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Phase III study of palbociclib combined with endocrine therapy in patients with hormone-receptor-positive, HER2-negative primary breast cancer and high relapse risk after neoadjuvant chemotherapy: First results from PENELOPE-B

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on behalf of the PENELOPE-B investigators

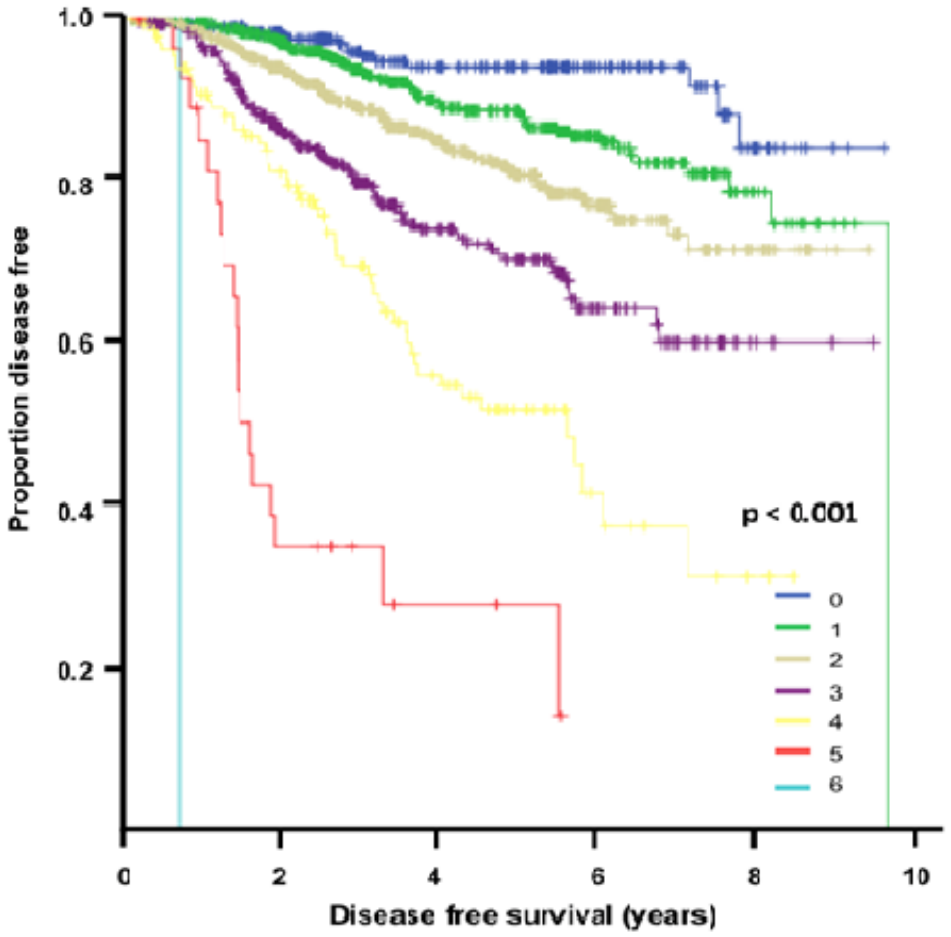
Disclosure Information

S. Loibl reports grants and other from Pfizer, during the conduct of the study; grants and other from Abbvie, Amgen, Celgene, Novartis, Astra Zeneca, Roche, Daiichi-Sankyo other from Seattle Genetics, PriME/ Medscape, Lilly, Samsung, Eirgenix, BMS, Puma, MSD, personal fees from Chugai, grants from Teva, Vifor, Immunomedics, outside the submitted work, and has a patent EP14153692.0 pending pending. **F. Marmé** reports personal fees from Roche, AstraZeneca, Pfizer, Tesaro, Novartis, Amgen, PharmaMar, GenomicHealth, CureVac, EISAI, outside the submitted work. **M. Martin** reports grants and personal fees from ROCHE, PUMA, NOVARTIS, personal fees from ASTRAZENECA, AMGEN, TAIHO ONCOLOGY, DAIICHI SANYO, PHARMAMAR, ELI LILLY, from PFIZER, outside the submitted work. **M. Untch** reports personal fees and non-financial support from Abbvie, Amgen GmbH, Astra Zeneca, personal fees from BMS, personal fees and non-financial support from Celgene GmbH, Daiji Sankyo, Lilly Int., Eisai GmbH, MSD Merck, Mundipharma, Myriad Genetics, Odonate, Pfizer GmbH, Roche Pharma AG, Sanofi Aventis Deutschland GmbH, TEVA Pharmaceuticals Ind Ltd, Novartis, Clovis Oncology, personal fees from Lilly Deutschland, PUMA Biotechnology, Pierre Fabre, outside the submitted work. **H. Bonnefoi** reports other from PFIZER, outside the submitted work. **SB. Kim** grants fromNovartis, Sanofi-Aventis, Kyowa-Kirin Inc, and DongKook Pharm Co. and honorarium for Novartis, AstraZeneca, Lilly, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, and Daiichi-Sankyo) **H. Bear** reports other from Pfizer, outside the submitted work. **N. Mc Carthy** reports Advisory Boards fees from Pfizer, Roche, Novartis, Eli Lily, assistance with conference travel from Roche, Amgen, Novartis. **K. Gelmon** reports other from BC Cancer, during the conduct of the study; personal fees and other from Astra Zeneca, BMS, personal fees from Pfizer, Novarits, Eli Lilly, Merck, Mylan, Roche, Genomic Health, other from Genentech, outside the submitted work. **J.A. García- Sáenz** reports grants and other from Novartis, grants from Lilly, grants from Pfizer, Daiichi Sankyo, Celgene, other from AstraZeneca, Roche, during the conduct of the study. **C. Kelly** reports advisory board fees from Novartis, BMS, Roche and conference/travel fees from Pfizer, Roche. **T. Reimer** reports personal fees from Roche, Pfizer, AstraZeneca, LILLY, Novartis, outside the submitted work. **M. Toi** reports grants and personal fees from Chugai, Takeda, Pfizer, Kyowa-Hakko-Kirin, C & C Res Lab, Taiho, grants from JBCRG association, grants and personal fees from Eisai, Daiichi-Sankyo, grants Astra Zeneca, personal fees from Eli Lilly, MSD, Genomic Health, Novartis, Konica Minolta, grants from Astellas, outside the submitted work; and Board of directors JBCRG association, Organisation for Oncology and Translational Research, Kyoto Breast cancer Research Network. **H.S. Rugo** reports grants from Pfizer, Novartis, Lilly, Genentech/Roche, Macrogenics, OBI, Merck, Eisai, Immunomedics, Daiichi, Seattle Genetics, Odonaate, non-financial support from Daiichi, Mylan, Pfizer, Merck, AstraZeneca, Novartis, Macrogenics, other from Samsung Puma, outside the submitted work. **S. Seiler** reports other from Pfizer, during the conduct of the study; other from Novartis, outside the submitted work. **C. Denkert** reports personal fees from Novartis, Roche, MSD Oncology, Daiichi Sankyo, grants from Myriad Genetics, other from Sividon Diagnostics/Myriad, outside the submitted work, and has a patent EP18209672 pending, a patent EP20150702464 pending, and a patent Software (VMscope digital pathology) pending. **M. Gnant** reports personal fees / travel support from Amgen, AstraZeneca, Celgene, EliLilly, Invectys, Pfizer, Novartis, Puma, Nanostring, Roche, Medison, LifeBrain, all outside the submitted work; an immediate family member is employed by Sandoz. **A. Makris** reports personal fees from Pfizer Advisory Board, personal fees from Unrelated project involving Pfizer, outside the submitted work. **G. von Minckwitz** reports grants from Pfizer, during the conduct of the study; other from CaraGmbH, outside the submitted work. All remaining authors have declared no conflicts of interest.

Background

- Patients without pCR have an inferior prognosis compared to those with pCR even in HR+/HER2-primary BC [1]
- CPS-EG score identifies patients at high risk of relapse after NACT.[2]
- Results could be validated on GBG meta-database for HR+/HER2-.[3]
- Patients with a CPS-EG score 3 or 2 with ypN+ (about 25% of the total population) have a 3-year DFS of 77%
- The CDK4/6 inhibitor palbociclib in combination with endocrine therapy prolongs PFS and OS in metastatic BC [4,5]
- The aim of PENELOPE-B trial was to evaluate whether palbociclib would prevent relapses postneoadjuvant
- The trial started in December 2013

Clinical pathological stage–estrogen/grade Staging System (CPS-EG) as Selection Criterion[2]



1. von Minckwitz et al. J Clin Oncol 2013 ;2. Mittendorf et al. J Clin Oncol 2011; 3. Marmé, et al. Eur J Cancer 2016
4. Finn, et al. N Engl J Med 2016; 5. Turner, et al. N Engl J Med 2015 & 2018

Study Design

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

Neoadjuvant Chemotherapy → **Surgery +/- Radiotherapy** → **R 1:1**

Palbociclib
125 mg once daily p.o.
d1-21, q28d for 13 cycles

Placebo
d1-21, q28d for 13 cycles

All patients will receive concomitantly endocrine therapy according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746

Main Eligibility Criteria

- Residual invasive disease post-neoadjuvant either in the breast or the lymph nodes
- Centrally confirmed HR+/HER2- breast cancer assessed preferably on tissue from post-neoadjuvant residual invasive disease or core biopsy of the breast, or if not possible, of residual nodal invasion
- CPS-EG score ≥ 3 or 2 and ypN+
- Neoadjuvant chemotherapy ≥ 16 weeks (incl. 6 weeks of taxanes)
- < 16 weeks since final surgery or <10 weeks from completing radiotherapy and date of randomization
- Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer

Endpoints

- **Primary Endpoint**
  - Invasive disease-free survival (iDFS)
- **Selected Secondary Endpoints**
  - iDFS excluding second primary invasive non-breast cancers
  - Distant disease-free survival
  - Locoregional recurrence-free interval
  - Overall survival
  - Safety, compliance
  - QoL
  - Subgroup analysis by gene expression
  - Health economy

Statistical Considerations

- Initially **255 iDFS events and** 1100 pts required to detect a **HR of 0.685 with 85% power reflecting** an increase of **3year -iDFS from 77% to 83.6%**
  - Two-sided stratified log-rank test, overall significance level of 0.05 based on the ITT population
- Adaptive design with two interim analyses
- O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function were used in the interim analyses[1]
  - **1st interim analysis** → increase to **290 events** and **1250 patients**
  - **2nd interim analysis** → at **194 events** for futility and efficacy
  - **Final analysis** of **iDFS** → **nominal significance level 0.0463**
- To address the concern of possible inflation of the type I error due to a sample size increase based on the interim analysis, statistical significance was determined using a weighted statistic based on the method of Cui L et al with CHW interim monitoring implemented in EAST version 6.5 (Cytel Inc.)[2]

1. O'Brien & Fleming. Biometrics. 1979; 2. Cui L et al. Biometrics 1999.

Disposition of Patients

Patient Status	Palbociclib N (%)	Placebo N (%)	Overall N (%)
Number of patients screened			1708
Number of patients randomized	631	619	1250
Number of patients started treatment	628	616	1244
Completed at least 7 cycles of treatment	559 (88.6)	559 (90.3)	1118 (89.4)
Completed all 13 cycles regularly	508 (80.5)	523 (84.5)	1031 (82.5)
Discontinued endocrine therapy prematurely	28 (4.4)	36 (5.8)	64 (5.1)
Discontinued study treatment	123 (19.5)	96 (15.5)	219 (17.5)
- Disease recurrence	25 (4.0)	40 (6.5)	65 (5.2)
- Second primary (non-breast)	2 (0.3)	3 (0.5)	5 (0.4)
- Death	2 (0.3)	1 (0.2)	3 (0.2)
- Adverse event	33 (5.2)	5 (0.8)	38 (3.0)
- Patient´s wish	56 (8.9)	41 (6.6)	97 (7.8)
- Investigator´s decision	5 (0.8)	6 (1.0)	11 (0.9)

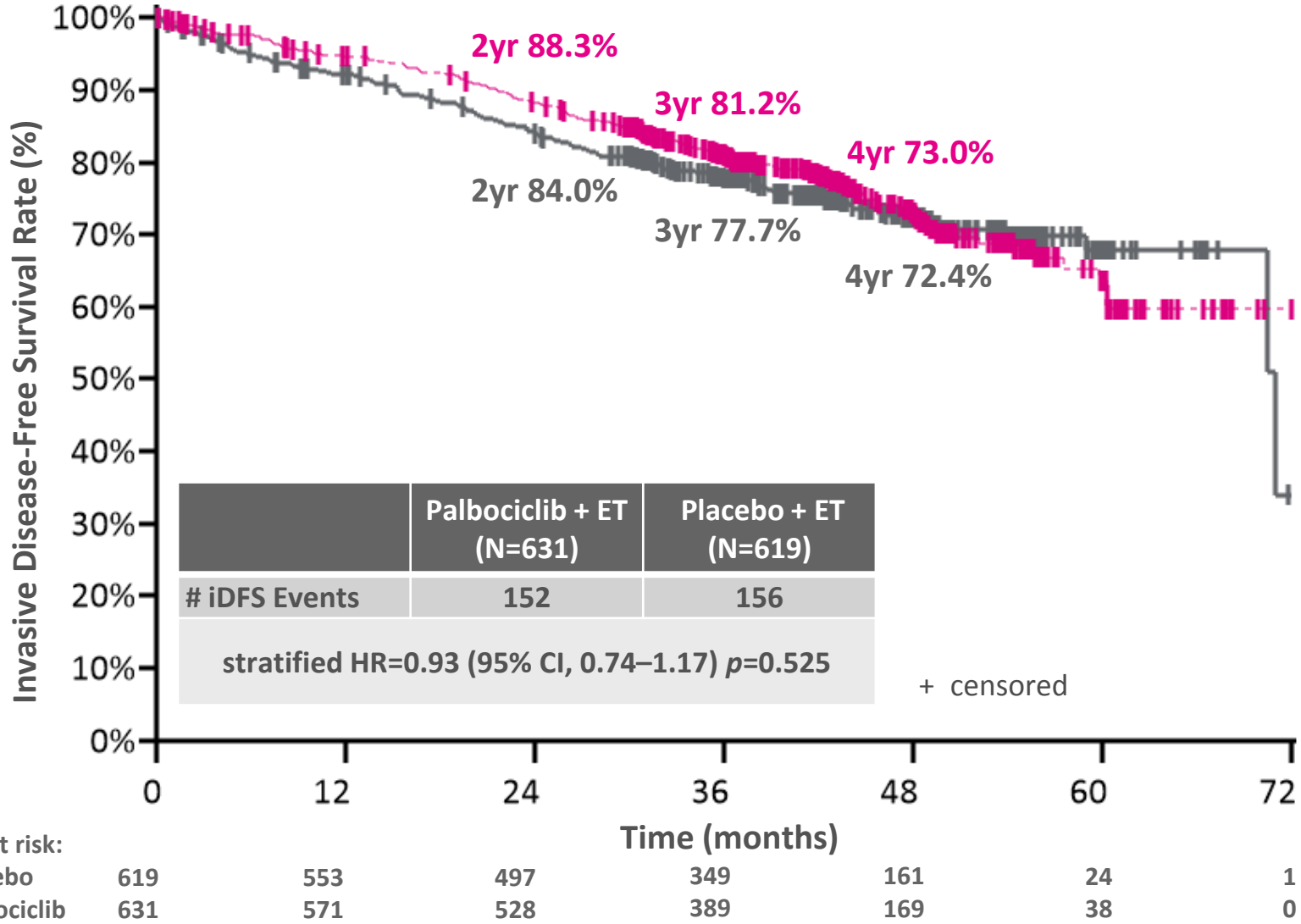
Main Baseline Characteristics

Parameter	Category	Palbociclib (N=631) N (%*)	Placebo (N=619) N (%*)	Overall (N=1250) N (%*)
Age	median (range)	49 (22.76)	48 (19.79)	49 (19.79)
Age, years	≤50	353 (55.9)	348 (56.2)	701 (56.1)
Histological lymph node status at surgery	ypN 0-1	310 (49.1)	310 (50.1)	620 (49.6)
	ypN 2-3	321 (50.9)	309 (49.9)	630 (50.4)
Ki-67%, central pathology	>15%	161 (25.5)	158 (25.5)	319 (25.5)
CPS-EG score	2 and ypN+	253 (40.1)	255 (41.2)	508 (40.6)
	≥3	378 (59.9)	364 (58.8)	742 (59.4)
Tumor stage at surgery	ypT0-1	238 (37.7)	208 (33.7)	446 (35.7)
	ypT2-3	368 (58.3)	389 (62.9)	757 (60.6)
	ypT4	25 (4.0)	21 (3.4)	46 (3.7)
Histological type	lobular	58 (9.2)	52 (8.5)	110 (8.8)
Grading	G3	294 (46.7)	297 (48.1)	591 (47.4)
Ovarian ablation		108 (17.1)	113 (18.3)	221 (17.7)
Endocrine therapy Tamoxifen	overall	314 (49.8)	308 (49.8)	622 (49.8)

stratification factors

*valid percent

Results Primary Endpoint iDFS



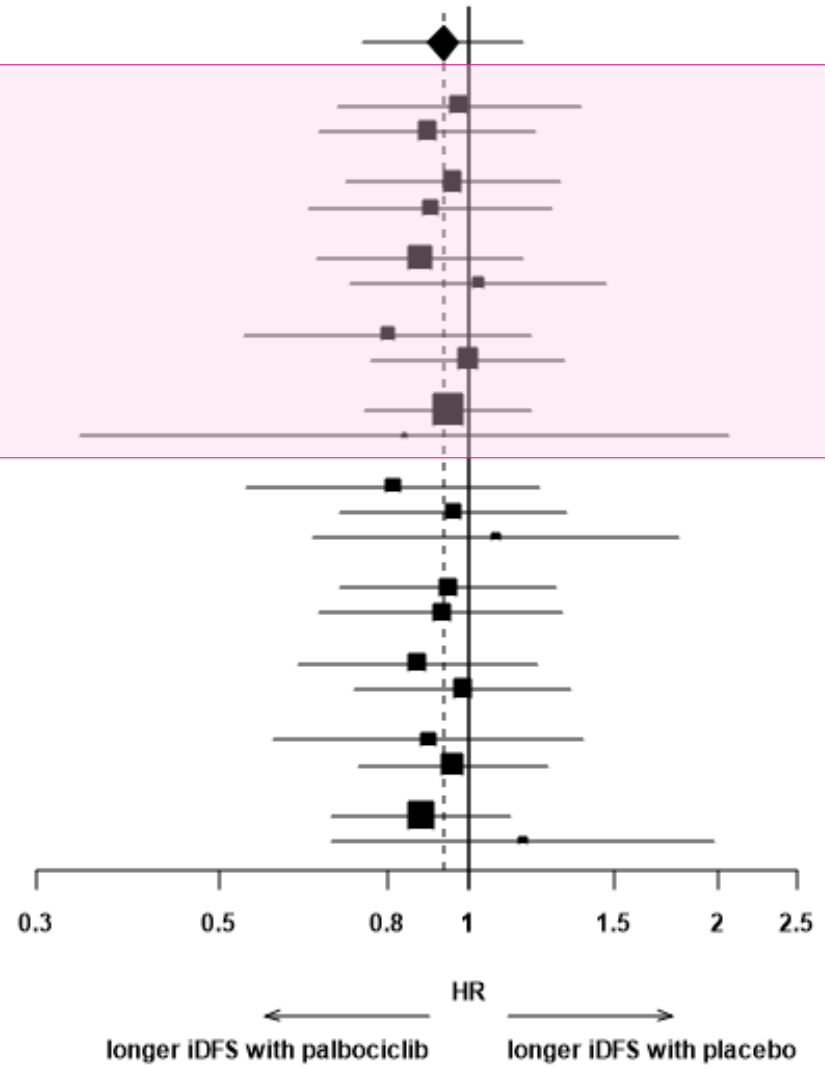
	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	152	156
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Median Follow-Up 42.8 Months

* Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group-sequential nature of the design

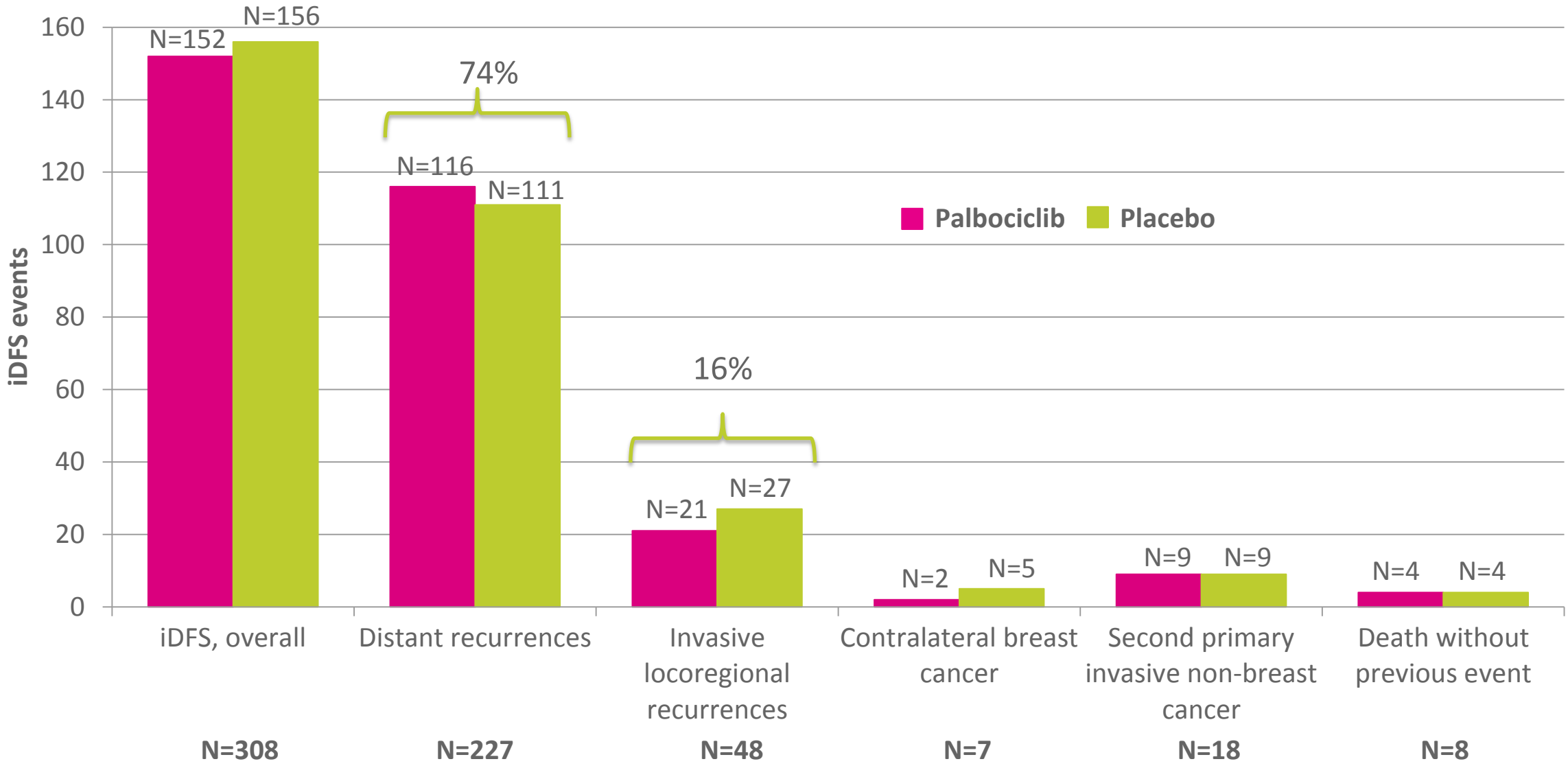
Subgroups iDFS

Subgroup	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall	1250	.931 (.744, 1.16)	.532	
ypN				.714
ypN 0-1	620	.974 (.696, 1.36)	.880	
ypN 2-3	630	.891 (.660, 1.20)	.451	
Age years				.795
<=50	701	.955 (.709, 1.29)	.764	
>50	549	.899 (.641, 1.26)	.539	
Ki-67				.504
<=15%	931	.873 (.654, 1.16)	.355	
>15%	319	1.02 (.718, 1.46)	.895	
Risk status				.389
CPS-EG Score 2 and ypN+	508	.798 (.534, 1.19)	.272	
CPS-EG Score >=3	742	.996 (.760, 1.30)	.976	
Geographical region				.833
Non-Asian	1155	.943 (.749, 1.19)	.619	
Asian	95	.836 (.339, 2.06)	.697	
CPS-EG Score				.674
Score 1/2	497	.810 (.539, 1.22)	.311	
Score 3	561	.958 (.697, 1.31)	.789	
Score 4/5	192	1.08 (.648, 1.79)	.772	
First endocrine therapy				.924
Tamoxifen with or w/o ovarian suppression	622	.942 (.698, 1.27)	.698	
AI with or w/o ovarian suppression	628	.927 (.661, 1.30)	.659	
Duration of chemotherapy				.596
shorter (<=20 wks)	594	.867 (.621, 1.21)	.401	
longer (>20 wks)	656	.982 (.726, 1.33)	.904	
Type of surgery				.716
Breast conserving	432	.893 (.580, 1.37)	.605	
Mastectomy	818	.956 (.736, 1.24)	.738	
Overall response to NACT				.346
CR or PR	1050	.876 (.683, 1.12)	.297	
SD or PD	200	1.16 (.682, 1.98)	.579	

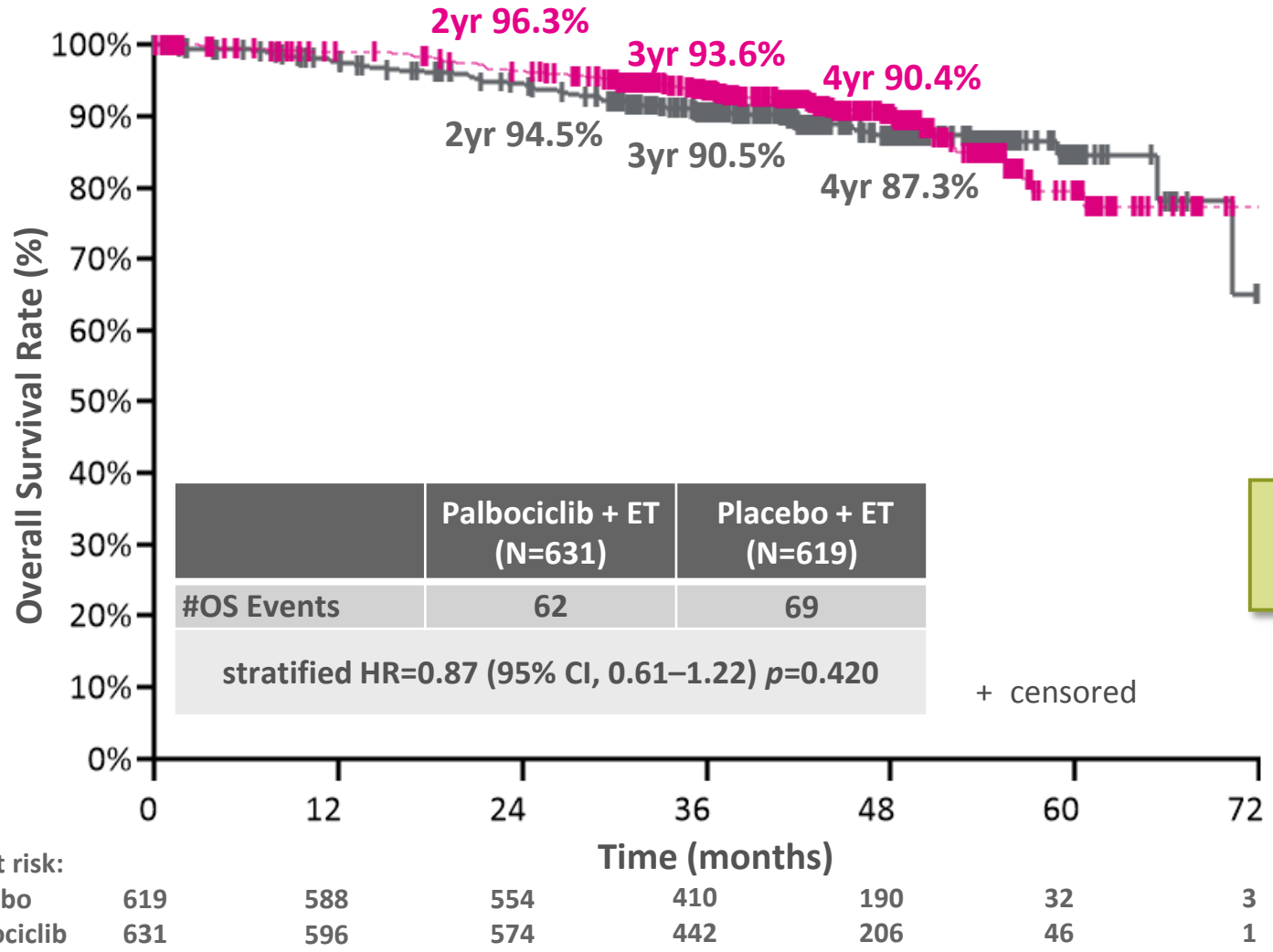


stratification factors

Type of iDFS Events



Overall Survival (Interim Analysis)



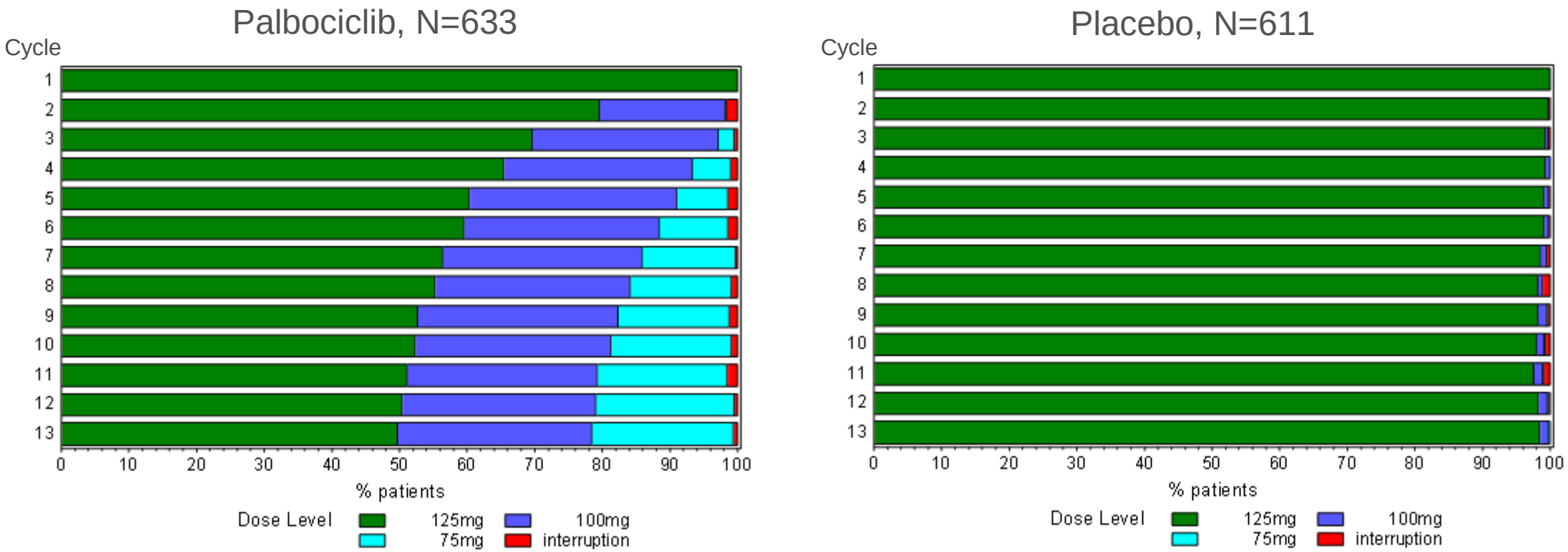
	Palbociclib + ET (N=631)	Placebo + ET (N=619)
#OS Events	62	69
stratified HR=0.87 (95% CI, 0.61–1.22) *p*=0.420		

Median Follow-Up 42.8 Months

Extent of Exposure

Parameter	Category	Palbociclib (N=633)	Placebo (N=611)	Overall (N=1244)	p-value
Duration of exposure (weeks)	Mean	48.6	48.1	48.4	<.001
	Median	52.9	52.0	52.1	
	Min, Max	1.1, 70.1	1.4, 66.0	1.1, 70.1	
Relative total dose intensity (%)	Mean	75.8	93.0	84.3	<.001
	Median	82.1	98.9	96.3	
	Min, Max	0.4, 105.9	0.7, 104.3	0.4, 105.9	

Dose Reductions



Interruption= cycle completely not received / cycle started and interrupted within the first 5 days

Summary of Adverse Events

	Palbociclib (N=633) N (%)	Placebo (N=611) N (%)	Overall (N=1244) N (%)	p-value
Patients with Adverse Event (AE)	632 (99.8)	610 (99.8)	1242 (99.8)	1.000
grade 3/4	504 (79.6)	123 (20.1)	627 (50.4)	<.001
Patients with hematological AE	628 (99.2)	483 (79.1)	1111 (89.3)	<.001
grade 3/4	463 (73.1)	8 (1.3)	471 (37.9)	<.001
Patients with non-hematological AE	630 (99.5)	609 (99.7)	1239 (99.6)	1.000
grade 3/4	126 (19.9)	116 (19.0)	242 (19.5)	0.720
Patients with Serious AE (SAE)	59 (9.3)	53 (8.7)	112 (9.0)	0.693
hematological SAE	5 (0.8)	0 (0.0)	5 (0.4)	0.062
non-hematological SAE	59 (9.3)	53 (8.7)	112 (9.0)	0.693

Summary and Conclusion

- After a median follow-up of 43 months, the addition of 1 year-palbociclib to endocrine therapy in patients with HR+/HER2- breast cancer at high-risk of relapse after NACT did not improve iDFS
  - Stratified HR 0.93, 95% CI [0.74, 1.16]; 2-sided CHW p=0.525
  - Estimated 3 year iDFS rate: 81.2% with palbociclib vs 77.7% with placebo
- At interim analysis no difference was observed for OS
- Compliance was lower in the palbociclib arm vs placebo
  - 80.5% vs 84.5% completed therapy
  - 88.6% vs 90.3% received at least 7 cycles of study treatment
  - Relative total dose intensity (RTDI) was 82% vs 99%
- No new safety signals were observed

- This is the first study showing mature iDFS results on a CDK4/6 inhibitor as part of (postneo)adjuvant therapy
- To date the results of Penelope-B do not support the addition of 1 year palbociclib to endocrine therapy
- Long term follow-up from other adjuvant CDK4/6 studies must be awaited
- Further translational research and subgroup analyses are ongoing

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HERZLICHEN DANK!

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Slides are available on the webpage of GBG www.gbg.de