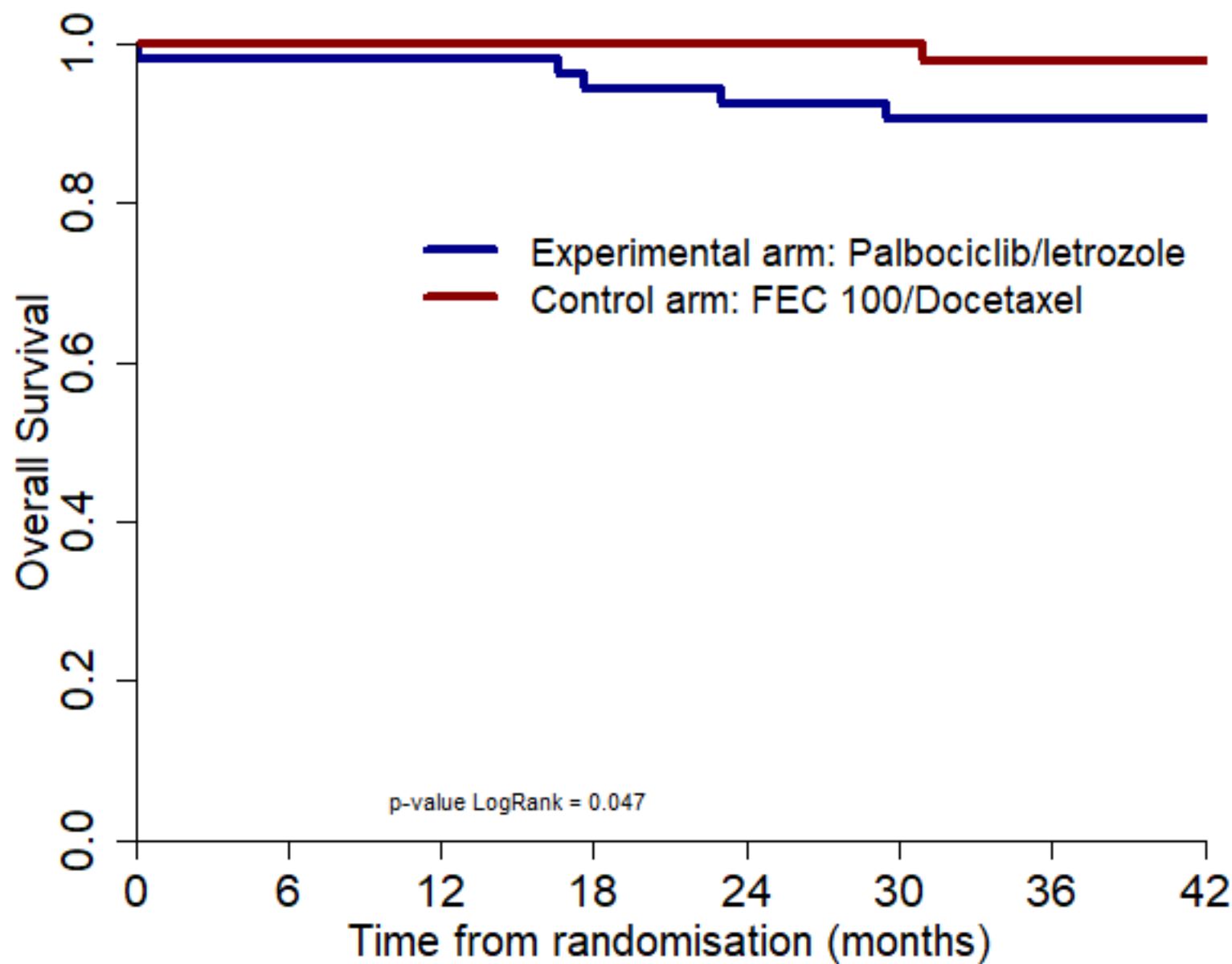
50
51

48
50

47
49

45
47

15
11



Number at risk

53
53

52
51

52
51

50
51

48
50

47
49

45
47

15
11