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PALLET: a neoadjuvant study to compare the clinical and antiproliferative effects of letrozole with and without palbociclib

Mitch Dowsett, Samuel Jacobs, Stephen Johnston, Judith Bliss, Duncan Wheatley, Chris Holcombe, Rob Stein, Stuart McIntosh, Peter Barry, David Dolling, Claire Snowdon, Sophie Perry, Leona Batten, Andrew Dodson, Vera Martins, Arjun Modi, Chester Cornman, Shannon Puhalla, Norman Wolmark, Thomas Julian, Katherine Pogue-Geile, Andre Robidoux, Louise Provencher, Jean Francois Boileau, Ibrahim Shalaby, Michael Thirlwell, Kate Fisher, Cynthia Huang Bartlett, Maria Koehler, Kent Osborne and Mothaffar Rimawi

San Antonio Breast Cancer Symposium
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San Antonio Breast Cancer Symposium® – December 4-8, 2018

rapid communication

Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial

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Why not have this as second slide

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Author conflicts of interest

- The PALLET trial received funding from Pfizer Inc., which contributed to the salary, travel, accommodation and expenses of several authors employed by The Institute of Cancer Research, The Royal Marsden Hospital NHS Foundation Trust and NSABP Foundation Inc.
- Drs Huang Bartlett and Koehler were employed by Pfizer Inc. at the time the study was conducted.
- Full disclosure of all authors is at SABCS.org

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Background (i)

- Almost all patients with ER+ breast cancer (BC) receive endocrine therapy (ET) but resistance is frequent through multiple mechanisms that promote the cell cycle.
- Palbociclib, a CDK4/6 inhibitor, causes cell cycle arrest in the G1 phase, resulting in reduced proliferation particularly in ER+ breast cancer.
- Efficacy demonstrated in combination with ET in PALOMA studies.

	PALOMA 1[1]	PALOMA 2[2]	PALOMA 3[3]
Design	Phase II, randomized, open label	Phase III, randomized, placebo controlled	Phase III, randomized, placebo controlled
Endocrine partner	Letrozole	Letrozole	Fulvestrant
Patients on study	165	666	521
Obj clinical response (measurable disease)	39% vs 56%	44% vs 55%	11% vs 25%
Median PFS (months)	10.2 vs 20.2	14.5 vs 24.8	4.6 vs 9.5
HR (95% CI)	0.49 (0.32-0.75)	0.58 (0.46-0.72)	0.46 (0.36-0.59)

1.Finn et al, Lancet Oncology 2015; 2.Finn et al, NEJM 2016;3.Cristofanilliet al, Lancet Oncology 2016

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Background (ii)

- Palbociclib is being investigated as adjuvant treatment in combination with ET
- No established biomarkers to identify those who benefit from added CDK4/6 inhibition
- Neoadjuvant treatment:
  - Facilitates breast conservation
  - Allows comparisons between treatments on primary disease
    - clinical response
    - change in Ki67: validated marker of response to endocrine therapy (predicts RFS)
  - Allows pre-treatment biomarker analyses of untreated index tumor
  - Allows sequential biopsies for biomarker assessment

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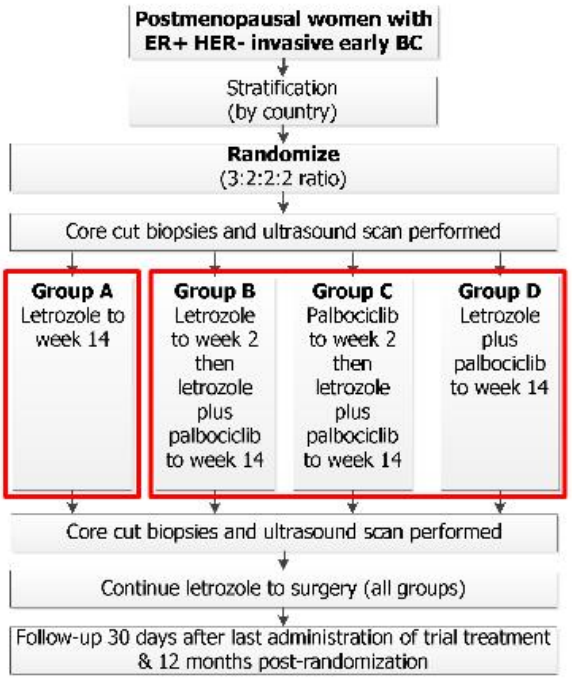
Trial design

- Phase II randomized trial
- Parallel protocols in the UK and North America
- Tumors ≥2cm by ultrasound, no evidence of metastatic disease
- Core cut biopsies taken at:
  - Baseline
  - 2 weeks (prior to commencement of second drug in Groups B and C)
  - 14 weeks/discontinuation of treatment (within 48 hours of last dose)
- Letrozole 2.5mg/d PO
- Palbociclib 125mg/d PO (21 days on, 7 days off) with dose reduction to 100mg and 75mg available



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Endpoints

Co-primary Endpoints *Group A vs. groups B+C+D*

- Change in the proliferation marker Ki67 after 14 weeks
- Clinical response by ultrasound after 14 weeks

Secondary Endpoints

- Effect of letrozole on Ki67 after 2 weeks and the **added** effect of palbociclib from weeks 2-14 (within group B)
- Effect of palbociclib on Ki67 after 2 weeks and the **added** effect of letrozole from weeks 2-14 (within group C)
- Assessment of safety and tolerability

Exploratory Endpoints

- Comprehensive biomarker analysis, including:
  - c-PARP (marker of apoptosis)
  - complete cell cycle arrest (Ki67≤2.7%) after 14 weeks

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Statistical and analytical considerations

- Powered (90%) using a conventional comparative design with alpha (α=5% overall) split between the **two co-primary endpoints**
  - **clinical response α=4%; Ki67 α=1%**
  - assumed a non-evaluable rate of 5%
  - recruitment target was 306 patients
- Treatment allocation was by computer generated random permuted blocks
- Randomization was stratified by country
- Clinical response measured locally by ultrasound and assessed according to ECOG criteria
- Ki67 and c-PARP tested centrally in Dowsett labs

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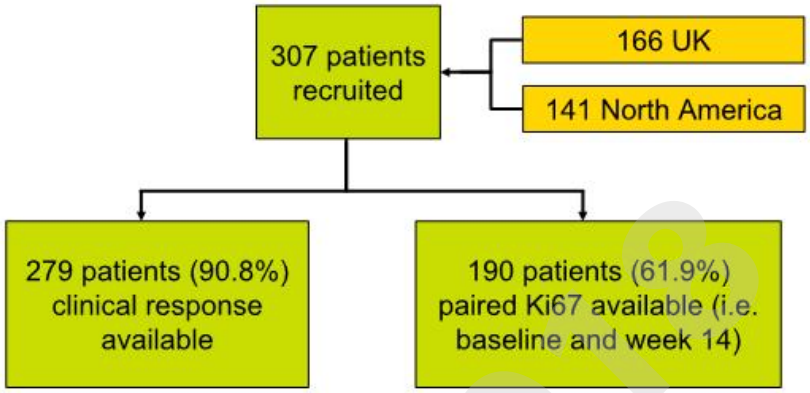
Patient flow and endpoint data availability

Recruitment took place over 3 years, from 27 February 2015 to 8 March 2018



Only geographical region and histological type were associated with availability of paired Ki67 results (p=0.008 and p= 0.001 respectively), models were adjusted accordingly.

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Baseline demographic and clinical characteristics

	LET alone 14wks		PAL+LET regimen	
	Group A (N=103)		Groups B+C+D (N=204)	
	Median	IQR	Median	IQR
Age (years)	66	59-72	64	60-71
	n	%	n	%
Tumor grade				
Low	13	**13**	19	**9**
Intermediate	70	**68**	157	**77**
High	19	**19**	27	**13**
Not known	1	**1**	1	**1**
Histological type				
Ductal	74	**72**	140	**69**
Lobular	24	**23**	51	**25**
Other	5	**5**	13	**5**
PgR status				
Positive	74	**72**	141	**69**
Negative	15	**15**	32	**16**
Not determined	14	**14**	31	**15**

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Summary of availability of paired Ki67 results

	LET alone 14wks Group A (N=103)		PAL+LET regimen Groups B+C+D (n=204)		Total (N=307)	
	n	%	n	%	n	%
Paired Ki67 data available	65	63	125	61	190	62
Paired Ki67 data not available	38	37	79	39	117	38
Baseline and end of treatment data not available	6	6	13	6	19	6
Baseline data only not available	3	3	9	4	12	4
End of treatment only not available	29	28	57	28	86	28
Sample taken outside of protocol 48 hour window	*2*	*1*	*6*	*3*	*8*	*3*
Sample analyzed but Ki67 result not evaluable	*13*	*13*	*27*	*13*	*40*	*13*
No sample taken	*14*	*14*	*24*	*12*	*38*	*12*

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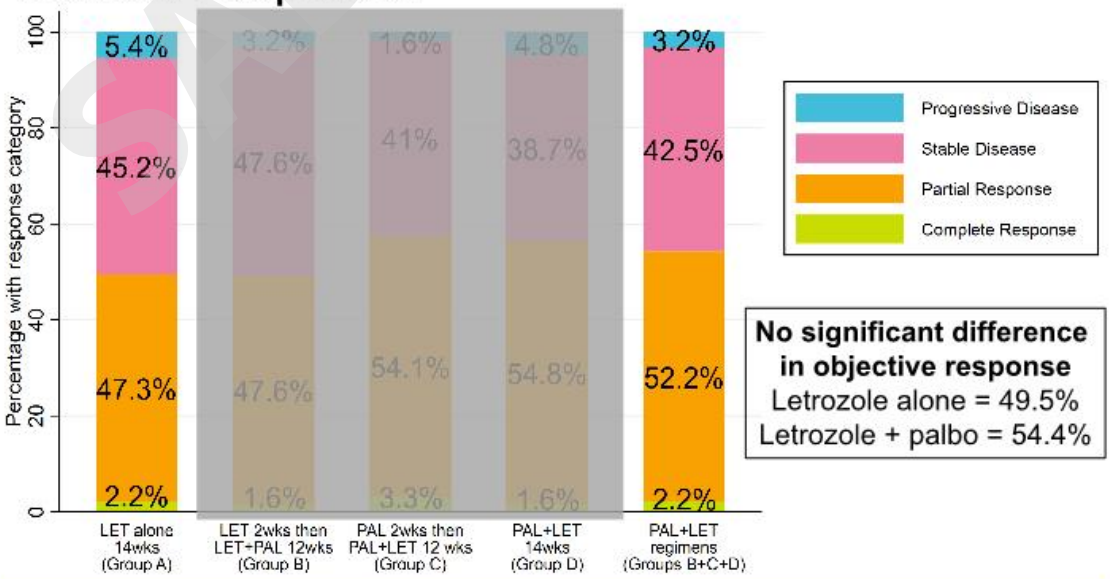
Co-primary endpoints: Clinical response

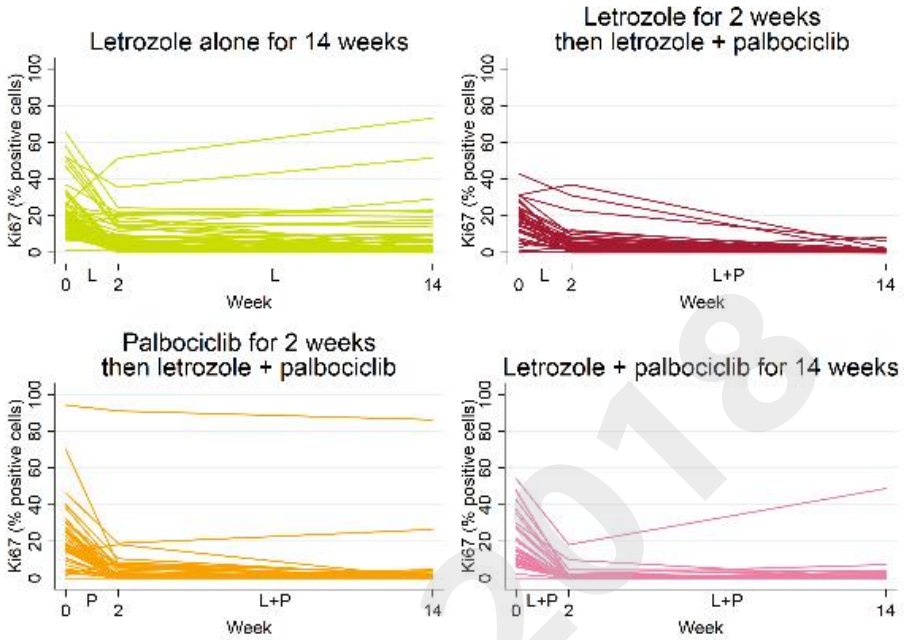


No significant difference in objective response
Letrozole alone = 49.5%
Letrozole + palbo = 54.4%

Clinical response between Group A and Groups B+C+D, p=0.20 Mann-Whitney (ordinal)

Co-primary endpoints:

Individual trajectories of Ki67 by randomized treatment group



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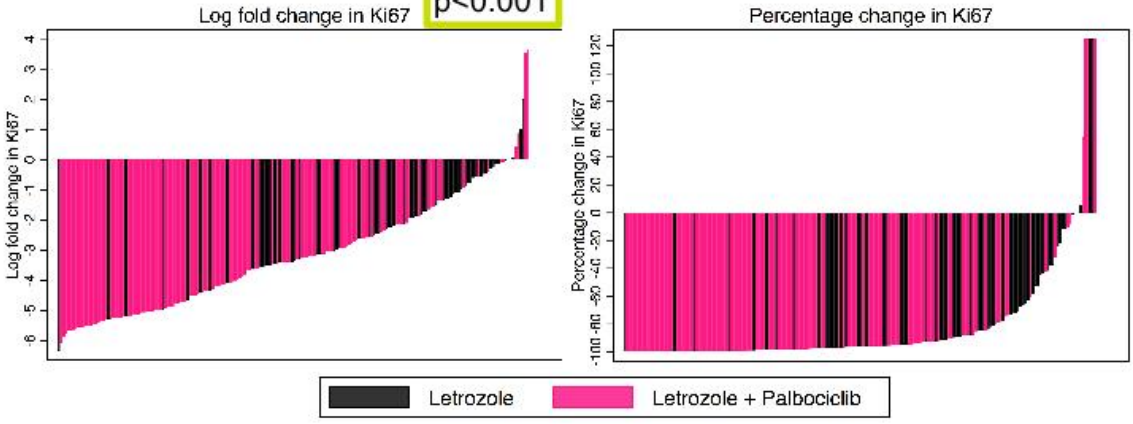
Co-primary endpoints:
Change in Ki67 at 14 weeks

		Log-Fold Change		Percentage Change	
Group	**N**	**Median**	**IQR**	**GeoMean**	**95% CI**
Letrozole alone (Group A)	65	-2.2	-3.4 to -1.0	-88.5%	-92.3% to -82.9%
Letrozole + Palbociclib (Groups B+C+D)	125	-4.1	-5.0 to -2.8	-97.4%	-98.1% to -96.4%
		p<0.001			



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Exploratory endpoints: Complete cell cycle arrest (CCCA)

CCCA defined as Ki67≤2.7%

Complete cell cycle arrest		Week 2 n	Week 2 %	Week 14 n	Week 14 %
LET 14wks	(A)	37/87	43	38/65	59
LET 2wks then LET+PAL 12wks	(B)	24/58	41	37/40	93
PAL 2wks then LET+PAL 12wks	(C)	44/61	72	43/47	92
PAL+LET 14wks	(D)	47/53	89	33/38	87
PAL+LET regimens	(B+C+D)			113/125	90

OR=6.83
(95% CI 3.12-14.98)
p<0.001

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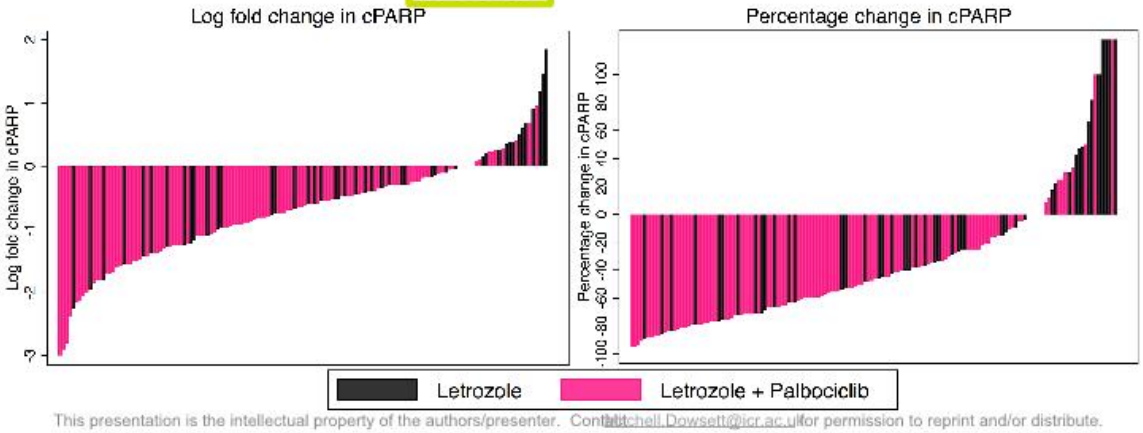
Exploratory endpoints: Change in c-PARP (apoptosis) at 14 weeks

Change in c-PARP	N	Log-fold Change Median	Log-fold Change IQR	Percentage Change GeoMean	Percentage Change 95% CI
Letrozole alone (Group A)	47	-0.42	-0.99 to 0.20	-31.4%	-46.9% to -11.5%
Letrozole+Palbociclib (Groups B+C+D)	99	-0.80	-1.35 to -0.29	-56.8%	-62.9% to -49.7%
		p=0.003			



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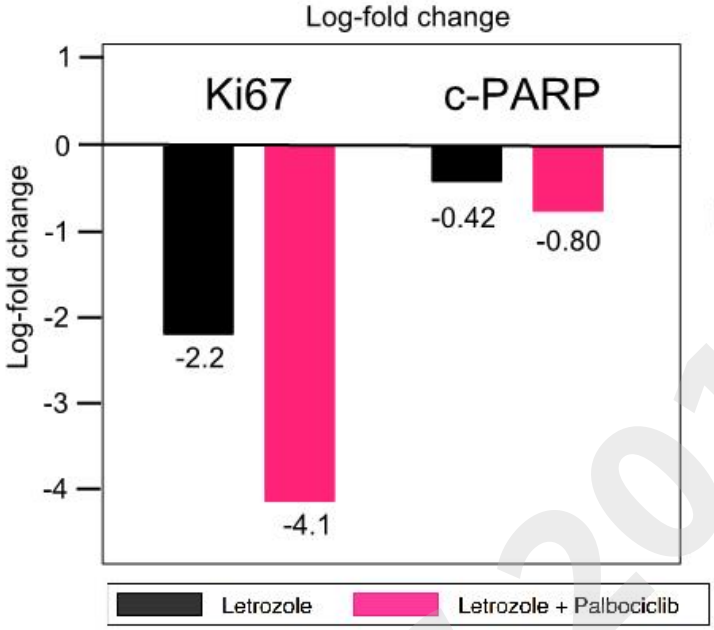
Comparison of changes at 14 weeks: Ki67 vs c-PARP



"Signals that promote proliferation promote apoptosis"

Green and Evan
A matter of life and death
Cancer Cell,2002,1,19-30

Secondary endpoints: Safety and tolerability

NO new safety signals

MedDRA coded AE preferred term	Letrozole alone Group A (N=100)		Palbociclib+letrozole regimen Groups B+C+D (N=201)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Fatigue	41 (41.0)	0 (0.0)	117 (58.2)	4 (2.0)
Neutrophil count decreased	2 (2.0)	0 (0.0)	110 (54.7)	82 (40.8)
Hot flush	40 (40.0)	0 (0.0)	54 (26.9)	0 (0.0)
Nausea	18 (18.0)	0 (0.0)	50 (24.9)	0 (0.0)
Arthralgia	26 (26.0)	0 (0.0)	37 (18.4)	1 (0.5)
Headache	21 (21.0)	0 (0.0)	37 (18.4)	0 (0.0)

More patients had a grade ≥3 toxicity on palbociclib + letrozole than letrozole alone (49.8% vs 17.0%:p<0.001) mainly asymptomatic neutropenia

1 recorded case of grade 4 neutropenic sepsis (arm B)

Conclusions

Compared with letrozole alone, treating patients with ER+ primary breast cancer with palbociclib + letrozole over 14-weeks:

- Enhanced the suppression of malignant cell proliferation as assessed by Ki67 (log-fold change -2.2 to -4.1, one-sided p<0.0001) equivalent to a geometric mean change of −88.5% to −97.4%
- Enhanced the proportion of patients achieving CCCA (58.5% to 90.4%, p<0.0001)
- Did not substantially increase the clinical response rate (49.5% to 54.4%, p=0.20) → possibly due to less apoptosis, as measured by c-PARP
- Did not identify any new safety signals

Comprehensive secondary biomarker analyses on-going

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The PALLET Global Trial Steering Committee, UK Trial Steering Committee and Independent Data Monitoring Committee

James Morden, ICR-CTSU Senior Statistician & PALLET Trial Statistician, died September 2017

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