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Update on Breast Cancer Systemic Therapy for Clinical Practice and Perspectives

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November 2018

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Disclosures

Conflict of interests (Speaker & advisory role):

Roche, Lilly, Amgen, ESAI, BMS, Pfizer, Novartis, MSD

Breast Cancer: Adjuvant Setting

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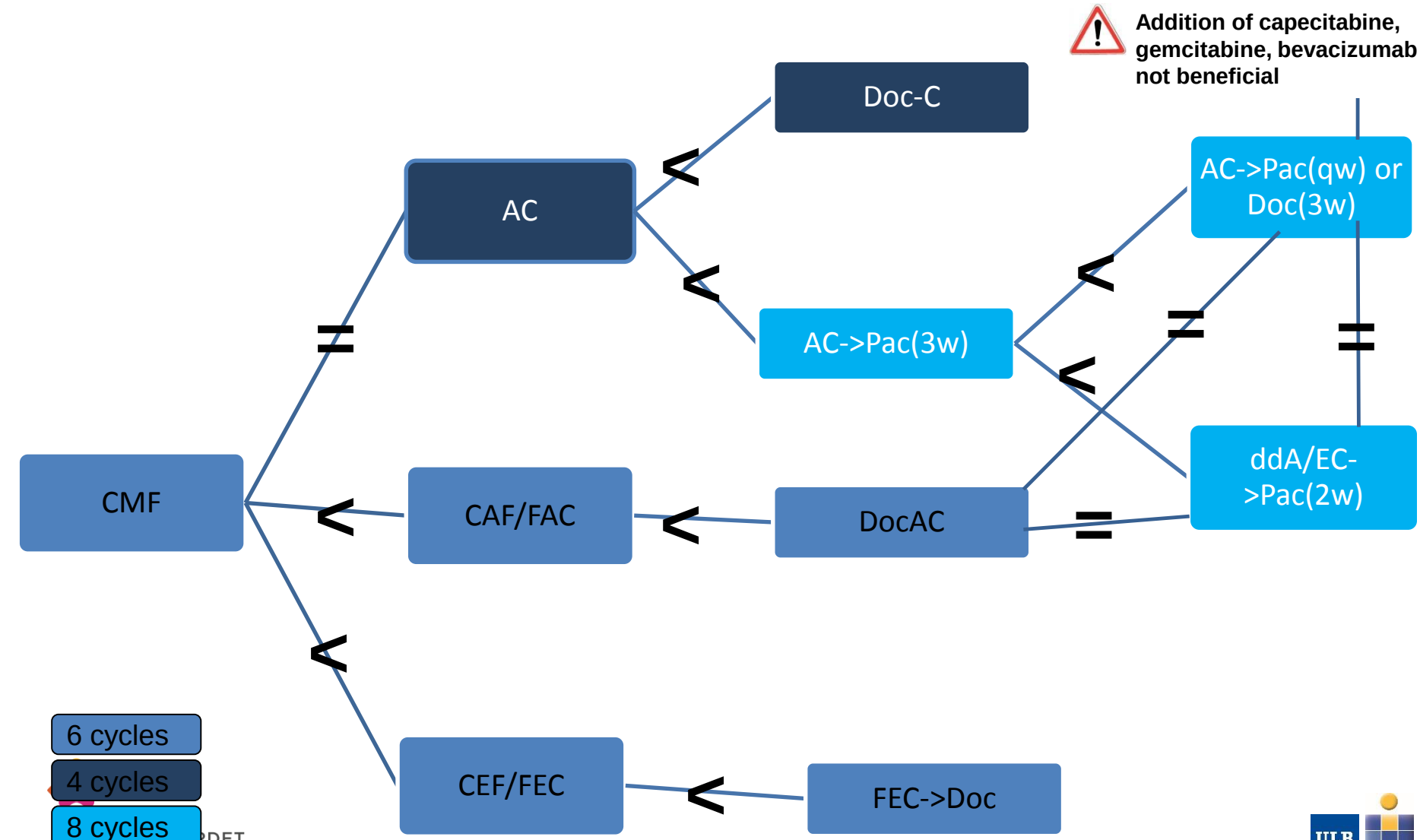
Recent Therapy Studies Changing (Influencing) Clinical Practice (Adjuvant Setting)

- EBCTCG meta-analysis : Dose density of adjuvant CT
- ABCSG-16 trial : 2 vs 5 y of anastrozole after 5 y of adjuvant endocrine therapy
- HER2 positive adjuvant therapy : Escalation/de-escalation strategy

Adjuvant Chemotherapy

Overview of the most important adjuvant chemotherapy studies in early breast cancer



5-FU: No benefit in nodes + (Cognetti et al)

Wildiers H, …, Awada A, *Belg J Med Oncol.* 2014

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Increasing the dose intensity of adjuvant chemotherapy : an EBCTCG meta-analysis

Richard Gray, Rosie Bradley, Jeremy Braybrooke, Christina Davies, Hongchao Pan, Richard Peto, Judith Bliss, David Cameron, John Mackey, Lucia Del Mastro, Sandra Swain, Michael Untch, Jonas Bergh, Kathleen Pritchard, Larry Norton, for the

Early Breast Cancer Trialists' Collaborative Group

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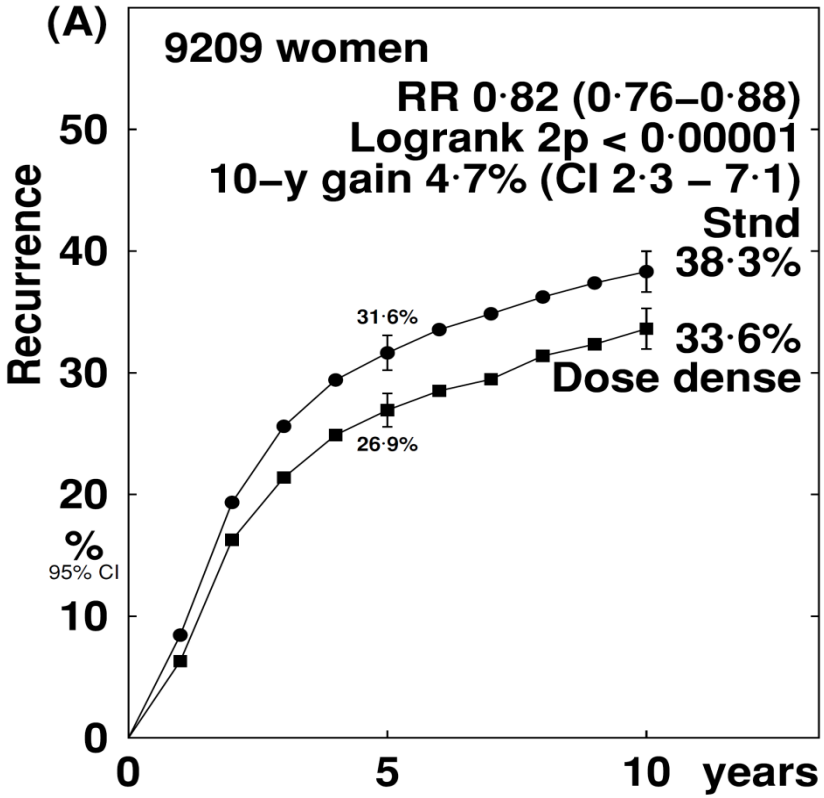
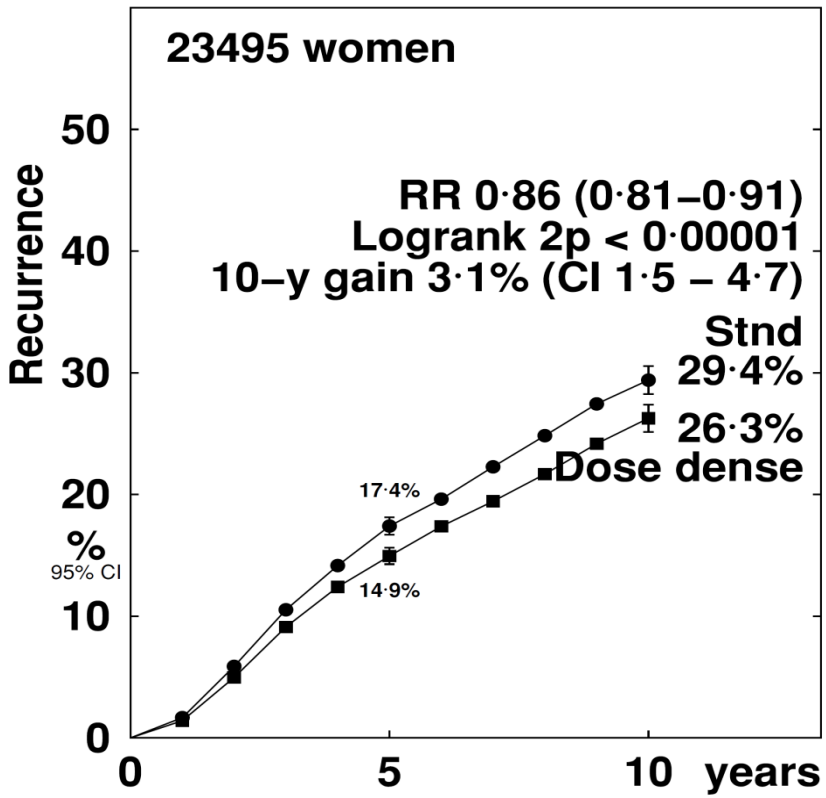
ER- Negative

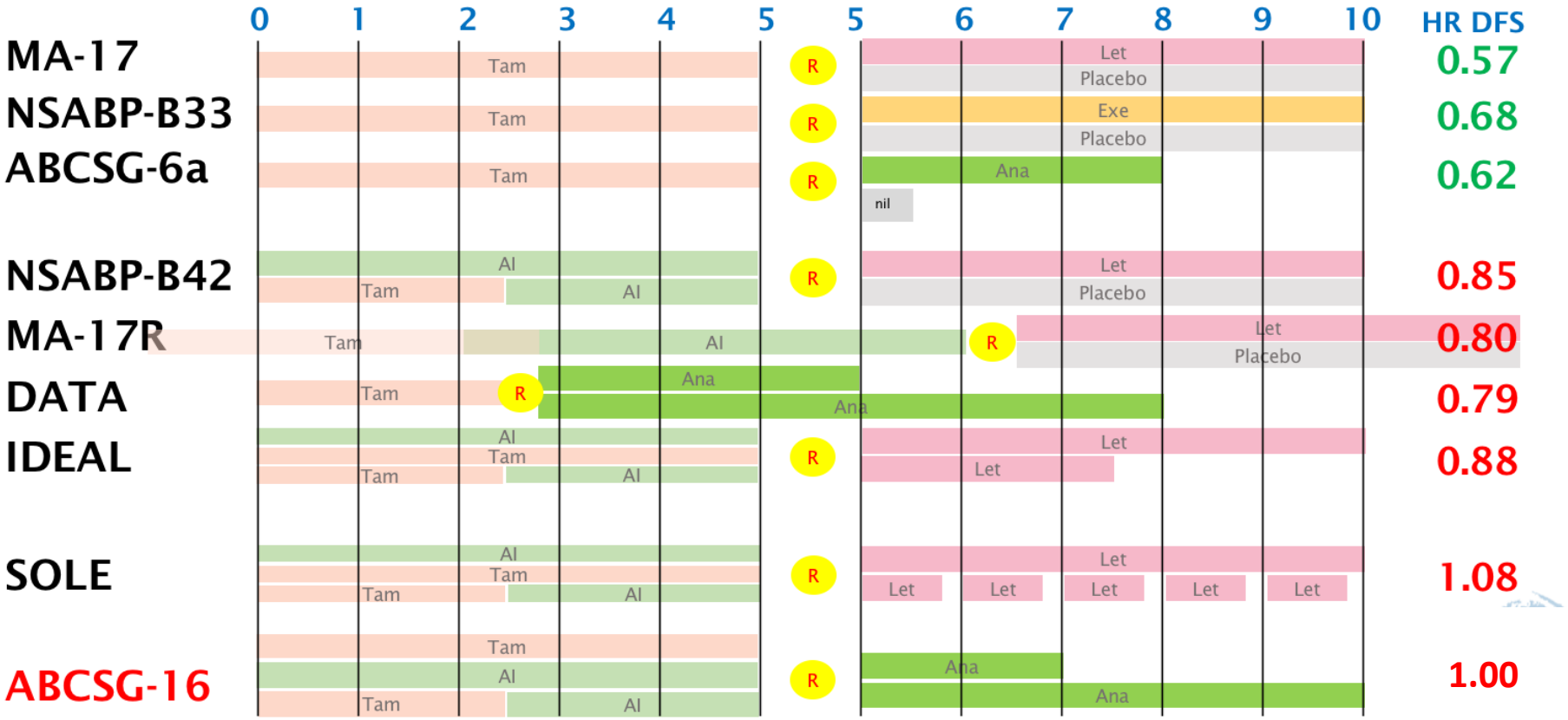


ER - Positive

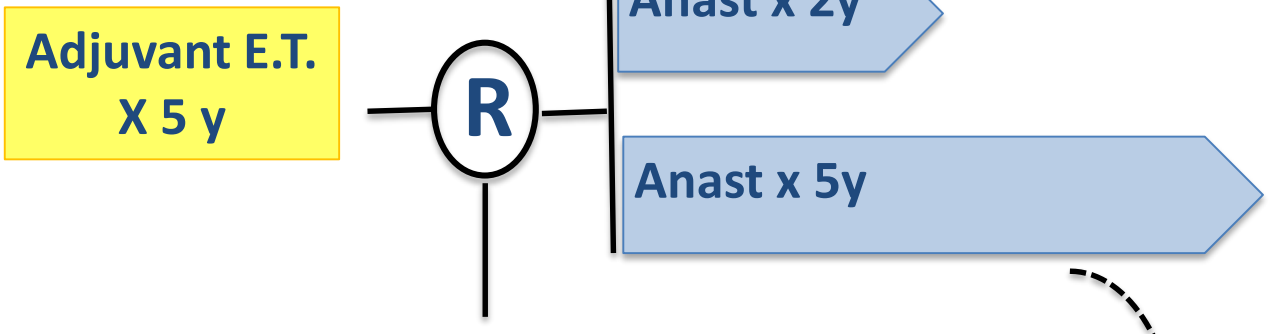


Adjuvant endocrine therapy

Extending Adjuvant AIs



SABCS 2017 - Luminal Breast Cancers Clinical Trials : ABCSG16 (extended A.I.)



Same DFS (HR 1.007)
Same OS
Same control BC rate
Same 2nd primary rate

Median age 65

N+	31%
G3	20%
CTX	29%

40% drop off

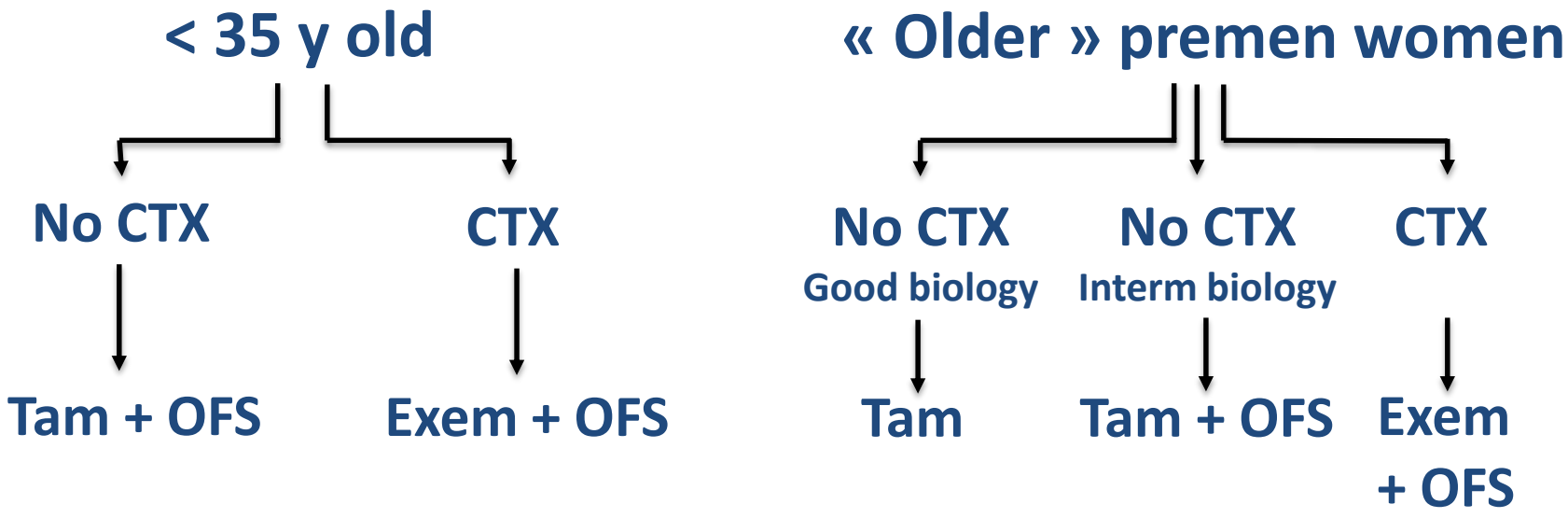
Fractures 6.3% (vs 4.7%)

M. Gnant et al, abst GS3-01

SABCS 2017 - Luminal Breast Cancers Take home message regarding extended endocrine therapy

In case an AI has been incorporated in the first 5 years of therapy, AI total duration should not exceed 7 years

SABCS 2017 - Luminal Breast Cancers
Clinical Trials : SOFT/TEXT
Premenopausal patients: Take home messages



No benefit yet in OS for Exem + OFS…

Courtsey to M. Piccart

Selected Adverse Events

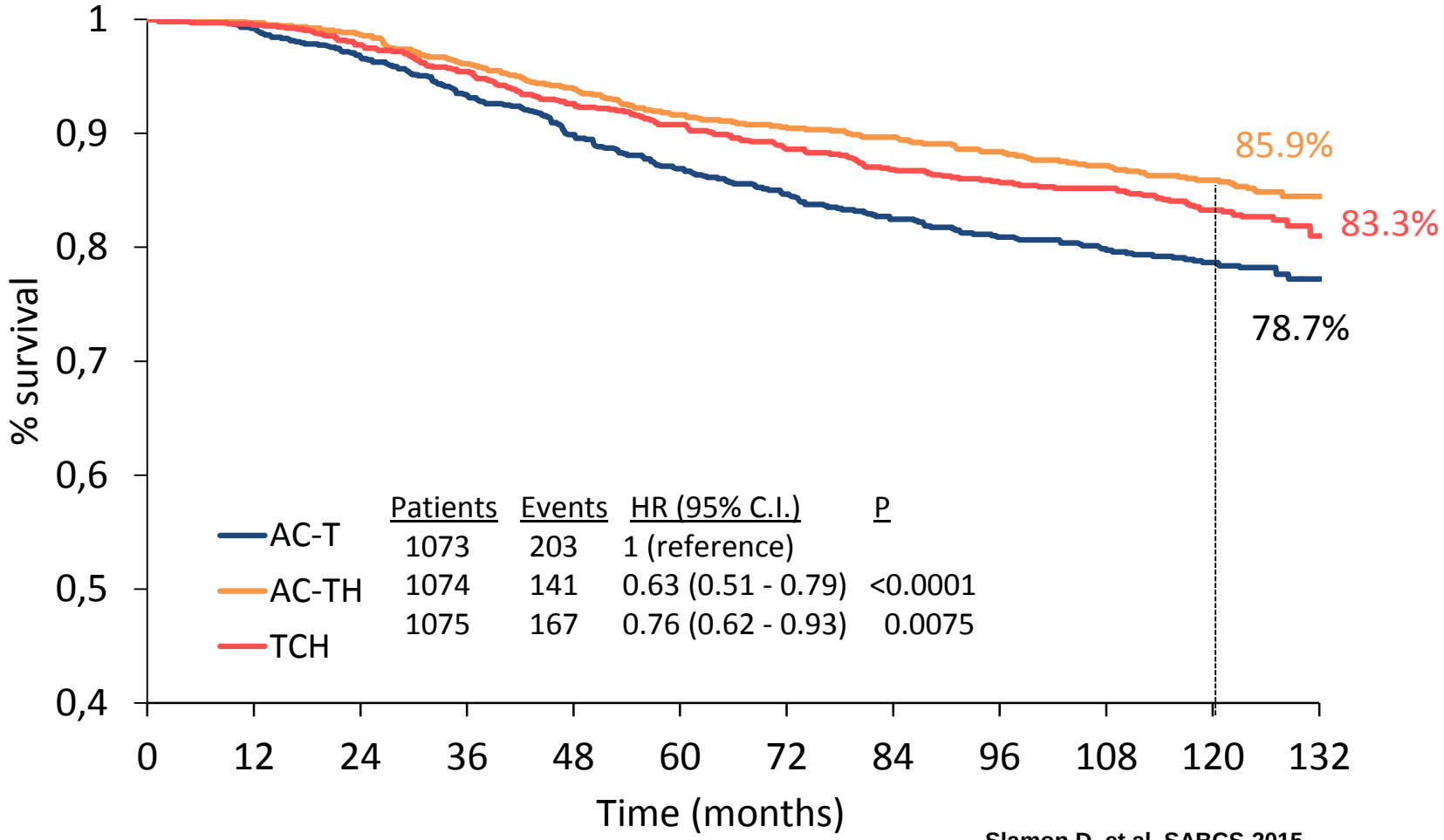
	T (N=1005)	T + OFS (N=1006)	E + OFS (N=1000)
Endometrial cancer (n)	N=7	N=4	N=3
Thrombosis/embolism (G2-4)	2.2%	2.2%	0.9%
Hot flashes (G3)	7.8%	13.2%	10.7%
Libido decrease (G2)	11.5%	15.9%	17.5%
Musculoskeletal symptoms (G3-4)	6.7%	5.9%	12.0%
Osteoporosis (G2-4; T score<-2.5)	3.9%	6.1%	11.9%
Depression (G3-4)	4.1%	4.5%	3.9%

Courtesy to G. Fleming

HER-2 and Breast Cancer

- A driver in breast cancer carcinogenesis (amplification & mutation)
- A prognostic and predictive biomarker
- A target for therapy (through the whole disease evolution!) (MoAbs, TKIs, ADC, Vaccines)
- HER-2 dual inhibition concept
- HER-2 and immune function (Immune signature; TILs)
- HER-2 as a target for molecular imaging

BCIRG 006 Overall Survival



Slamon D, et al. SABCS 2015

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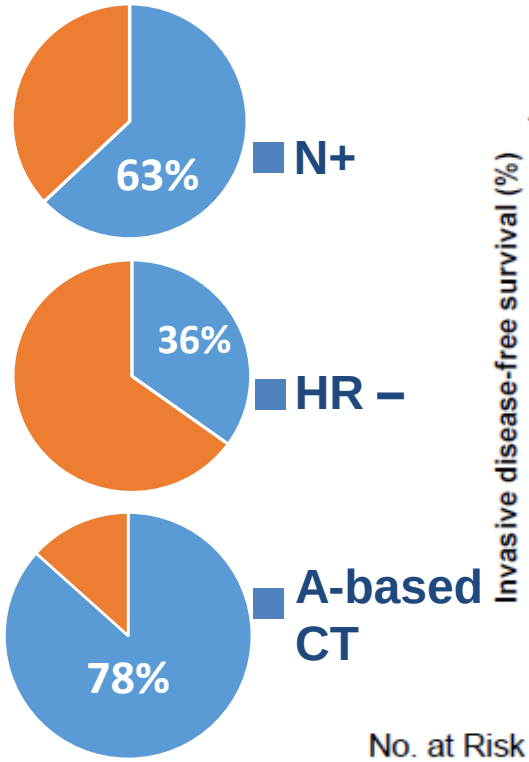
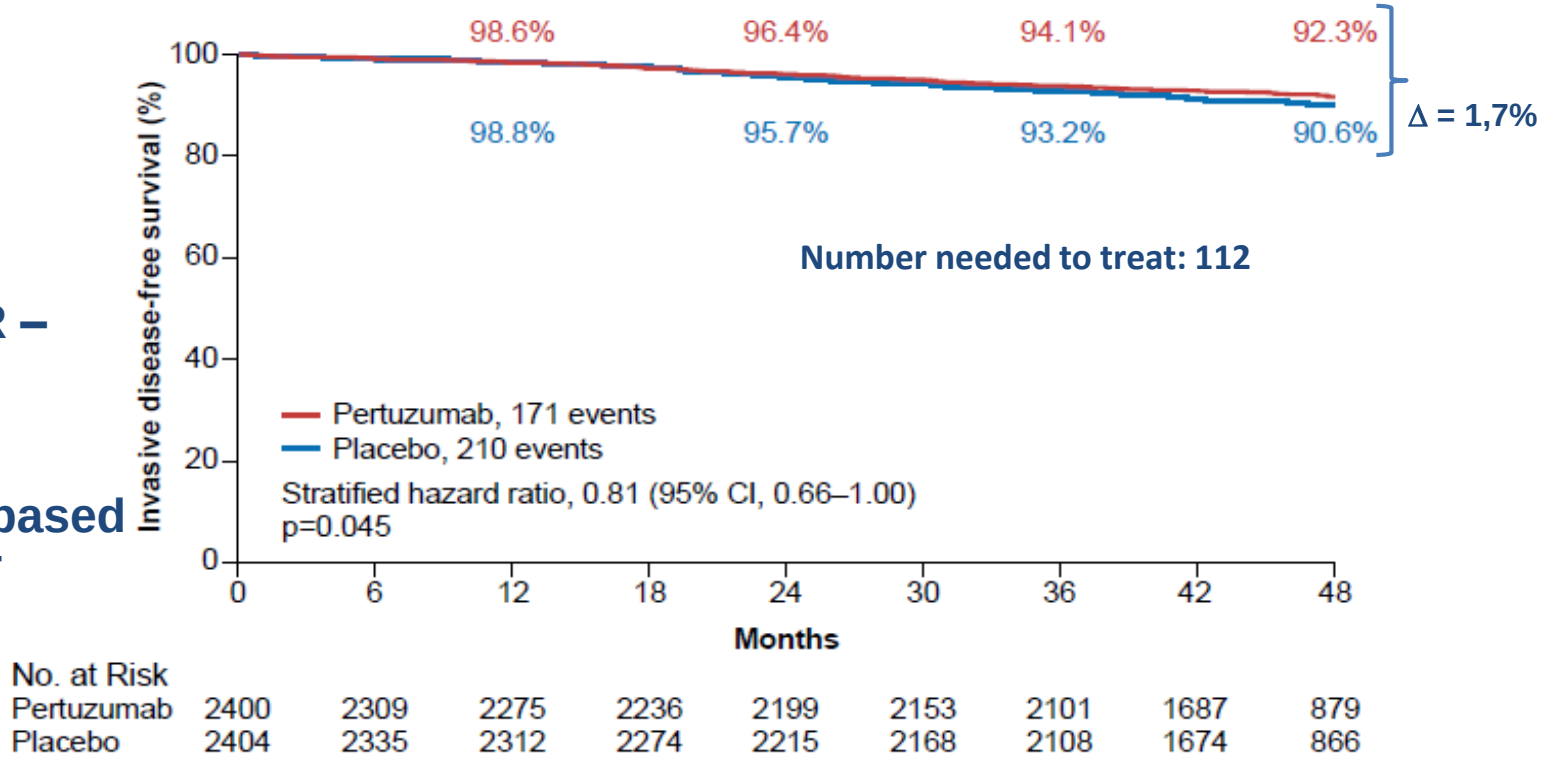
HER2 POSITIVE TREATMENT ESCALATION STRATEGY

APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival





ASCO 2017, LBA 500

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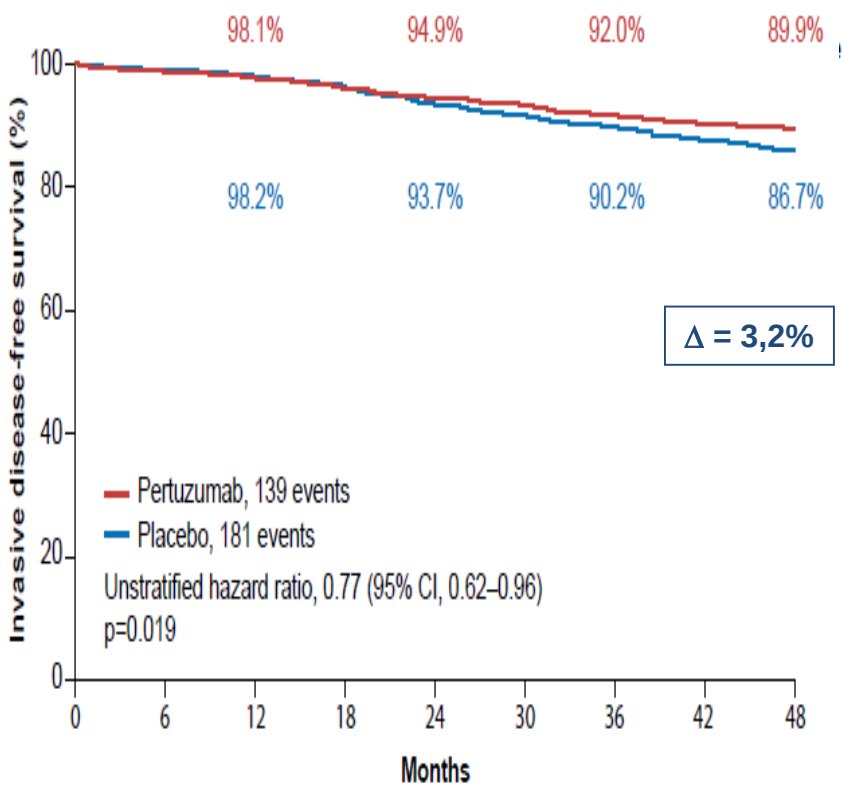
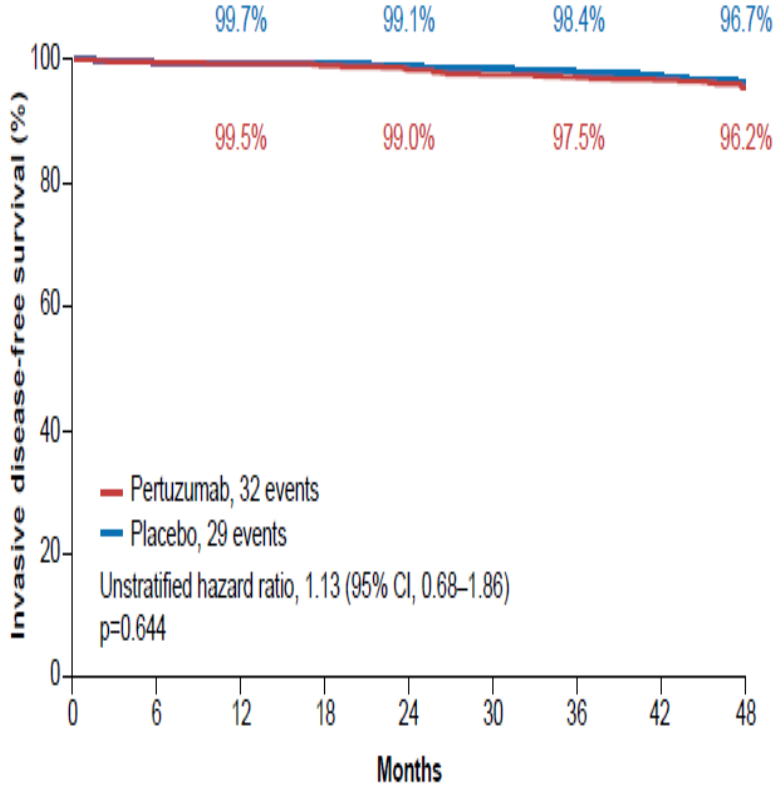
APHINITY: Outcome on nodal status

Node-positive



No. at Risk									
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

Node-negative



No. at Risk									
Pertuzumab	897	865	856	849	841	826	818	775	456
Placebo	902	882	873	866	856	849	844	792	461

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Von Minchwitz, NEJM 2017

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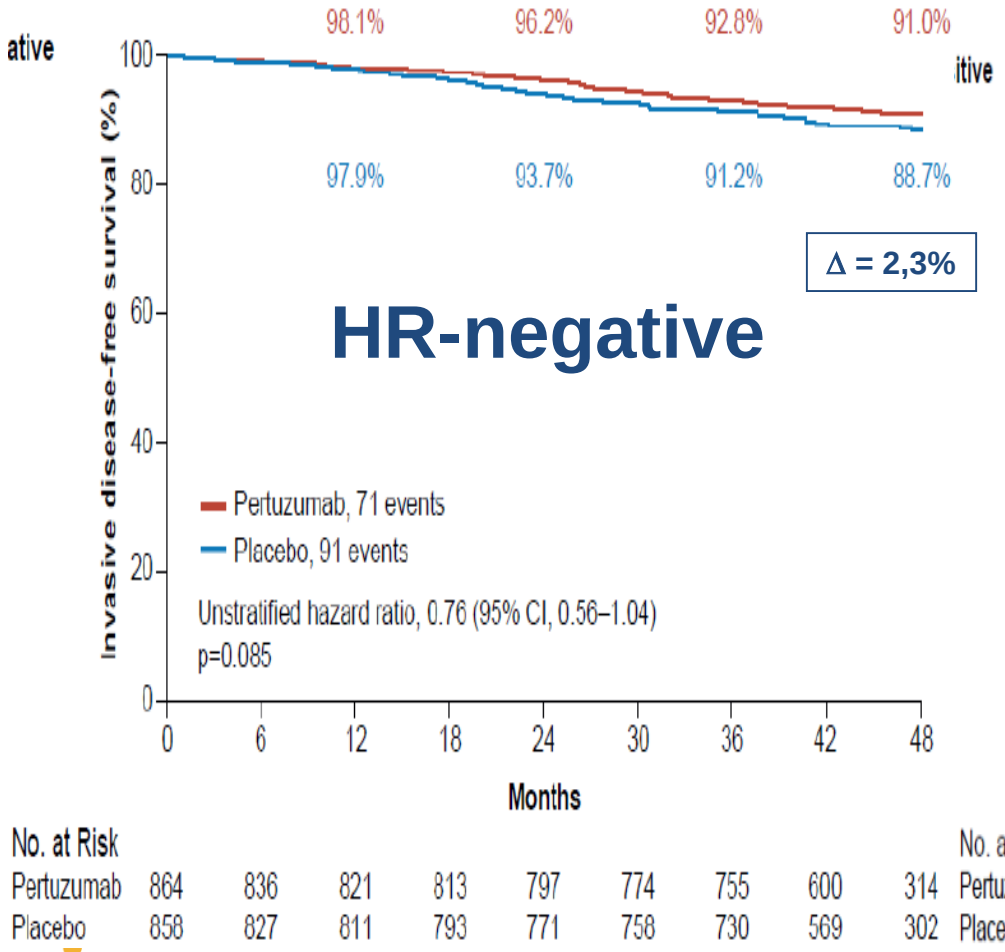
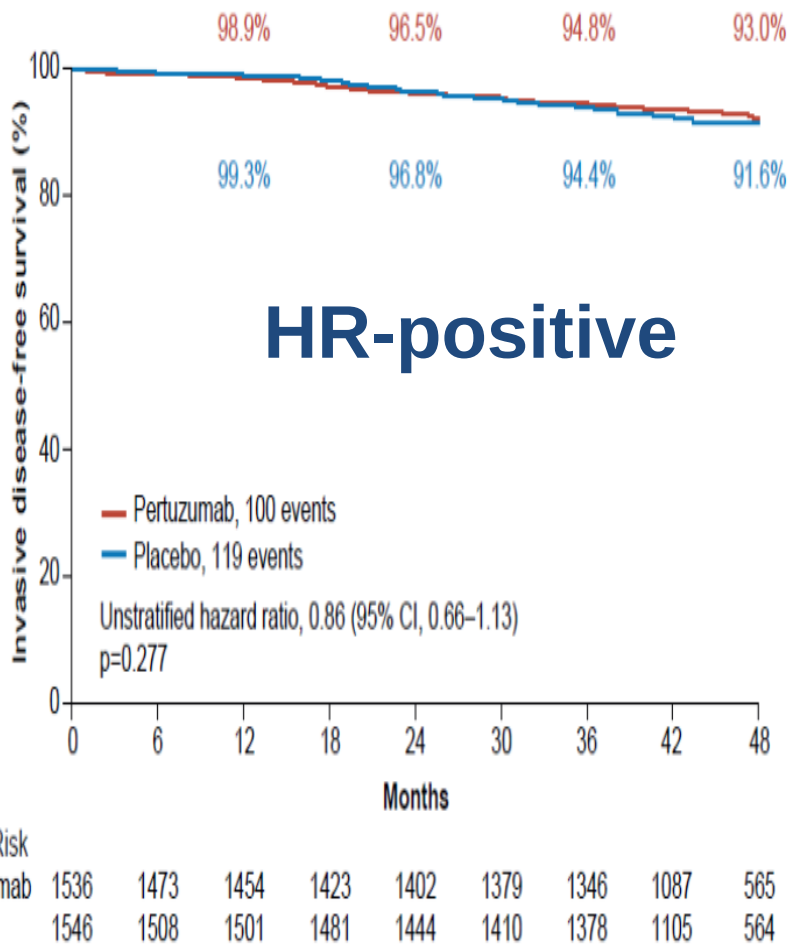
APHINITY: Outcome on hormone receptor status





Von Minchwitz, NEJM 2017

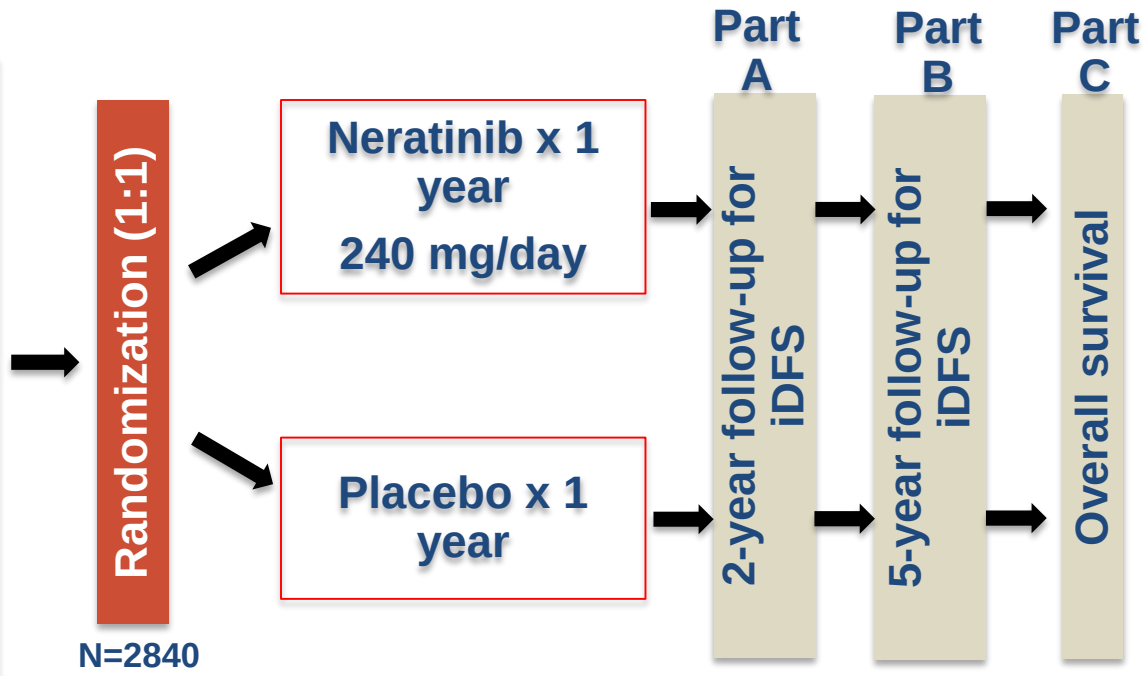
Neratinib

- Oral irreversible tyrosine kinase inhibitor of HER1, 2, 4

- Phase 2 trial (n=136) trastuzumab-pretreated cohort (66) – naïve (70)
  - ORR: 24% & 56% respectively
  - 16-week PFS: 59% & 78% respectively

ExteNET: study design

- HER2+ breast cancer
- IHC 3+ or ISH amplified (locally determined)
- Prior adjuvant trastuzumab + chemotherapy
- Lymph node +/–, or residual invasive disease after neoadjuvant therapy
- Stratified by: nodal status, hormone receptor status, concurrent *vs* sequential trastuzumab



Primary endpoint: invasive disease-free survival (iDFS)

Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

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Chan et al. Lancet Oncol 2016
Clinicaltrials.gov identifier: NCT00878709

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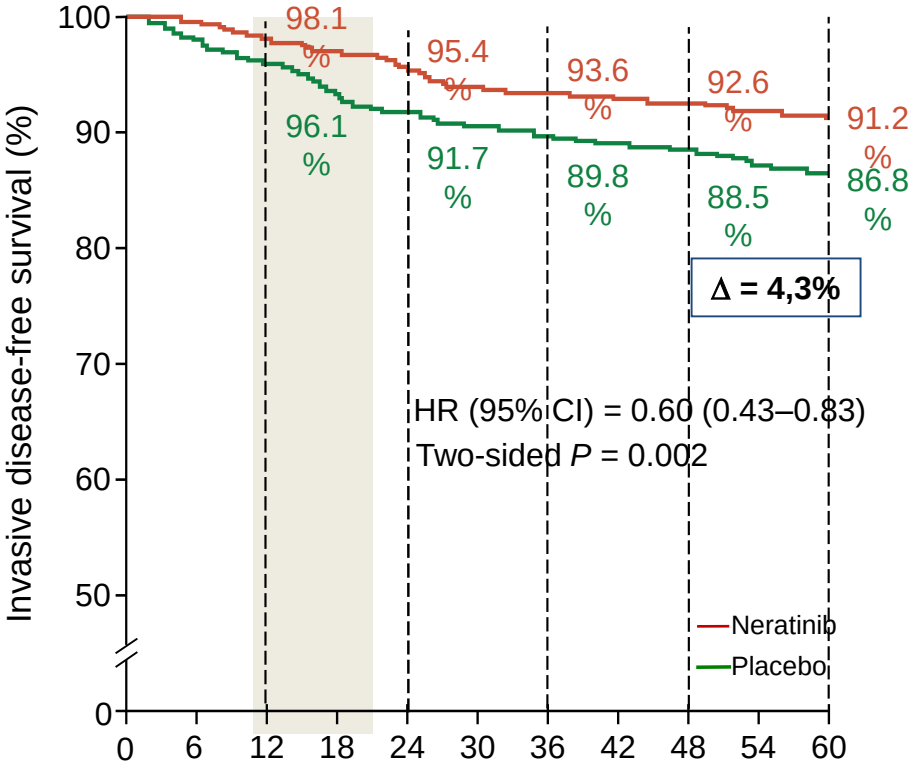
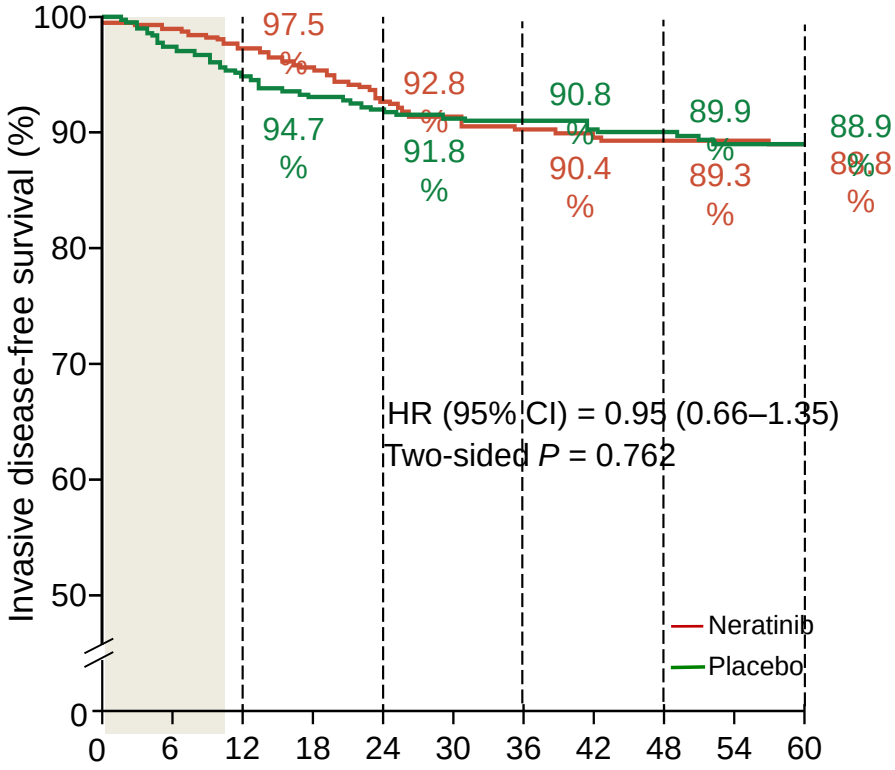
ExteNET: iDFS by hormone receptor status

HR-positive subgroup



No. at risk											
Neratinib	816	757	731	705	642	571	565	558	554	544	523
Placebo	815	779	750	719	647	581	567	556	551	542	525

HR-negative subgroup



No. at risk											
Neratinib	604	559	541	520	464	407	400	391	384	376	362
Placebo	605	575	548	529	495	448	444	435	427	416	402

Intention-to-treat population. Cut-off date: March 1, 2017

HER2 POSITIVE TREATMENT DE-ESCALATION STRATEGY

Chemotherapy de-escalation: for whom?

Phase II Adjuvant Paclitaxel and Trastuzumab (No anthracyclines)

Eligibility
- **HER2+ primary breast cancer**
- **Node negative**
- **Tumor measuring up to 3 cm in greatest dimension**

→

Paclitaxel
80 mg/m2 weekly
x 12 wks
+
Trastuzumab
4 mg/Kg weekly
x 12 wks

→

Trastuzumab
6 mg/kg every 3wks
X 40 wks

406 patients recruited; Follow-Up 4 years:
- 3-year survival free from invasive disease 98.7%
- Only 2 cases of distant metastasis
- No cases of breast-cancer-related deaths

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Tolaney SM, NEJM (2015)

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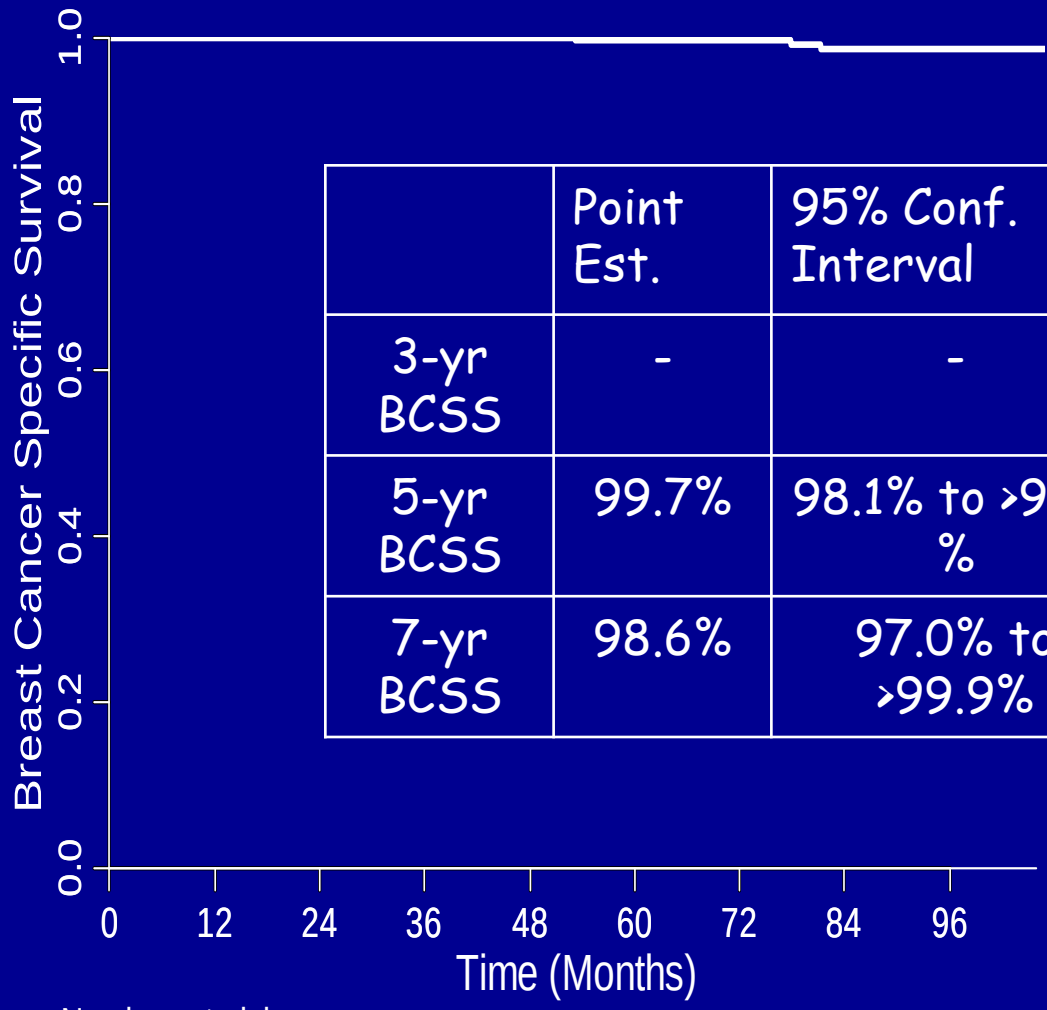
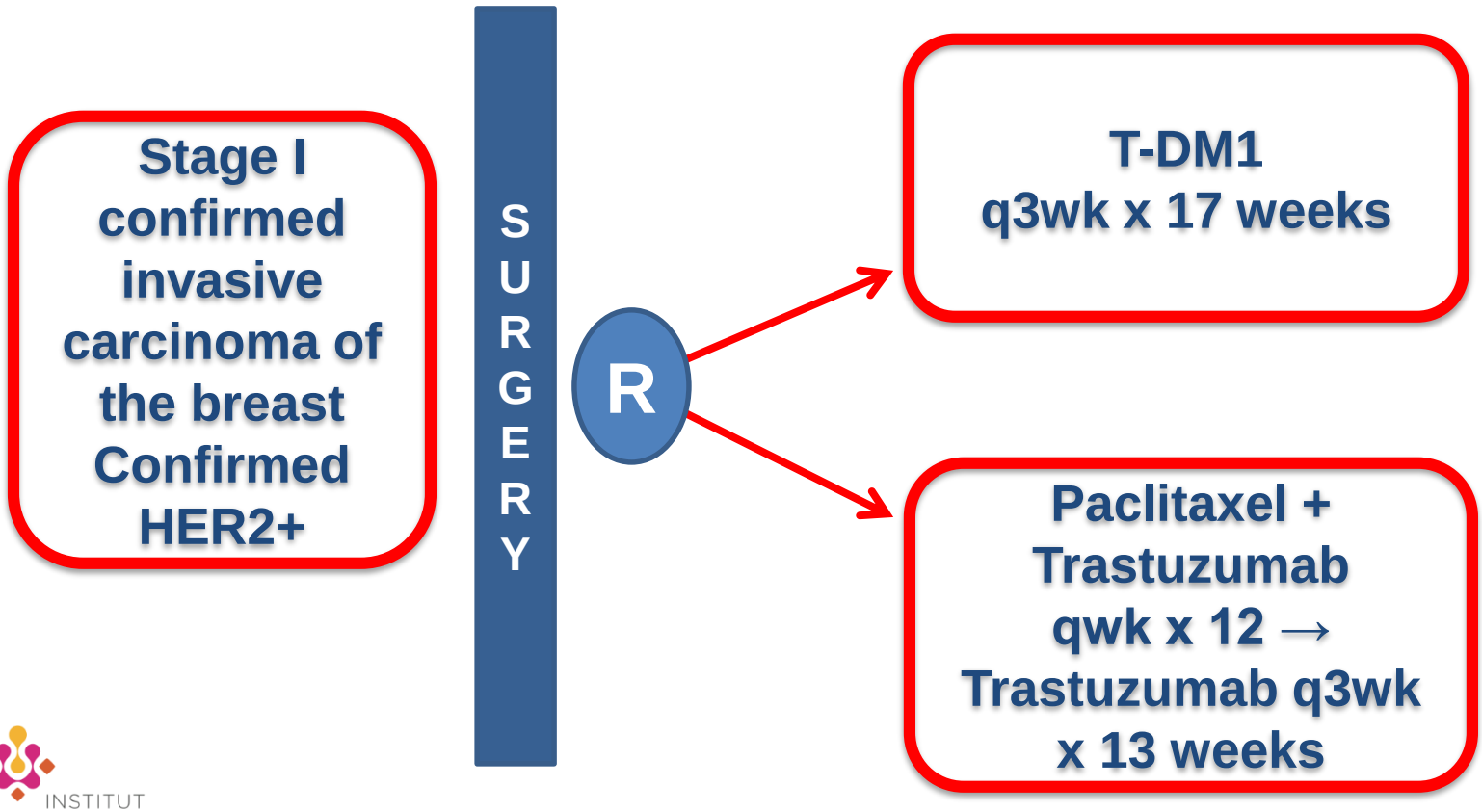
APT: Breast Cancer Specific Survival



	Point Est.	95% Conf. Interval	No. of events
3-yr BCSS	-	-	0
5-yr BCSS	99.7%	98.1% to >99.9 %	1
7-yr BCSS	98.6%	97.0% to >99.9%	3

Tolaney PASCO 2017

Phase II Study of T-DM1 vs Paclitaxel + Trastuzumab for Stage I HER2+ Breast Cancer (ATEMPT)



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De-escalation Therapy: Trials exploring shorter durations of adjuvant trastuzumab : status as of September 2018

Trial	N° of pts	Time needed	Pt charact	CTX/Trast	Non inf margins	Results
6 months vs 12 months						
PHARE[1-3]	3380	4(+2)Y	N- 55% HR+ 58%	A/T with trast concom or seq	1.15	HR 1.28 (1.05-1.56) (mostly driven by ER-sequential CTX group)
HELLENIC[2-4] NCT00615602	489	8 Y (!)	N- 17% HR+ 69%	A/T with trast concomitant	1.53	DFS events : 13% vs 10.4% HR 1.57 (0.86-2.10)
PERSEPHONE[2,3] NCT00712140	4089	8 Y (!)	?	?	?	?
3 months vs 12 months						
SHORT-HER[2,3] NCT00629278	1250	≈ 5 Y	N- 51% ER+ 67%	Conv A->T+H for 12m TH->A for 3m arm	1.29	Non-inferiority of the shorter treatment cannot be claimed
SOLD[2,3] NCT00593697	2176	≈ 6 Y	?	TH->A->Tx9m(12m) TH->A (3m)	Superior OS by 4%	Endpoint not met

1. PIVOT. Lancet Oncol. 2013; 2. Swain. The Oncologist. 2013; 3. Clinicaltrials.gov; 4. Mavroudis. Ann Oncol. 2015

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PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Randomised phase 3 non-inferiority trial with definitive 4-year disease-free survival results

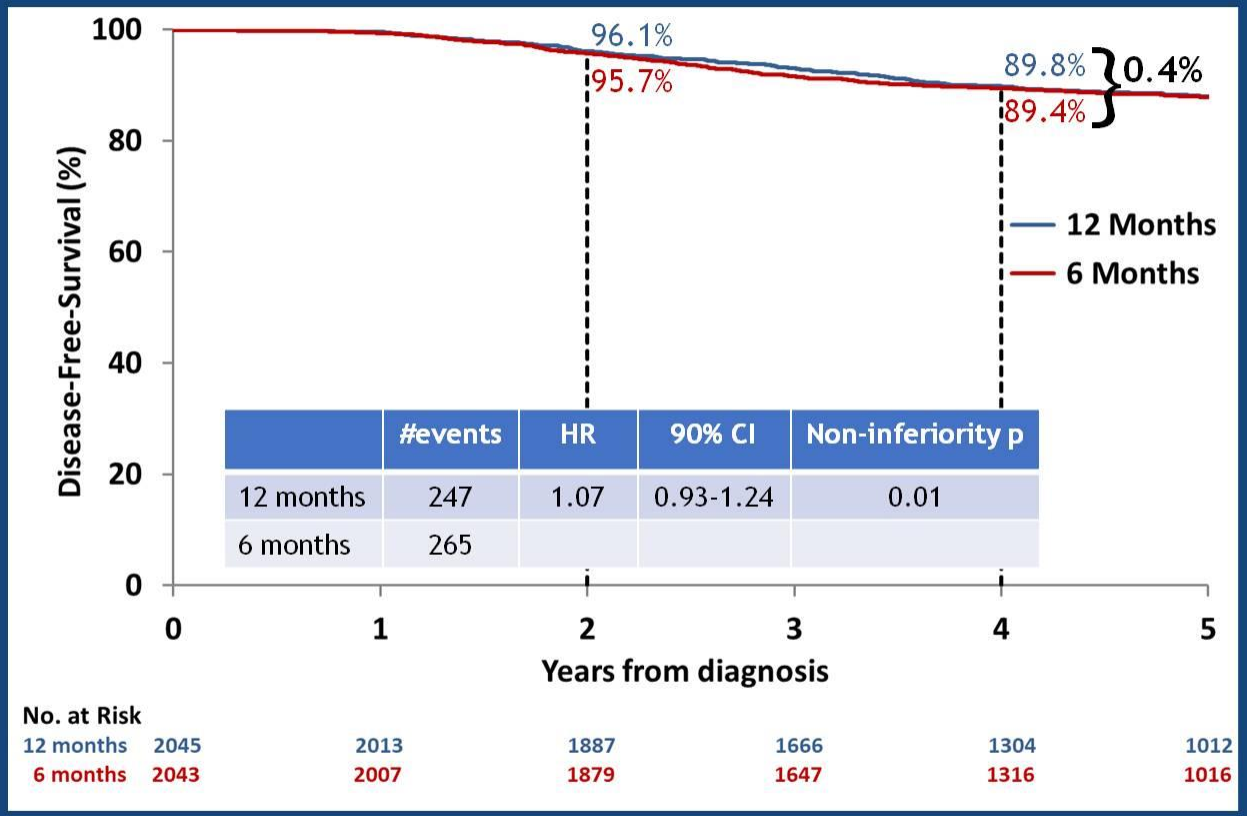
Helena Earl, Louise Hiller, Anne-Laure Vallier, Shrushma Loi, Donna Howe, Helen Higgins, Karen McAdam, Luke Hughes-Davies, Adrian Harnett, Mei-Lin Ah-See, Richard Simcock, Daniel Rea, Janine Mansi, Jean Abraham, Carlos Caldas, Claire Hulme, David Miles, Andrew Wardley, David Cameron, Janet Dunn, on behalf of the PERSEPHONE Trial Investigators

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Prof Helena Earl MD PhD

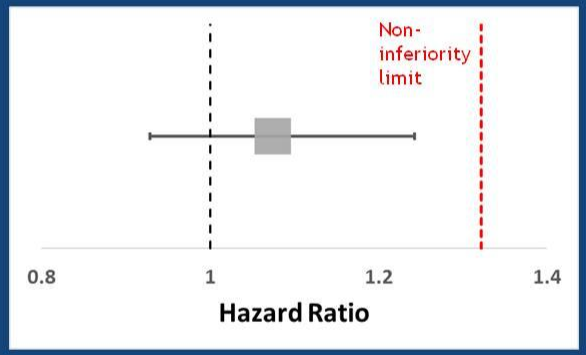
https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/persephone

Disease-free survival



	#events	HR	90% CI	Non-inferiority p
12 months	247	1.07	0.93-1.24	0.01
6 months	265			

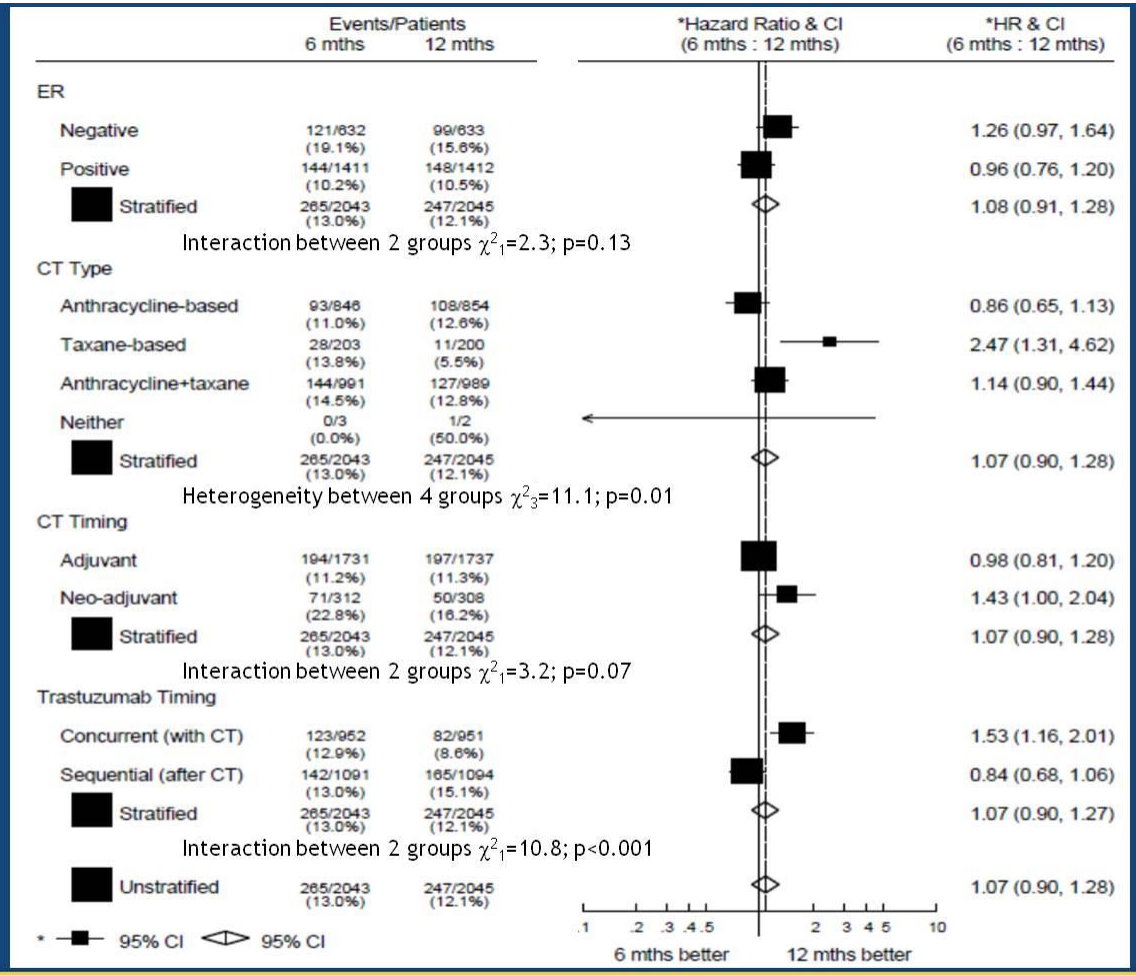
No. at Risk						
12 months	2045	2013	1887	1666	1304	1012
6 months	2043	2007	1879	1647	1316	1016



Presented By Helena Earl at 2018 ASCO Annual Meeting

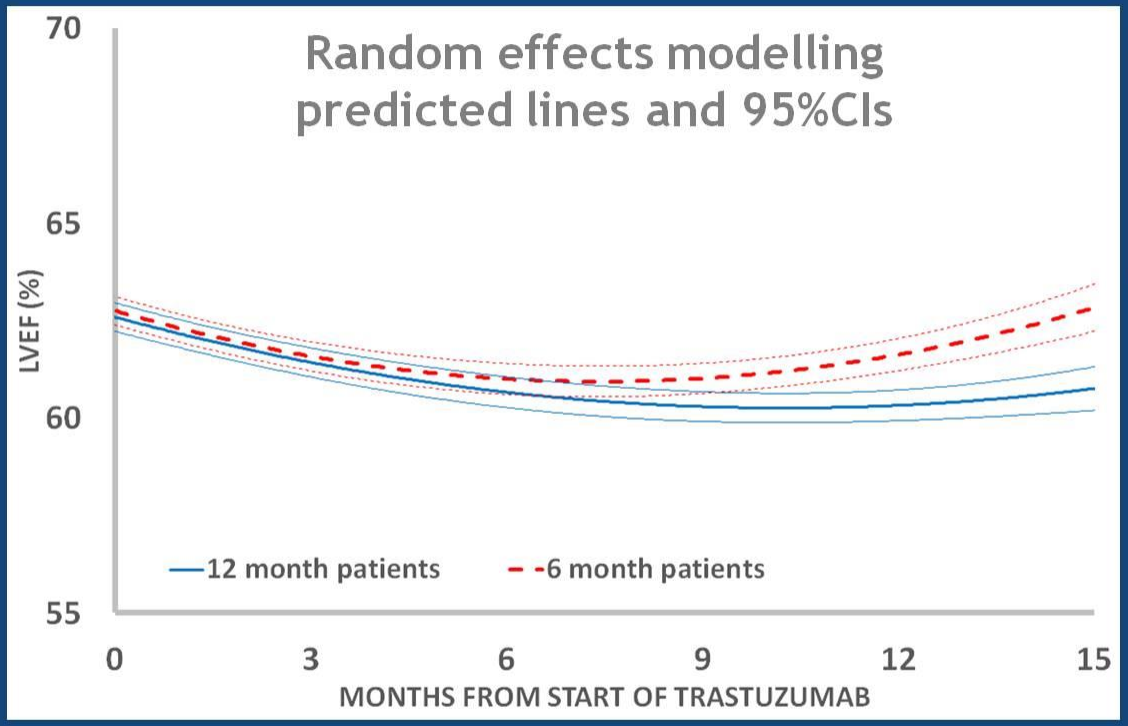
DFS:

Pre-defined subgroup analysis



https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/persephone

Cardiotoxicity



Stopped trastuzumab because of cardiotoxicity
- in **8%** of 12-month patients
- in **4%** of 6-month patients
(p<0.0001)

- Cardiac function recovers post-trastuzumab (p<0.0001)
- 6-month patients had a more rapid recovery (p=0.02)

Ref: Earl et al. British Journal of Cancer (2016) 115, 1462–1470

Presented By Helena Earl at 2018 ASCO Annual Meeting

Therapy of breast cancer: Current research questions (1)
(Neo)adjuvant therapy

Luminal disease: Role of CDK4/6 inhibitors in addition to endocrine therapy?

TNBC:

- **How to deal with residual disease following neoadjuvant therapy?**
- **Role of checkpoint inhibitors?**

Therapy of breast cancer: Current research questions (2)
(Neo)adjuvant therapy

BRCA - mutated tumors: Role of PARP/platinums in the (neo)adjuvant setting?

HER-2 disease:

- **De-escalation strategy (No anthracyclines; decrease in trastuzumab duration; role of T-DM1)**
- **Role of checkpoints inhibitors in addition to HER-2 therapy?**
- **How to deal with residual disease following neoadjuvant therapy**

Metastatic breast cancer

Therapy of breast cancer: Current research questions (1)
Metastatic setting

Luminal disease: Role of SERDs, PI3K inhibitors and checkpoint inhibitors? Role of antibody drugs conjugate? Best sequential strategy?

TNBC:

- **Role of checkpoint inhibitors?**
- **Role of antibody drugs conjugate?**

Therapy of breast cancer: Current research questions (2)
Metastatic setting

BRCA mutated: Position of PAR inhibitors / platinum compounds / Lurbinectidine / Checkpoint inhibitors? Role of combinations?

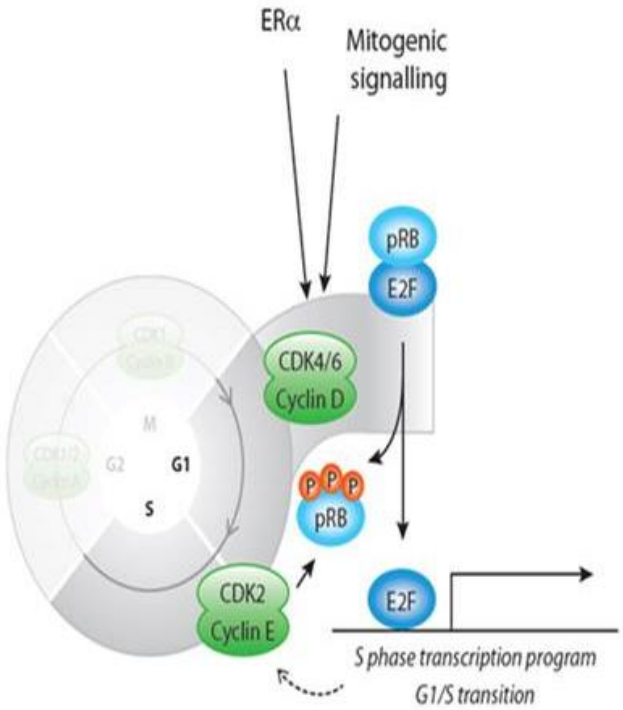
HER-2 disease:

- **Role of antibody drugs conjugate (including for low HER-2 expressors) and checkpoint inhibitors?**

HER+ MBC

CDK4/6 in Breast Cancer

- The growth of HR+ breast cancer is dependent on cyclin D1, a direct transcriptional target of ER.
- Cyclin D1 activates CDK 4/6 resulting in G1-S phase transition and entry into the cell cycle.[1]



1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

Use of CDK4/6 inhibitors in early setting (Δ~10 months) or later lines (Δ~5 months) significantly and consistently improved PFS and ORR

	PALOMA-2[1]	MONALEESA-2[2]	MONARCH-3[3]	MONALEESA-7[4]	PALOMA-3[5]	MONARCH-2[6]	MONALEESA-3[7]
Study design	Phase III Placebo-controlled **1st-line** (n=666)	Phase III Placebo-controlled **1st-line** (n=668)	Phase III Placebo-controlled **1st-line** (n=493)	Phase III Placebo-controlled **1st-line** (n=672)	Phase III Placebo-controlled **≥2nd-line** (n=521)	Phase III Placebo-controlled **2nd-line** (n=672)	Phase III Placebo-controlled **1st or 2d line** (n=726)
Prior therapy	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior ET up to 1 CT **for ABC**	Prior ET up to 1 chemo **for ABC**	**No more than one ET No prior chemo for ABC**	**≤ 1 line of ET for ABC**
Endocrine therapy	Letrozole	Letrozole	NSAI	Tamoxifen NSAI/LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
HR PFS	**0.56**	**0.57**	**0.55**	**0.55**	**0.50**	**0.55**	**0.59**
Median PFS (mo)	27.6 vs 14.5	25.3 vs 16.0	NR vs 14.7	23.8 vs 13.0	11.2 vs 4.6	16.4 vs 9.3	20.5 vs 12.8
ESMO-MCBS	3	3	2	3	4	3 or 2	-

Cross-trial comparisons need to be taken with caution due to differences in trial design

ABC, Advanced Breast Cancer; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; LHRHa, luteinising hormone-releasing hormone agonist; NR, not reached; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival.

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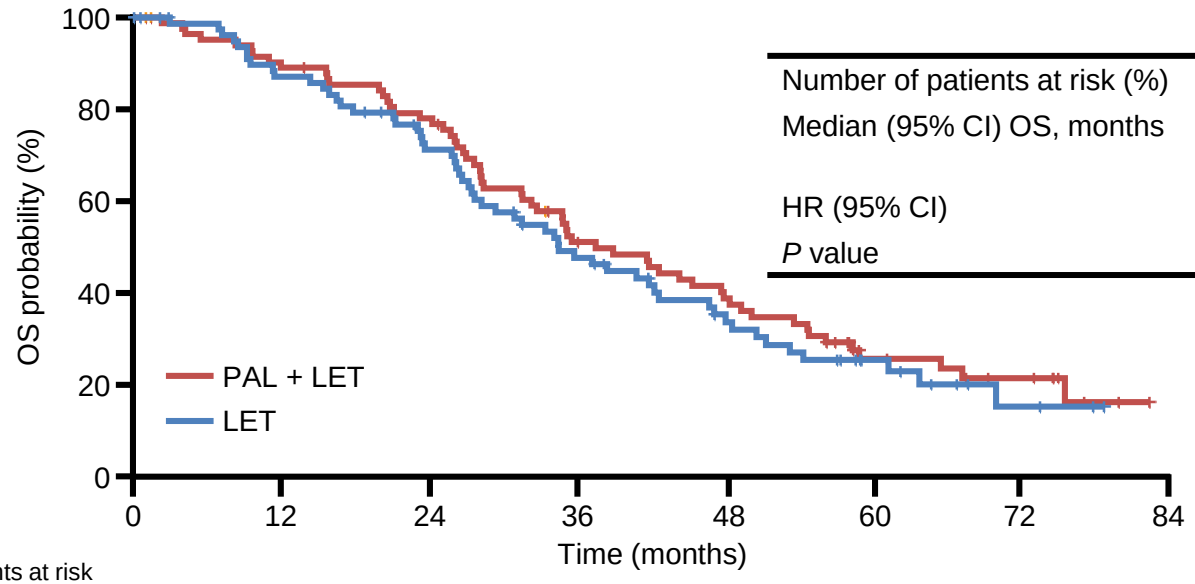
1. Rugo HS, et al. Presented at SABCS 2017; Abstract P5-21-03; 2. Hortobagyi G, et al. Presented at ASCO 2017. Abstract 1038; 3. Goetz MP, et al. *J Clin Oncol.* 2017;35:3638–3646; 4. Tripathy D, et al. Presented at SABCS 2017. Abstract GS2-05; 5. Turner NC, et al. Presented at SABCS 2016. Abstract P4-22-06; 6. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875–2884; 7. Slamon DJ, ASCO 2018

Does the use of first-line CDK4/6 inhibitor impact OS?

No statistically significant improvement in OS in PALOMA-1, but there is a trend



Number of patients at risk

PAL + LET	84	73	63	38	28	13	8	–
LET	81	67	52	33	21	10	3	–

	PAL + LET (n=84)	LET (n=81)
Number of patients at risk (%)	60 (71)	56 (69)
Median (95% CI) OS, months	37.5 (31.4–47.8)	34.5 (27.4–42.6)
HR (95% CI)	0.897 (0.623–1.294)	
P value	0.281	

Phase II
Small sample size
UNDERPOWERED

CI, confidence interval; LET, letrozole; OS, overall survival; PAL, palbociclib.

Finn RS, et al. Presented at ASCO 2017. Abstract 1001.

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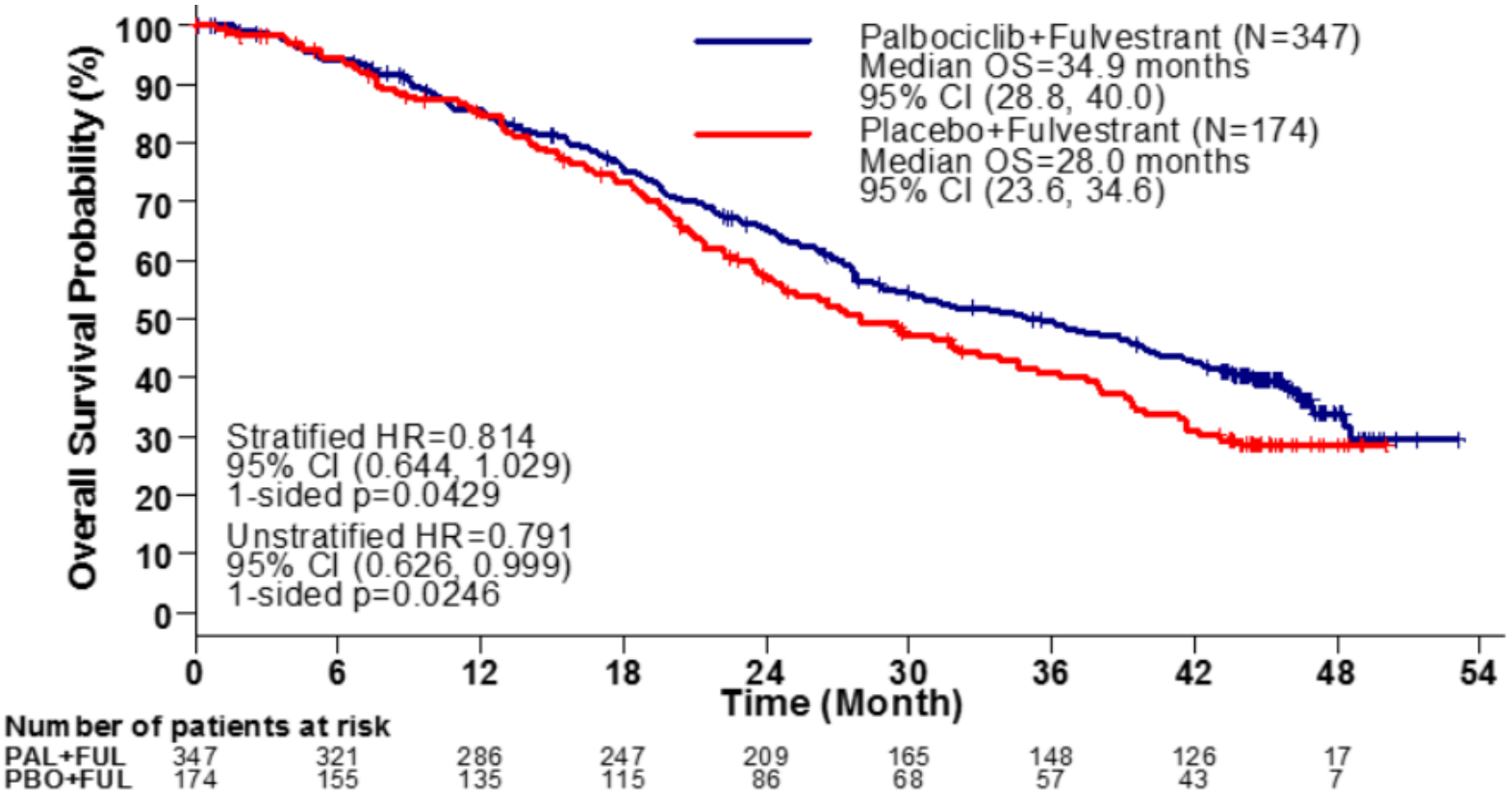
Overall Survival (ITT) in PALOMA3 Trial



- Absolute improvement in median OS in the palbociclib arm vs the placebo arm was 6.9 months.

MUNICH 2018 ESMO congress

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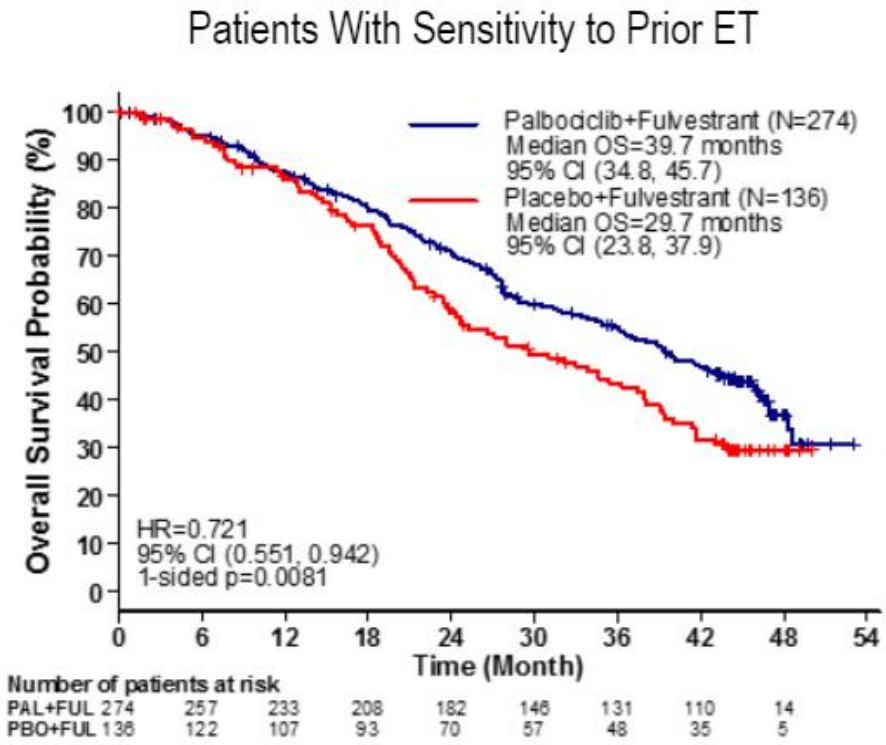
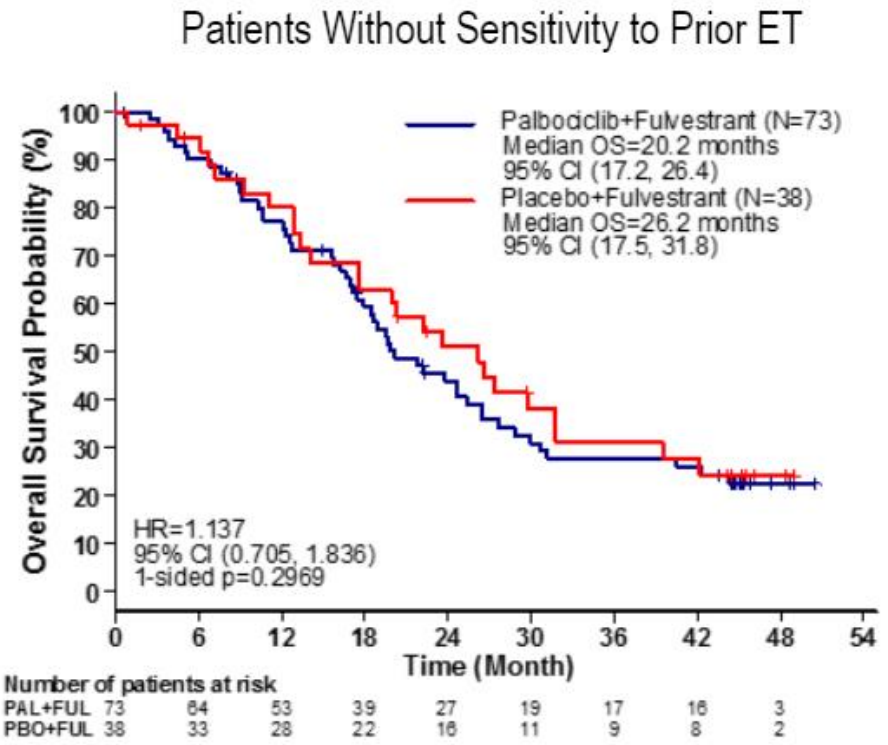
PALOMA3 Trial: Overall Survival by Sensitivity to Prior ET





- In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months.

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Disease and patients characteristics leading to no CDK4/6 inhibitors

- “Very” old and unfit patients
- Risk of no compliance during therapy
- Severe co-morbidities
- Risk of significant drugs interaction

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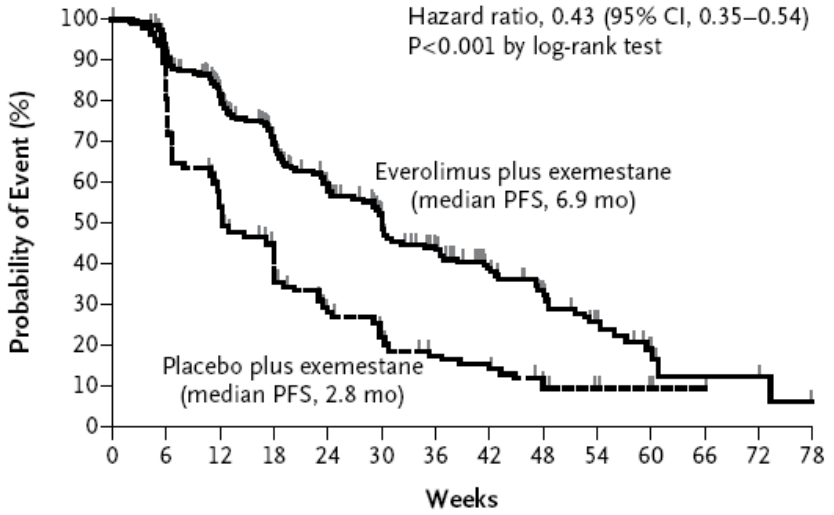
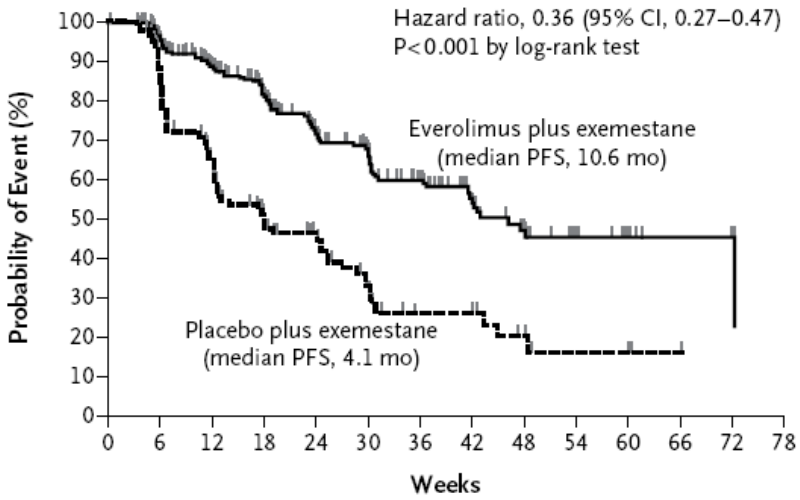
BOLERO-2 Phase III Study: Significant PFS Improvement But No Statistically Significant Difference on Survival

Local assessment



No. at Risk														
Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

Central assessment



No. at Risk														
Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

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Baselga J, et al. N Engl J Med. 2012;366:520-529.

Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) *v* FULV in patients (pts) with estrogen receptor (ER)-positive, *PIK3CA*-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER

José Baselga,[1] Susan Dent,[2] Javier Cortés,[3] Young-Hyuck Im,[4] Véronique Diéras,[5] Nadia Harbeck,[6] Ian E. Krop,[7] Sunil Verma,[8] Timothy R. Wilson,[9] Huan Jin,[9] Lijia Wang,[9] Frauke Schimmoller,[9] Jerry Y. Hsu,[9] Jing He,[9] Michelino De Laurentiis,[10] Pamela Drullinsky,[1] William Jacot[11]

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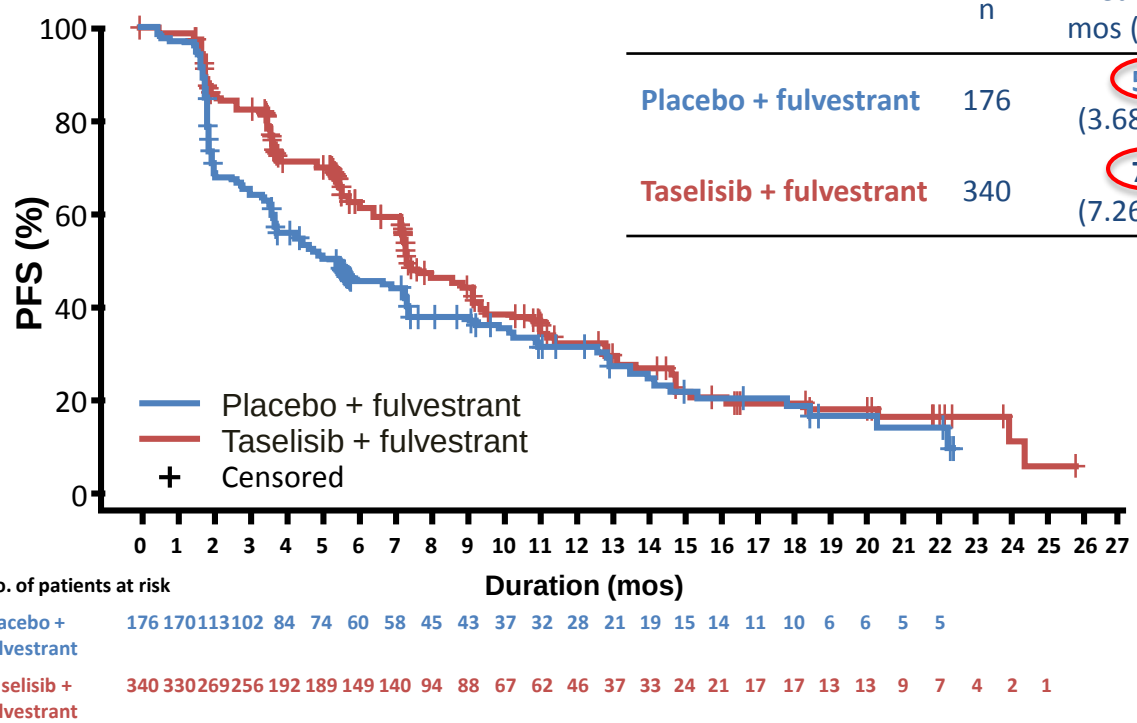
PRIMARY ENDPOINT:
INV-PFS in patients with PIK3CA-*mutant tumors*



	n	Median PFS, mos (95% CI)	Stratified HR (95% CI)	p-value (stratified log rank)
Placebo + fulvestrant	176	5.4 (3.68, 7.29)		
Taselisib + fulvestrant	340	7.4 (7.26, 9.07)	0.70 (0.56, 0.89)	0.0037

	Placebo + fulvestrant	Taselisib + fulvestrant
Events	67.6%	57.1%

- **PFS was defined as the time from randomization to first disease progression as determined by investigator using RECIST v1.1, or death from any cause.**
- **RECIST, Response Evaluation Criteria In Solid Tumors.**

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ALPELISIB + FULVESTRANT FOR HR+, HER2– ADVANCED BREAST CANCER: RESULTS OF THE PHASE III SOLAR-1 TRIAL

Fabrice André,[1] Eva Maria Ciruelos,[2] Gabor Rubovszky,[3] Mario Campone,[4] Sibylle Loibl,[5] Hope S Rugo,[6] Hiroji Iwata,[7] Pierfranco Conte,[8] Ingrid A Mayer,[9] Bella Kaufman,[10] Toshinari Yamashita,[11] Yen-Shen Lu,[12] Kenichi Inoue,[13] Masato Takahashi,[14] Zsuzsanna Pápai,[15] Anne-Sophie Longin,[16] David Mills,[17] Celine Wilke,[17] Samit Hirawat,[18] Dejan Juric[19]

ESMO 2018

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SOLAR-1 Trial

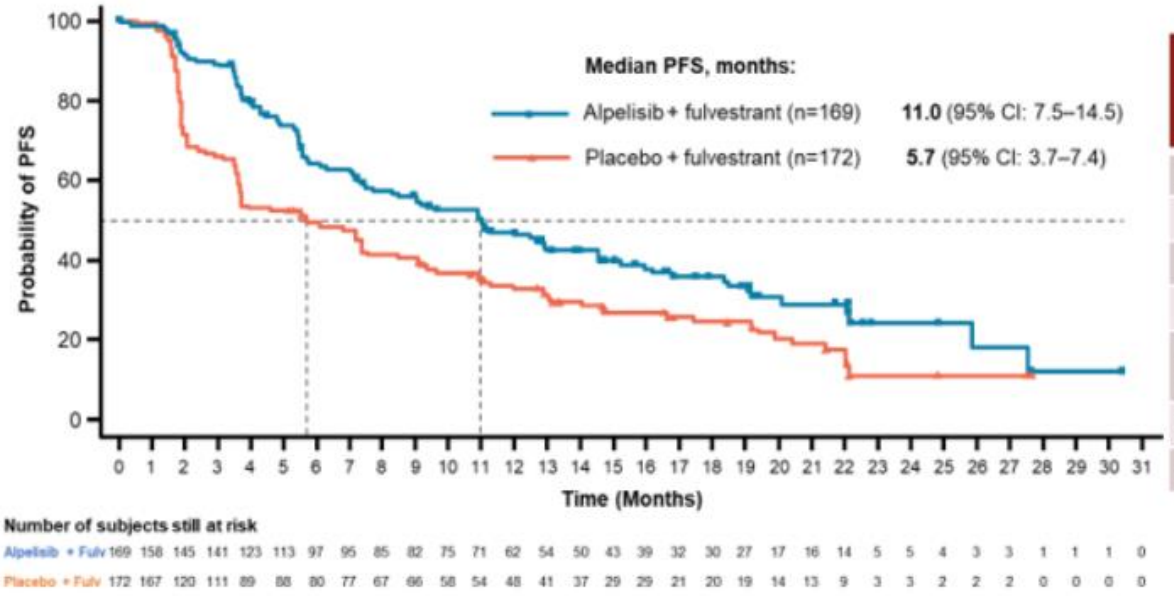
Baseline characteristics

Characteristic*	*PIK3CA*-mutant		*PIK3CA*-non-mutant	
	Alpelisib + fulvestrant (N=169)†	Placebo + fulvestrant (N=172)‡	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Median age, years (range)	63 (25–87)	64 (38–92)	62 (39–82)	63 (32–88)
Race				
Caucasian	117 (69.2)	109 (63.4)	82 (71.3)	69 (59.5)
Asian	34 (20.1)	40 (23.3)	25 (21.7)	26 (22.4)
Other/unknown	18 (10.7)	23 (13.4)	8 (7.0)	21 (18.1)
Metastatic sites				
Visceral disease	93 (55.0)	100 (58.1)	66 (57.4)	74 (63.8)
Lung/liver metastases	84 (49.7)	86 (50.0)	56 (48.7)	56 (48.3)
Bone-only disease	42 (24.9)	35 (20.3)	26 (22.6)	23 (19.8)
Line of advanced anti-cancer treatment				
First line	88 (52.1)	89 (51.7)	71 (61.7)	62 (53.4)
Second line	79 (46.7)	82 (47.7)	42 (36.5)	53 (45.7)
Endocrine resistance status§				
Primary resistance	23 (13.6)	22 (12.8)	31 (27.0)	26 (22.4)
Secondary resistance	120 (71.0)	127 (73.8)	66 (57.4)	65 (56.0)
Sensitive	20 (11.8)	19 (11.0)	16 (13.9)	20 (17.2)
Prior chemotherapy				
Neo-adjuvant	25 (14.8)	29 (16.9)	20 (17.4)	23 (19.8)
Adjuvant	78 (46.2)	86 (50.0)	64 (55.7)	58 (50.0)
Prior CDK4/6 inhibitor treatment	9 (5.3)	11 (6.4)	7 (6.1)	8 (6.9)

*Characteristics are given as n (%) unless otherwise stated;
†One man was enrolled in the alpelisib group in the *PIK3CA*-mutant cohort. All other study participants were postmenopausal women;
‡1 patient in the *PIK3CA*-mutant cohort randomized to placebo was not treated. §Primary and secondary resistance as per ESMO definition;
1. Cardoso F, et al. *Ann Oncol* 2018;29:1634–57.

SOLAR-1 Trial

Primary endpoint: Locally assessed PFS in the *PIK3CA*-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

- The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

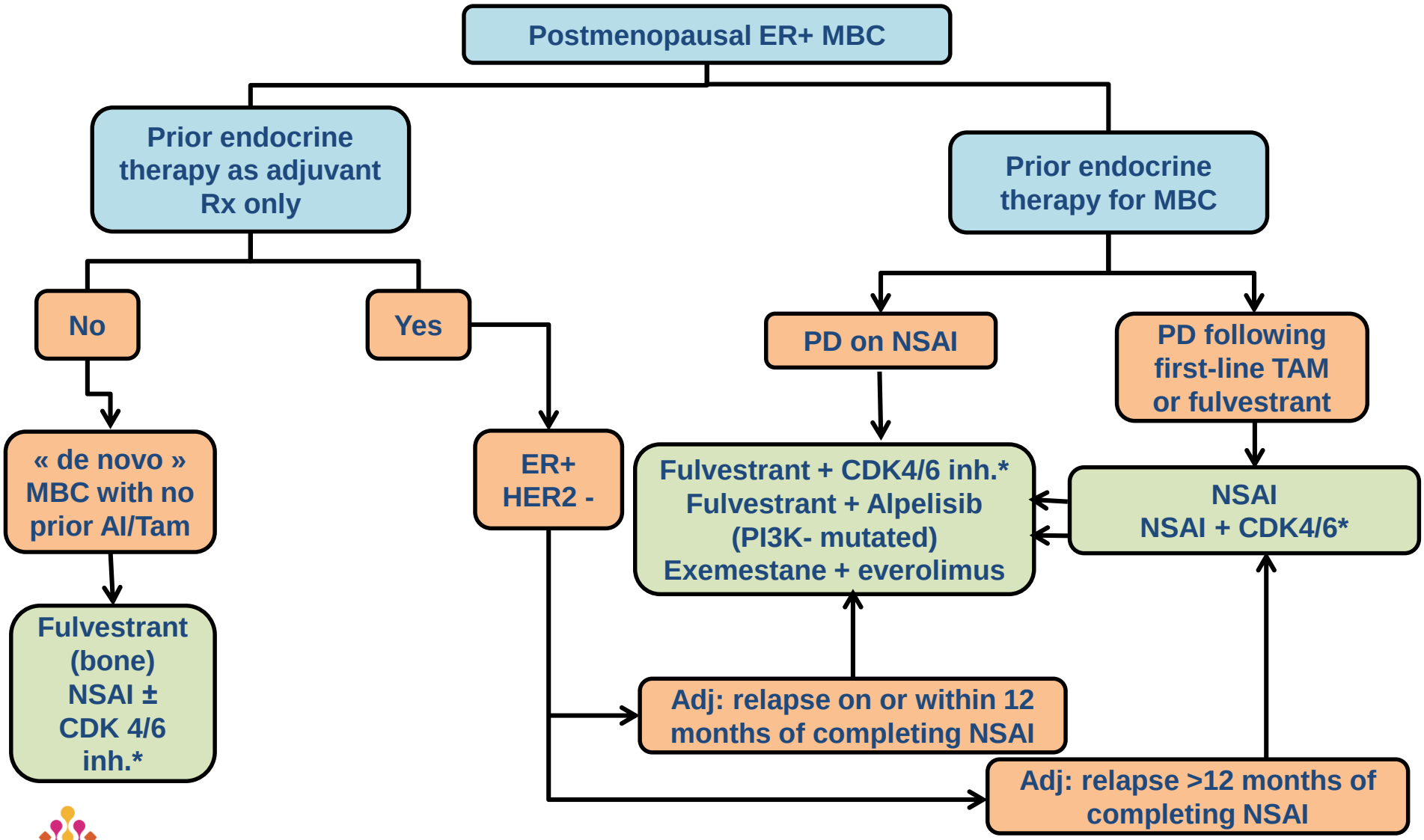
Adverse events in the total population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

Proposed Therapeutic Algorithm for Luminal Subtype in 2018



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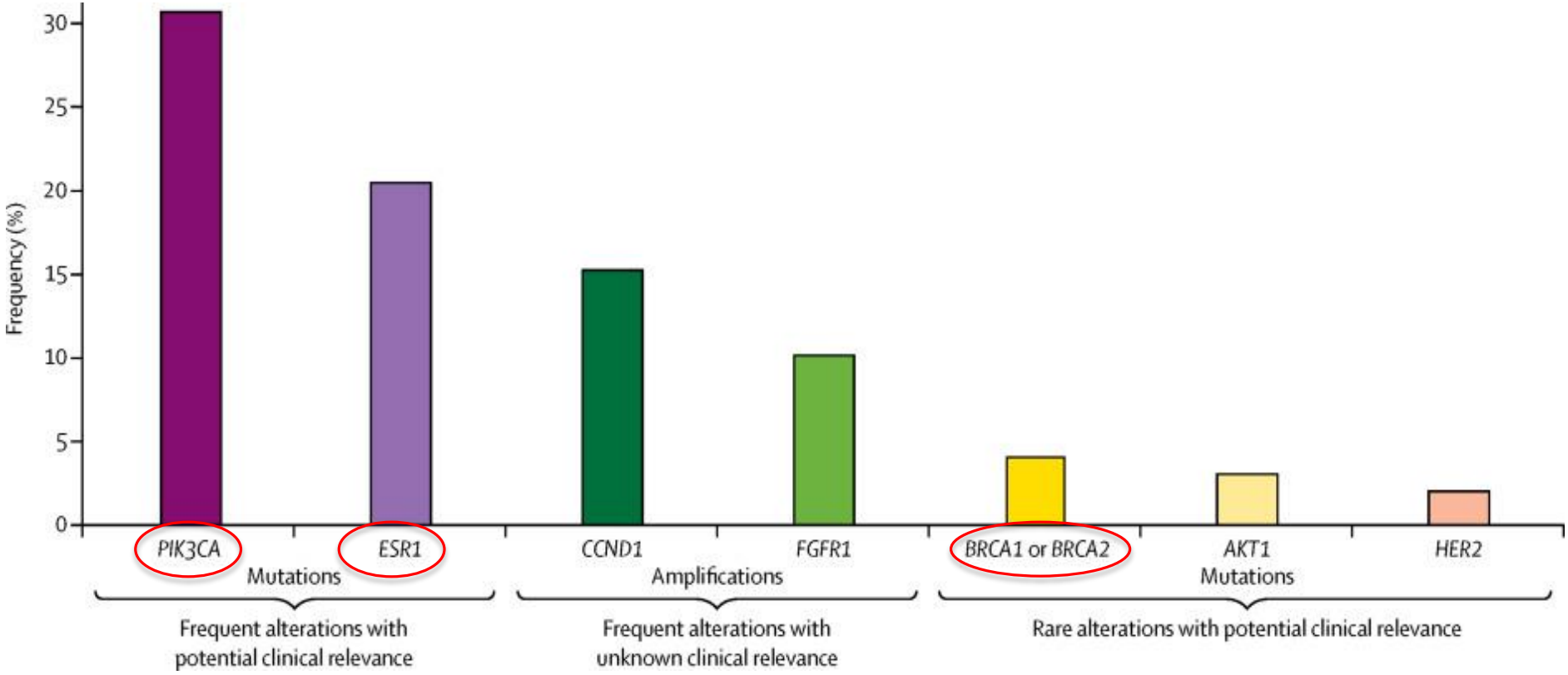
*Inclusion of CDK4/6 inhibitors is based on the results of phase 3 trials (PALOMA-2, MONALEESA-2, MONALEESA-7, MONARCH-3, PALOMA-3, MONARCH-2, MONALEESA-3)

Ahmad Awada, personal communication

Perspectives Targetable Genomic Alterations under Clinical Investigation or with Potential Clinical Relevance in Metastatic ER+ HER2- Breast Cancer



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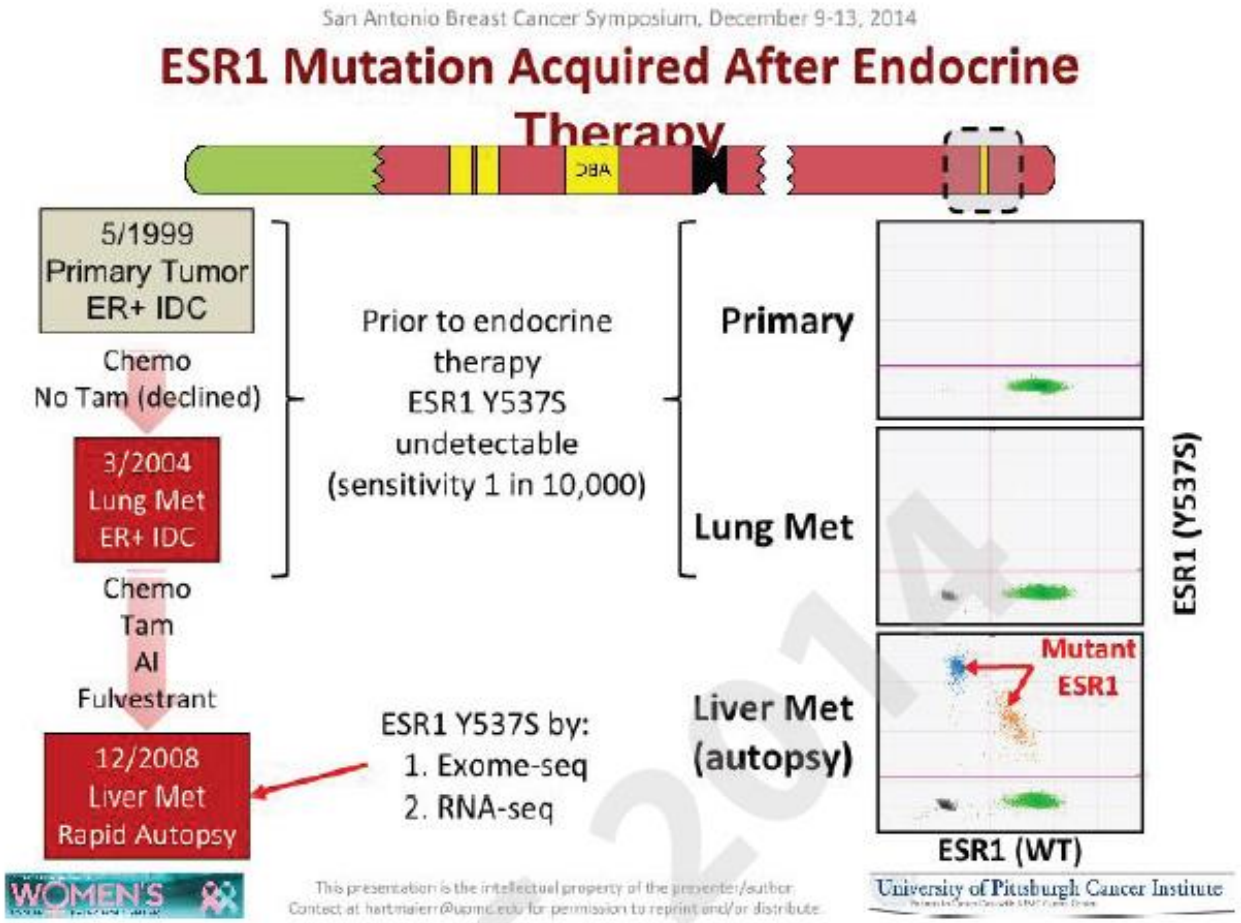
Turner NC, et al. Lancet 2017; 389:2403-2414

ESR1 Y537S Mutation is Undetectable in Primary and Metastatic Disease before Endocrine Therapy



SABCS 2017 - Luminal Advanced Breast Cancers

New oral SERD ; GDC – 0927 : phase I completed

- Escalation : 600 → 1400 mg daily
- Encouraging activity in heavily pretreated patients at 1400 mg : CBR 36%, obj RR 13%
- Robust PD engagement (FES-PET)
- Well tolerated (GI toxicity, grade 1-2)

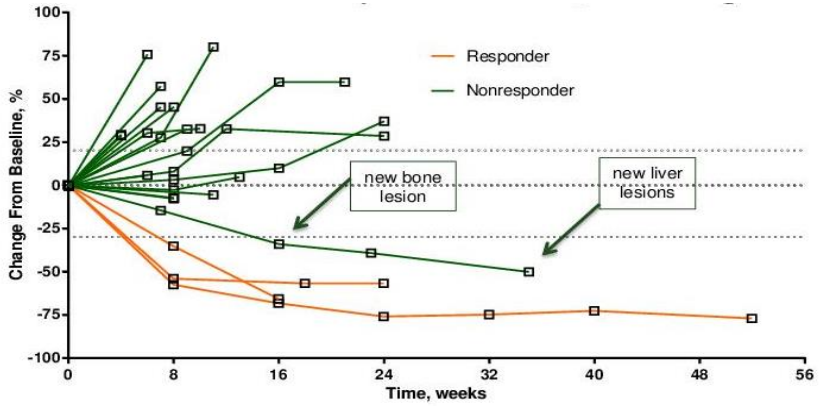
M. Dickler et al, PD5-10 (poster)

KEYNOTE-028 : Pembrolizumab in HR+/HER2- Breast Cancer

- **Anti-tumour activity (RECIST 1.1)**

	n (%)	95% CI
Overall response rate	3 (12.0)	2.5 – 31.2
Complete response	0 (0.0)	0.0 – 13.7
Partial response	3 (12.0)	2.5 – 31.2
Stable disease	4 (16.0)	4.5 – 36.1
Clinical benefit	5 (20.0)	6.8 – 40.7
Progressive disease	15 (60.0)	38.7 – 78.9
NE	3 (12.0)	2.5 – 31.2

Responses are uncommon but appear to be durable!



Pembrolizumab is an investigational agent in this setting
NE, not evaluable

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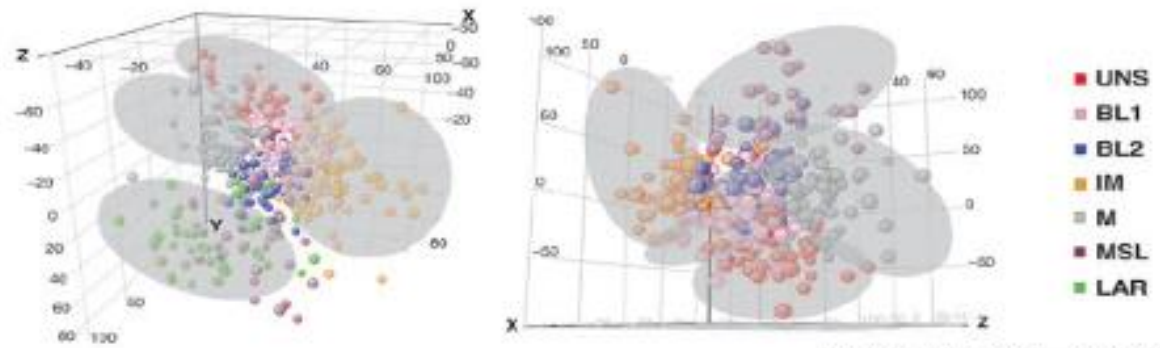
Rugo HS et al., SABCS 2016, S5-07

Heterogeneity of TNBC: An Opportunity for New Targeted Agents?!

Heterogeneity of TNBC



Lehmann et al. JCI 2011

- Genomic instability common
- Multiple subsets with varying targets
  - Basal-like 1 and 2 – DNA damage response genes
  - Immunomodulatory
  - Mesenchymal and mesenchymal / stem cell – PI3K/mTOR pathway
  - LAR – androgen receptor signaling

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Selected anticancer agents (cytotoxics, biologicals) studied in TNBC

CYTOTOXICS

- Anthracyclines and taxanes
- Platinum compounds
- Antimetabolites (e.g., capecitabine, …)
- Eribulin
- Antibody drugs conjugates

BIOLOGICALS

- PARP inhibitors
- Bevacizumab
- Anti-EGFR (e.g., Cetuximab,….)
- Checkpoints inhibitors (e.g., atezolizumab)
- Androgen receptor modulators

IMPASSION 130 TRIAL

IMpassion130: Results from a global, randomised, double-blind, Phase III study of atezolizumab + *nab*-paclitaxel vs placebo + *nab*-paclitaxel in treatment-naive locally advanced or metastatic triple-negative breast cancer

Peter Schmid,[1] Sylvia Adams,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Carlos H. Barrios,[5] Hiroji Iwata,[6] Véronique Diéras,[7] Roberto Hegg,[8] Seock-Ah Im,[9] Gail Shaw Wright,[10] Volkmar Henschel,[11] Luciana Molinero,[12] Stephen Y. Chui,[12] Roel Funke,[12] Amreen Husain,[11] Eric P. Winer,[13] Sherene Loi,[14] Leisha A. Emens[15]

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IMPASSION 130 TRIAL

MUNICH 2018 ESMO congress

IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

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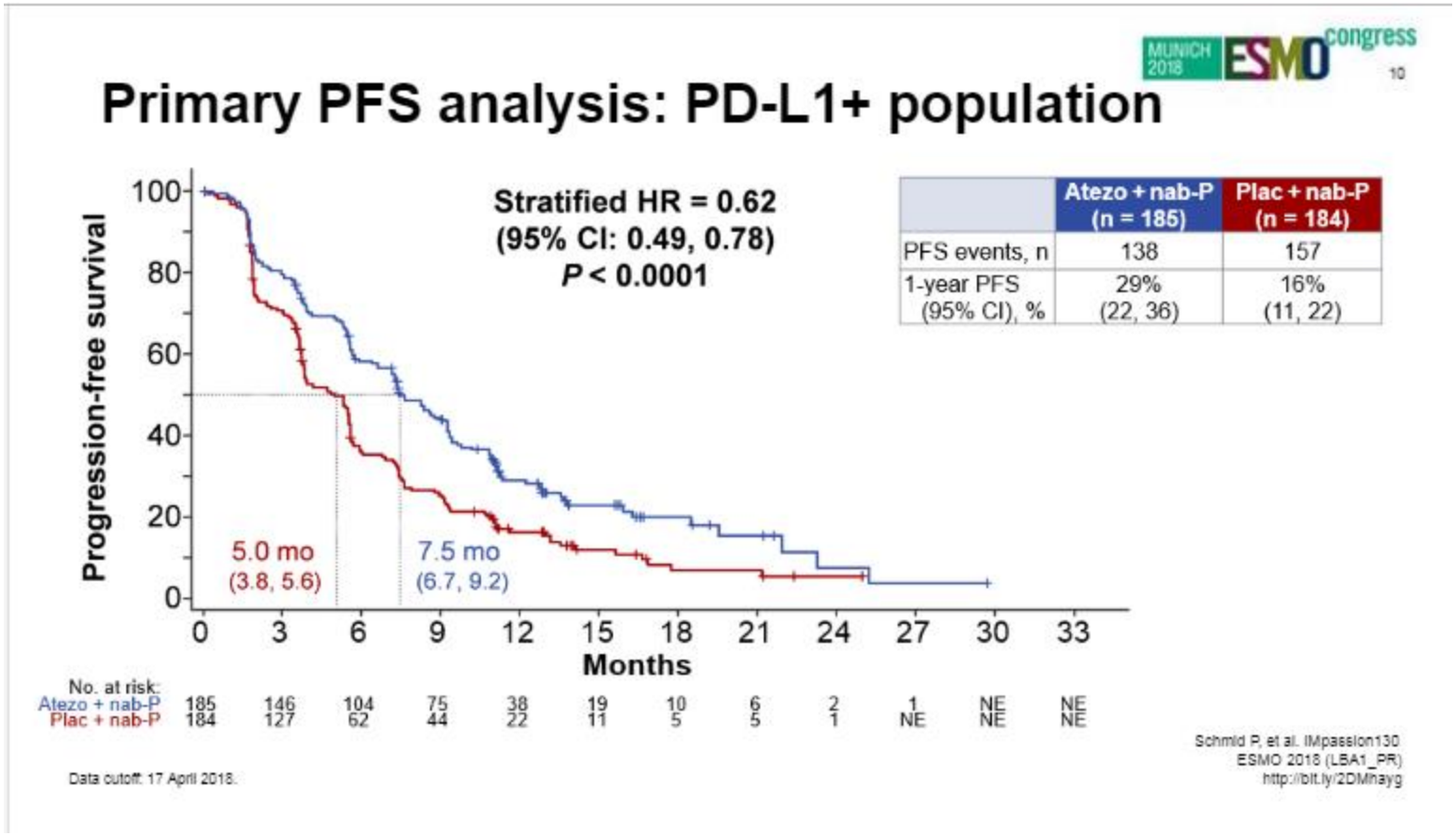
IMPASSION 130 TRIAL



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

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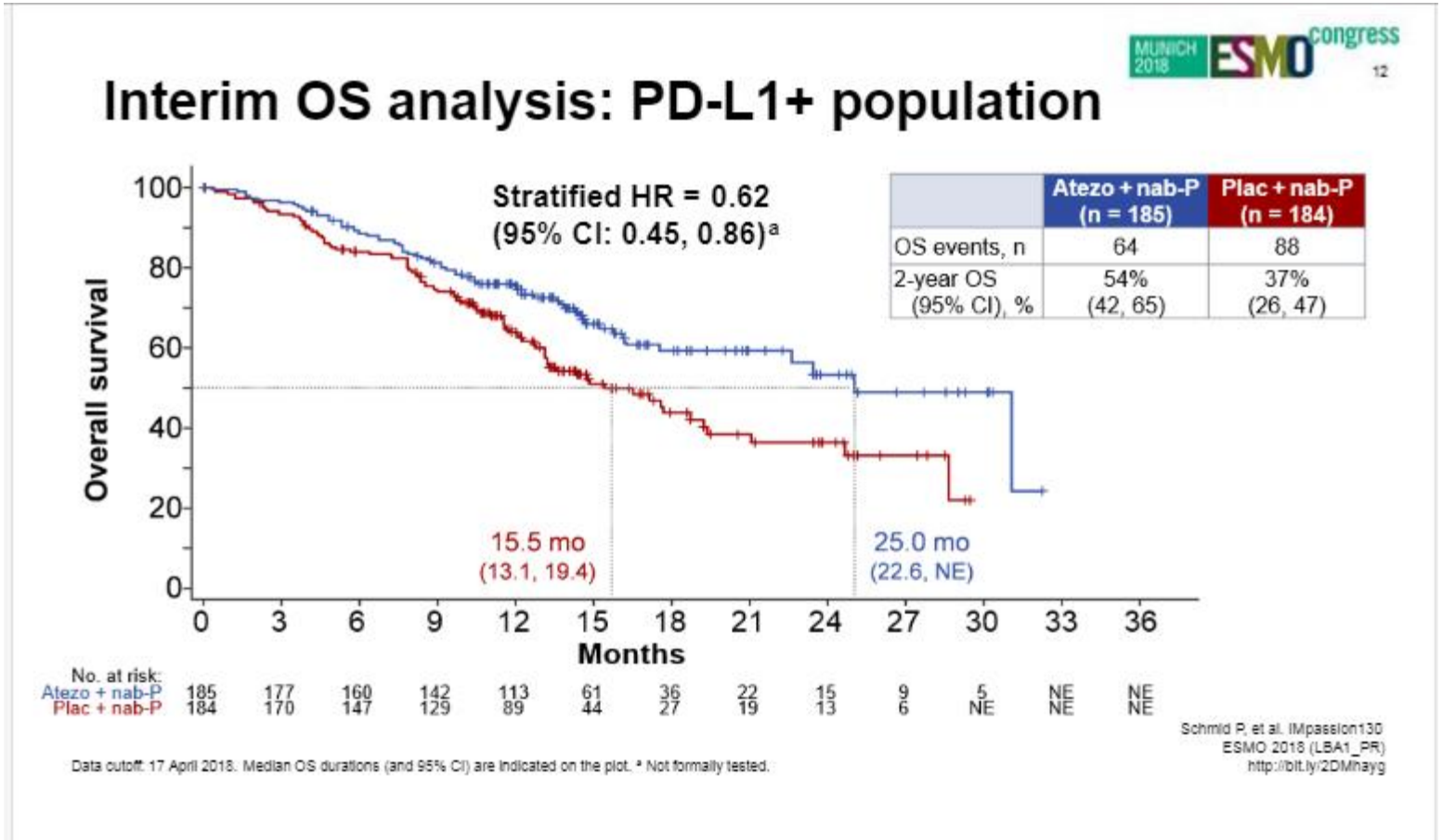
IMPASSION 130 TRIAL



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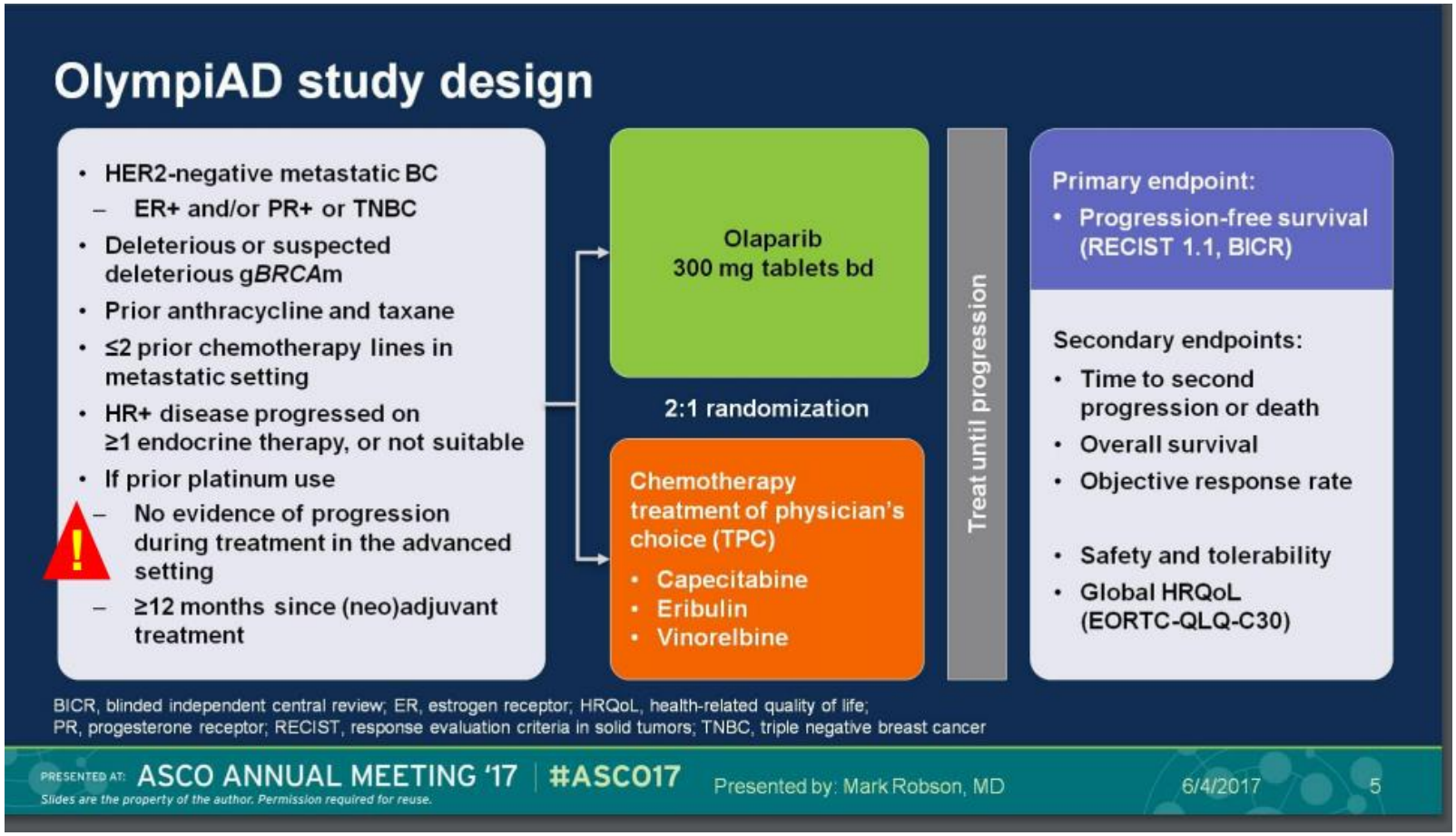
OlympiAD Study in HR+ or TNBC (g*BRCA*m+)



Olaparib is an investigational agent in this setting

Robson ME, et al. ASCO 2017 (Abstract LBA4)

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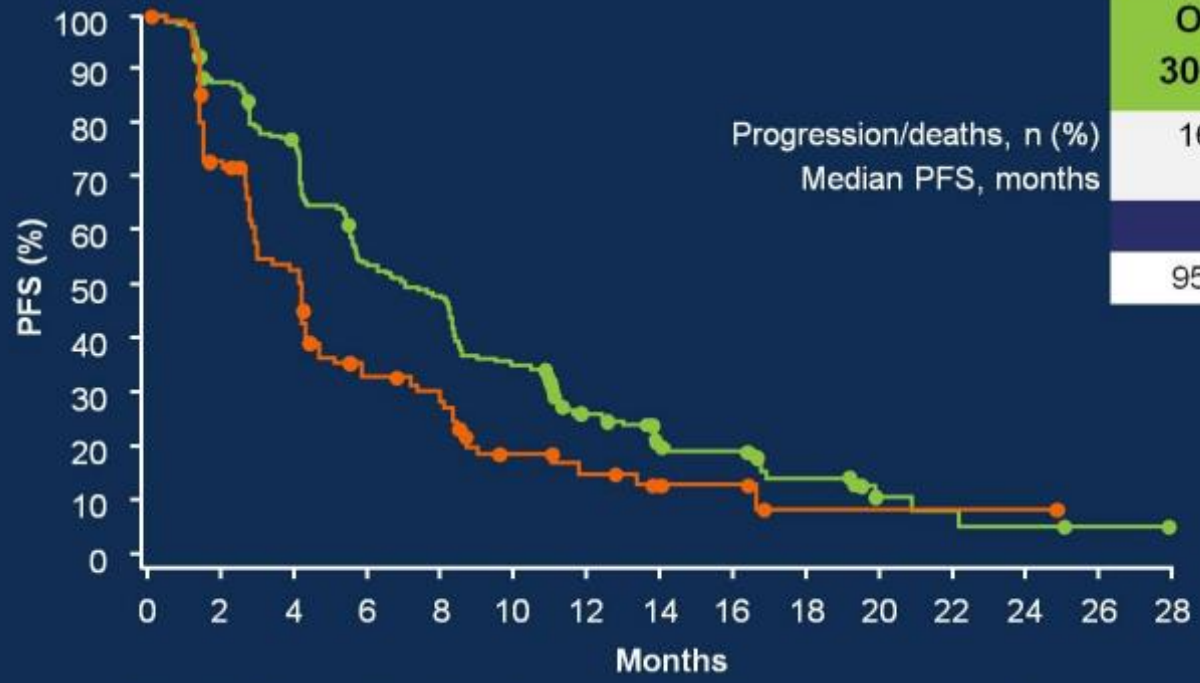
Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

Olaparib is an* investigational *agent in this setting

Robson ME, et al. ASCO 2017 (Abstract LBA4)

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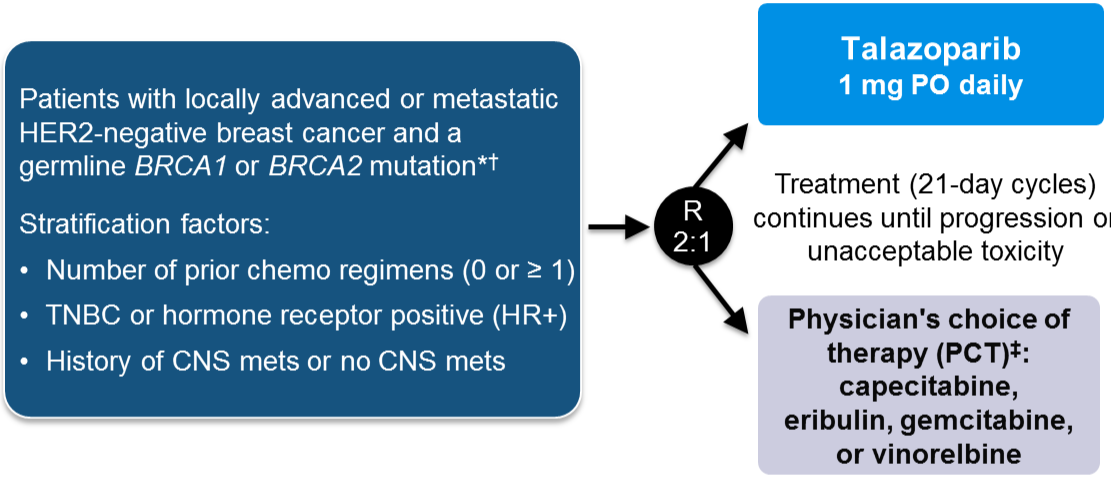
Study Design: EMBRACA



Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

Primary endpoint

- Progression-free survival by RECIST by blinded central review

Key secondary efficacy endpoints

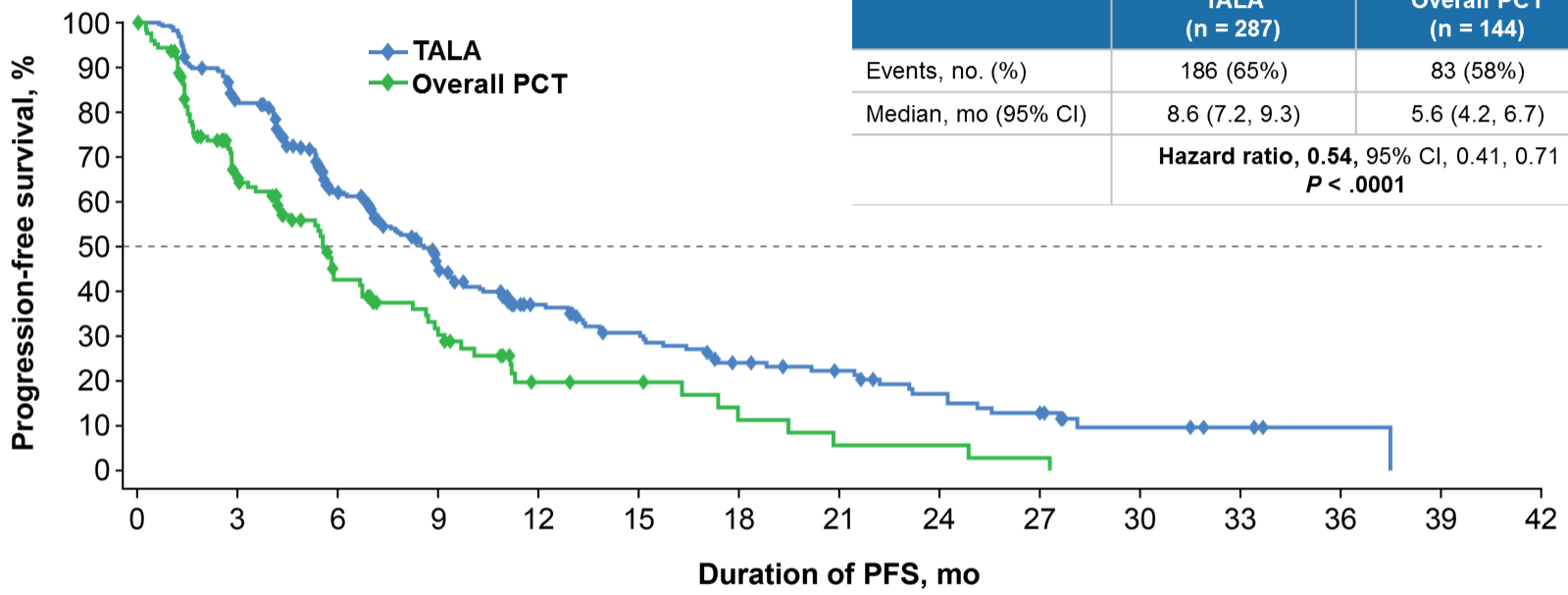
- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.
*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.
www.clinicaltrials.gov (NCT01945775)

Primary Endpoint: PFS by Blinded Central Review



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-line Therapeutic Option for Patients With Relapsed/Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Aditya Bardia,[1] Linda T. Vahdat,[2,†] Jennifer R. Diamond,[3] Kevin Kalinsky,[4] Joyce O'Shaughnessy,[5] Rebecca L. Moroose,[6] Steven J. Isakoff,[1] Sara M. Tolaney,[7] Alessandro D. Santin,[8] Vandana Abramson,[9] Nikita C. Shah,[6] Serengulam V. Govindan,[10] Pius Maliakal,[10] Robert M. Sharkey,[10] William A. Wegener,[10] David M. Goldenberg,[10] Ingrid A. Mayer[9]

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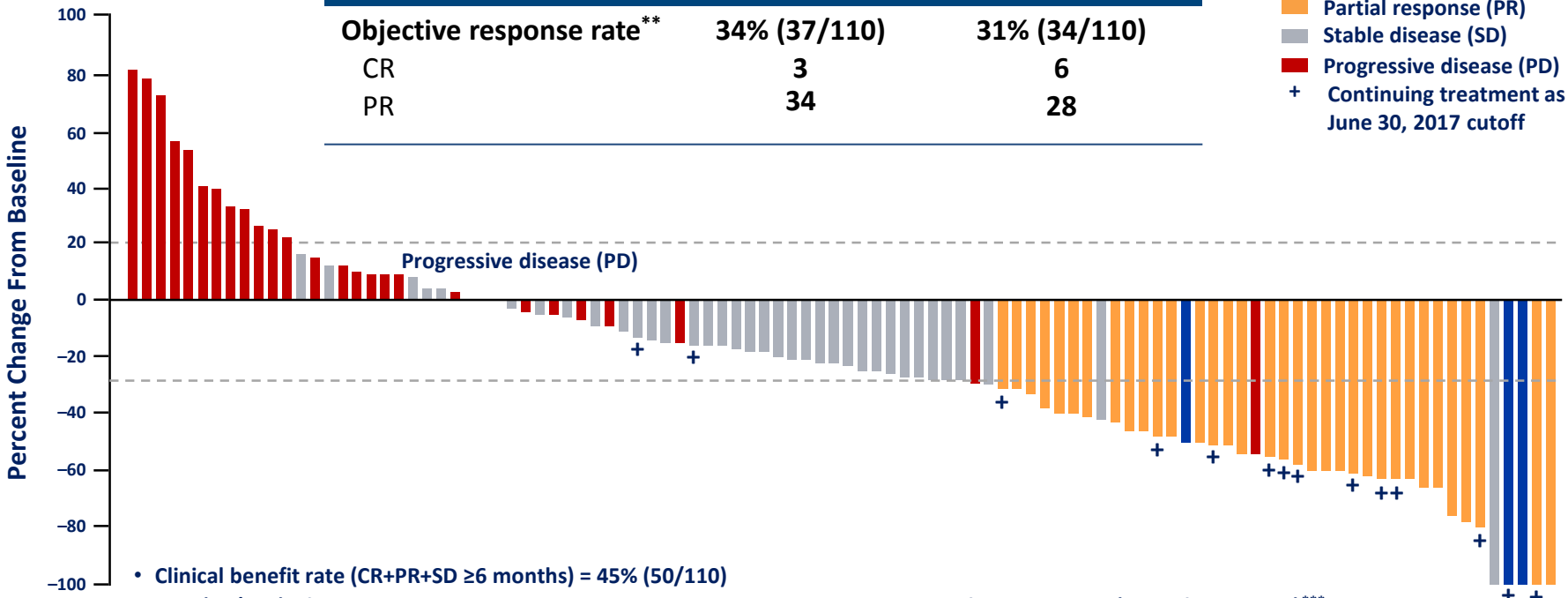
Sacituzumab Govitecan: Tumor Response to Treatment

	Local	BICR*
Objective response rate**	**34% (37/110)**	**31% (34/110)**
CR	**3**	**6**
PR	**34**	**28**



- Clinical benefit rate (CR+PR+SD ≥6 months) = 45% (50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)***
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

*Patients with at least 20% tumor reduction (n = 56) were reviewed; **Confirmed objective response rate per RECIST; ***Waterfall is based on local assessment; BICR = Blinded Independent Adjudicated Central Review.

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HER2-positive breast cancer: The perfect targeted therapy strategy

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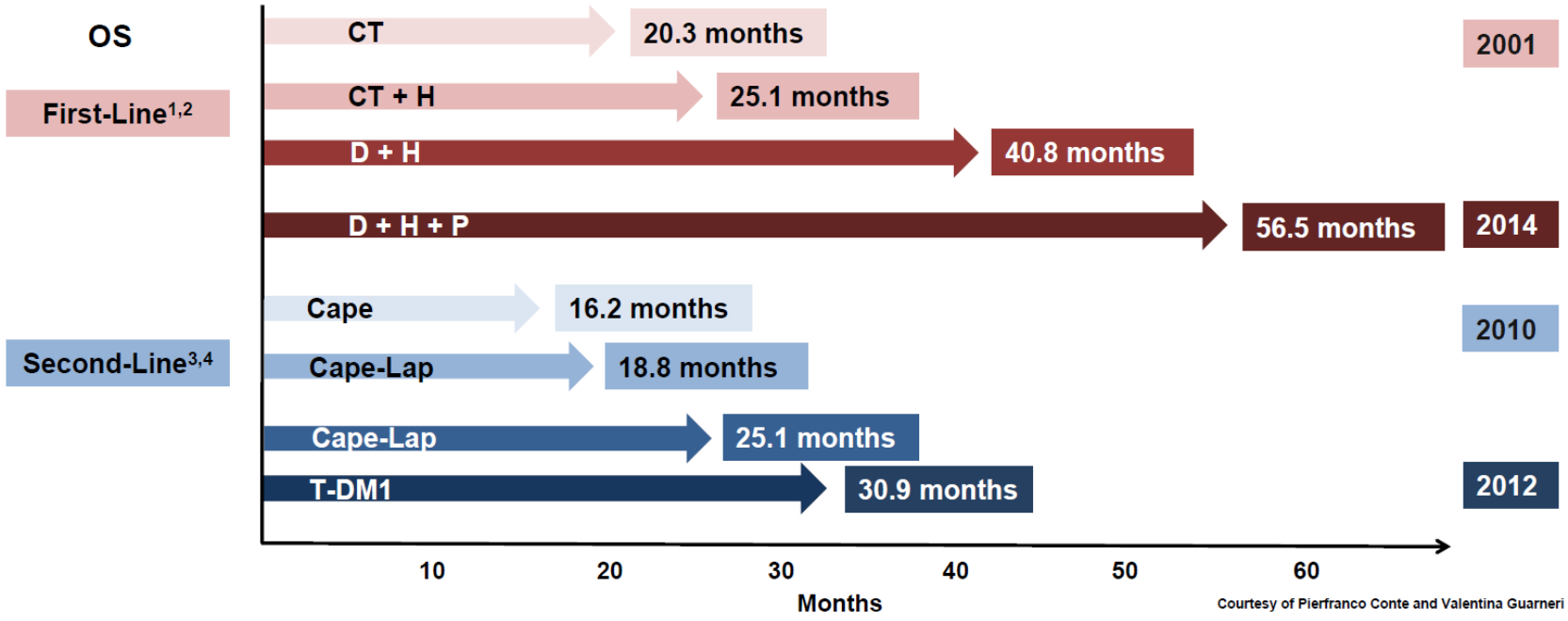
Treatment of HER2-positive MBC
Progress Over Time



Cape, capecitabine; CT, chemotherapy; D, docetaxel; H, trastuzumab; Lap, lapatinib; OS, overall survival; P, pertuzumab; T-DM1, trastuzumab emtansine

1. Slamon D, et al. *N Engl J Med.* 2001;15(1);344:783-792. 2. Swain S, et al. *N Engl J Med.* 2015;372(8):724-734. 3. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 4. Verma S, et al. *N Engl J* Med. 2012;367(19):1783-1791.

Metastatic BC: Elderly patients

OFFICIAL best of SABCS

EORTC 75111 – 10114 Phase II randomized Trial

N=80

HER2+ MBC

≥ 70 Years (or ≥65/≥60y with co-morbidity)

No prior chemo for MBC

≤1 line of antiHER2 + endocrine therapy

Prior endocrine therapy allowed

1:1

Primary endpoint:
PFS rate at 6 months

Pertuzumab + Trastuzumab

Pertuzumab + Trastuzumab + Metronomic Cyclophosphamide

PD →

T-DM1 *(optional)*

Stratification: ER and/or PR pos vs both negative, previous HER2 treatment (none vs adj only vs metastatic), G8< or equal 14 vs G8>14

Metronomic CT (chemotherapy): cyclophosphamide 50 mg/d po continuously
On progression: Option to have T-DM1 *(3.6 mg/kg iv q3w)* till progression

	N (%)
Age (years) – Median (Range)	77 (61 - 91)
WHO PS 2-3	19 (23.8)
ER and/or PgR positive	55 (68.8)
No prior anti-HER2 therapy for MBC	72 (91.1)
Prior adjuvant endocrine therapy	24 (30.4)
Visceral involvement	74 (93.3)
G8 score at baseline G8 ≤ 14	56 (70.9)
Frail (SPPB ≤ 7)	37 (52.9)

PD3-09 Wildiers
Lancet Oncol 2018 in Press

Metastatic BC: Elderly patients

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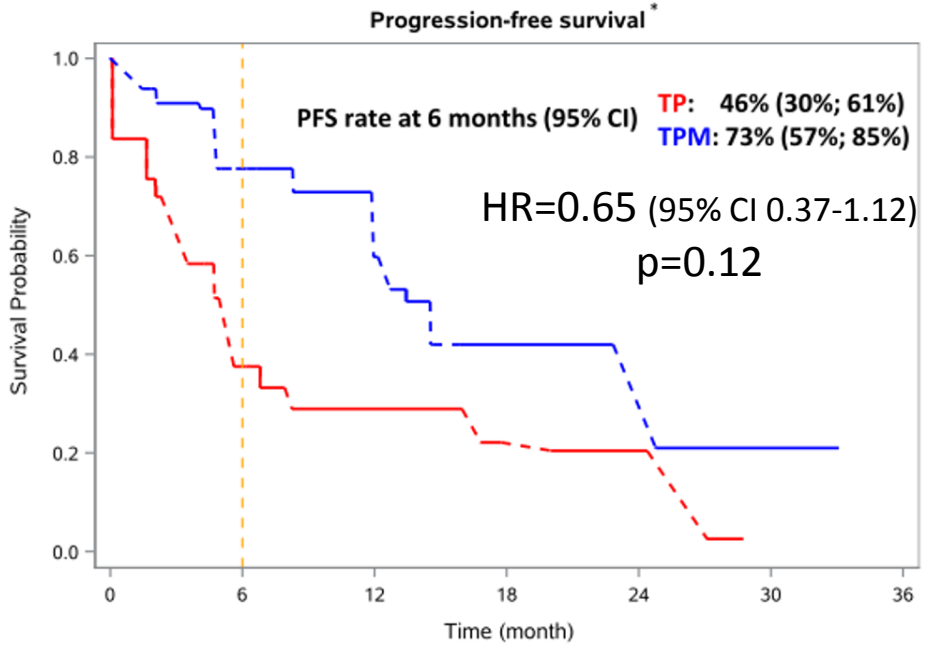
EORTC 75111 – 10114 Phase II randomized Trial



Median PFS was 5.6 months (95% CI 3.6-16.8) versus 12.7 months (95% CI 6.7-24.8)

- 33% grade III-IV lymphopenia for TPM vs 5% for TP, but no febrile neutropenia
- Other toxicities comparable
- No relevant difference in functional evolution between TP and TPM
- 9 (31%) of 29 deaths were not breast cancer related.
- TPM, followed by T-DM1 after progression, may delay or supersede taxane chemotherapy in this population.

TPM is not the new standard, but is a new treatment option

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ULB iris

Metastatic breast cancer: Immune therapy

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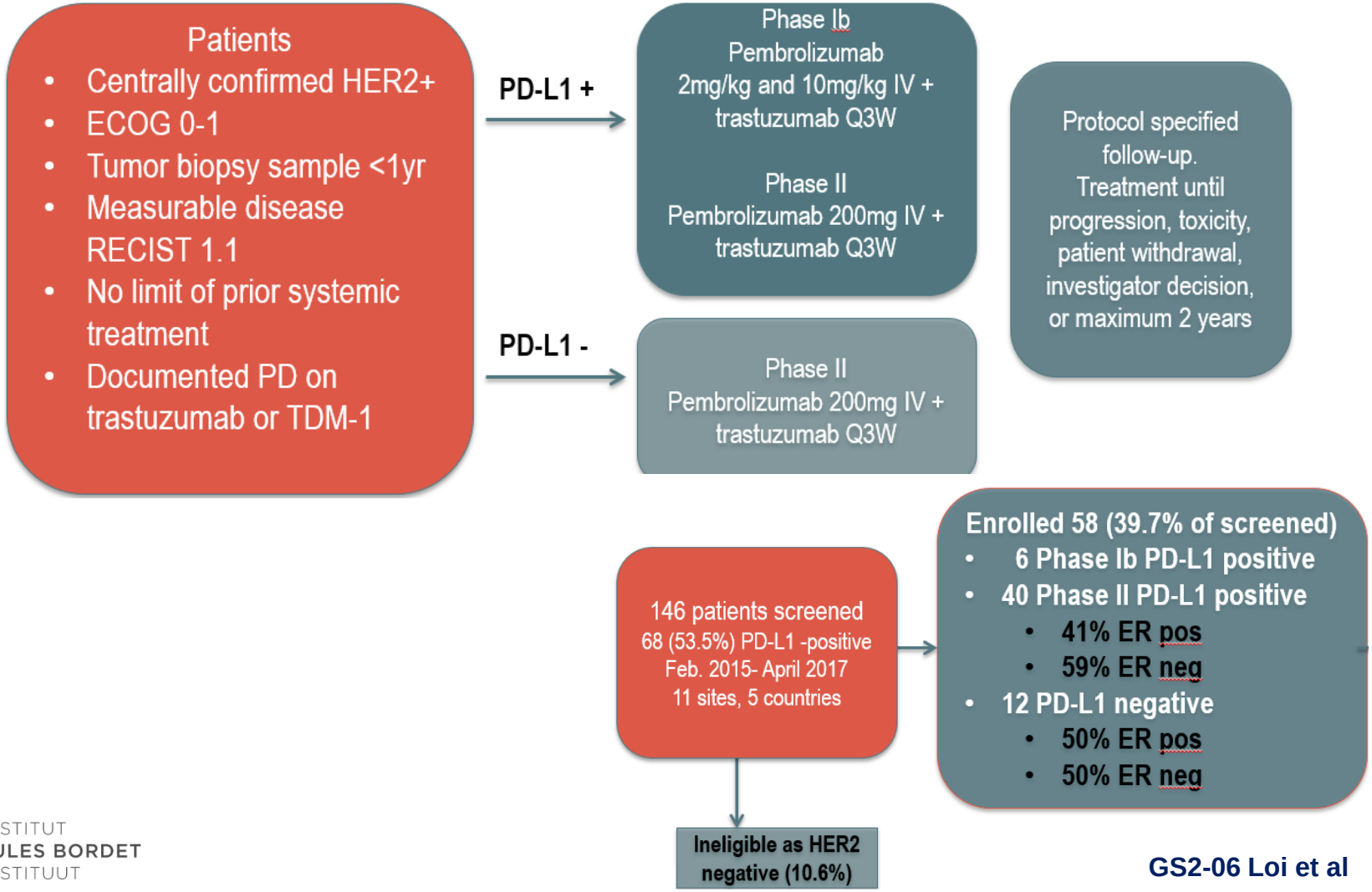
PANACEA IBCSG 45-13/BIG 4-13/KEYNOTE-014



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GS2-06 Loi et al

iris

Metastatic breast cancer: Immune therapy

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- Results
  - PD-L1+ cohort (n=46):
    - ORR: 15,2% (CI 7-27%)
    - No progression at 6 Mo: 24% (CI 14-36%)
    - Median PFS: 2,7 Mo
    - Median duration of disease control: 11,1 Mo
  - PD-L1- cohort (n=12):
    - ORR: 0%
  - Toxicity: 2/58 with grade III/IV pneumonitis, well tolerated
  - Stromal TILs from metastatic biopsy
    - Stromal TILs ≥ 5% present in 41% of PD-L1+ cohort
    - ORR 39% (sTILs+) versus 5% (sTILs-)

Immune therapy is upcoming (for a subset of pts) in HER2+

Metastatic BC: new antibody drug conjugates

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Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2+ metastatic breast cancers

N=130 (76 evaluable)

TABLE 3. Efficacy – Confirmed ORR, DCR, and PFS

Population	ORR, n/N (%)*	DCR, n/N (%)*	PFS (months), median (range)†
HER2-positive			
All	35/57 (61.4)	54/57 (94.7)	10.4 (1.2+, 16.8+)
HR-positive	22/39 (56.4)	36/39 (92.3)	NR (1.2+, 16.8+)
HR-negative	12/16 (75.0)	16/16 (100.0)	10.4 (1.2+, 14.1+)
Prior pertuzumab-treated	31/50 (62.0)	47/50 (94.0)	10.3 (1.2+, 16.8+)
HER2-low			
All	6/19 (31.6)	16/19 (84.2)	NR (0.5, 12.2+)
HR-positive	5/16 (31.3)	14/16 (87.5)	NR (1.2+, 12.2+)
HR-negative	0/2 (0.0)	1/2 (50.0)	7.6 (0.5, 7.6)

*Analysis set for ORR (CR+PR) and DCR (CR+PR +SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.
†Minimum and maximum of PFS include "+" after value indicates censoring.
CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

- Grade 3 toxicities occurred in <10% of the patients.
- Most frequent grade 3 toxicity was nausea.
- Phase II Open-Label Study of DS-8201a in HER2+ Metastatic Breast Cancer Resistant/Refractory to T-DM1 (DESTINY-Breast01) ongoing (also in Belgium)

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GS2-06 Modi

FDA breakthrough therapy designation

Advanced Breast Cancer Molecular Subtyping with Clinical Implications (1)

PAST

- Hormone receptor positive disease (Luminal A/B)
- HER-2 positive disease
- Triple negative breast cancer
- BRACA – mutated tumors

Advanced Breast Cancer Molecular Subtyping with Clinical Implications (2)

FROM ESMO 2018

- Hormone receptors positive + PI3K WT (60% of HR+)
- Hormone receptors positive + PI3K mutated (40% of HR+)
- Triple negative + PD-L1 ≥ 1 + on immune cells (40% of TNBC)
- Triple negative + PD-L1 negative = quadruple negative (~ 60% of TNBC)
- HER-2 positive disease (± HR+)
- BRACA – mutated tumors

Perspectives and Challenges

Breast cancer Therapy: Perspectives and challenges (1)
(Neo)adjuvant setting

- Gene profiling / NGS on tumor / liquid biopsy
  → More molecular segmentation of breast disease
  → personnalised therapy
- Molecular documentation of residual disease
- Molecular monitoring of early relapse
- Integration of new anticancer agents (mainly based on molecular abnormalities) in the therapeutic algorithms

Many Challenges in clinical research

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Breast cancer Therapy: Perspectives and challenges (2)
Metastatic setting

- Management of molecular versus clinical relapse
- Role of molecular imaging in disease mapping and monitoring
- Management of oligometastatic disease
- NGS on tumor / liquid biopsy → Molecular segmentation
  → personnalised therapy
- Integration of new anticancer agents (mainly based on molecular abnormalities) in the therapeutic algorithms

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Many Challenges in clinical research

THANK YOU

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