I SOTTOGRUPPI FENOTIPICI, LE INDICAZIONI TERAPEUTICHE E I RISULTATI.

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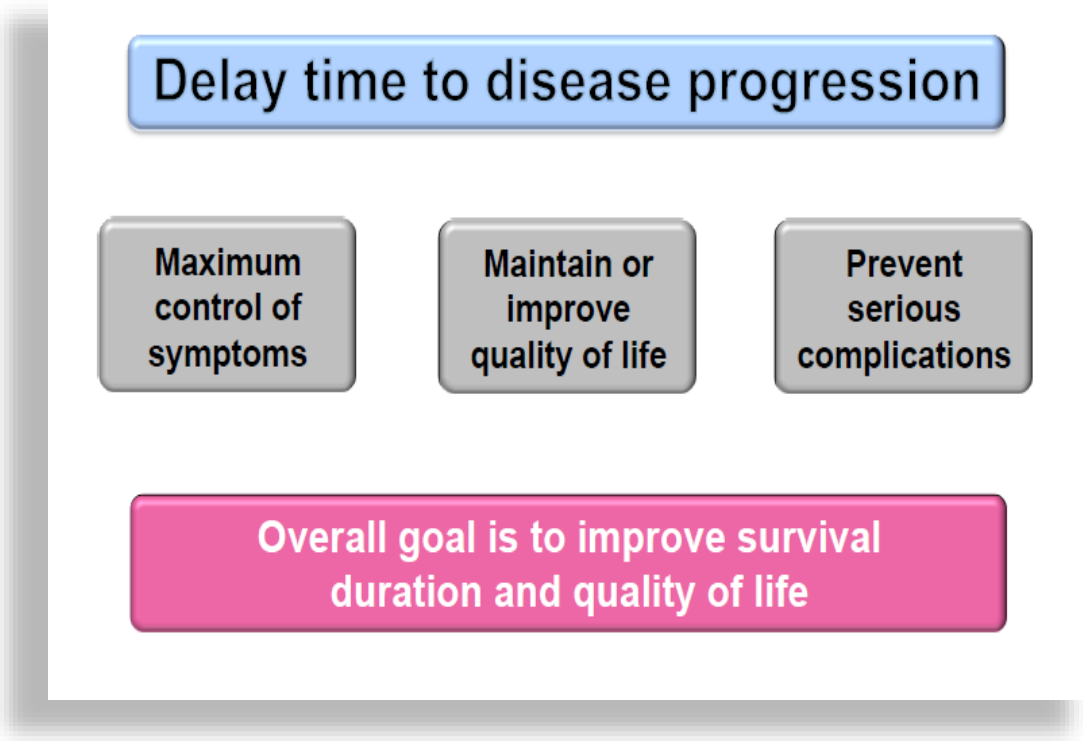
16 aprile 2018

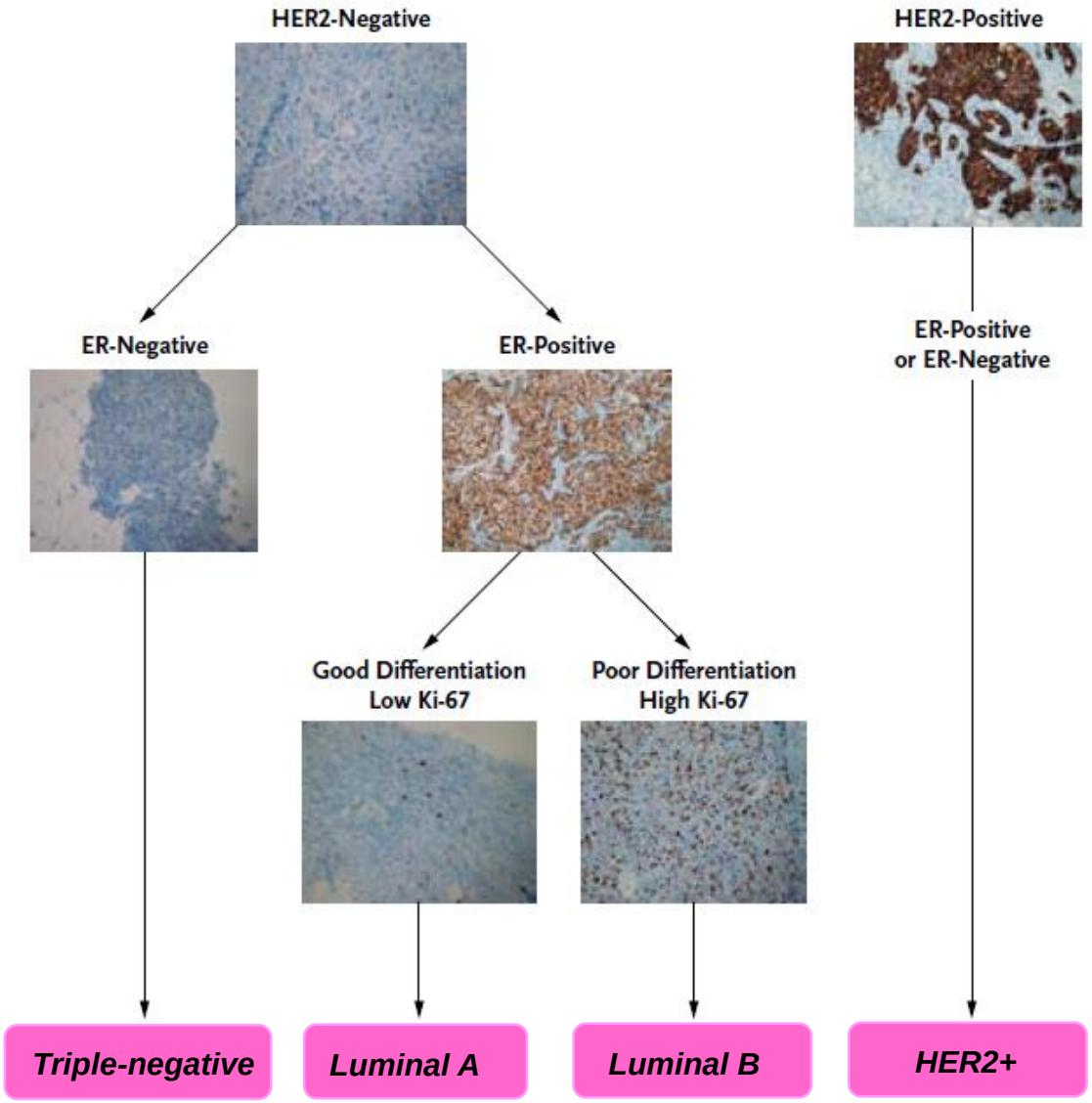
Metastatic Breast Cancer: treatments goals.



Strategies based on:

- **Hormonal Receptors (ER, PgR) expression**
- **HER2 expression**
- **Their absence**

Breast cancer subtypes:



Sotiriou C et al., NEJM 2009

Breast cancer subtypes:

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] <20% Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'Luminal A-like' and 'Luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' ≥20% PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b] **'Luminal B-like (HER2 positive)'** ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'Luminal A-like' and 'Luminal B-like (HER2 negative)'.
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

Goldhirsch A et al., Annals of Oncology 2013

Broad implications for systemic treatment selection:

'Subtype'	Type of therapy
'Luminal A-like'	Endocrine therapy is the most critical intervention and is often used alone.
'Luminal B-like (HER2 negative)'	Endocrine therapy for all patients, cytotoxic therapy for most.
'Luminal B-like (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy
'HER2 positive (non-luminal)'	Cytotoxics + anti-HER2
'Triple negative (ductal)'	Cytotoxics

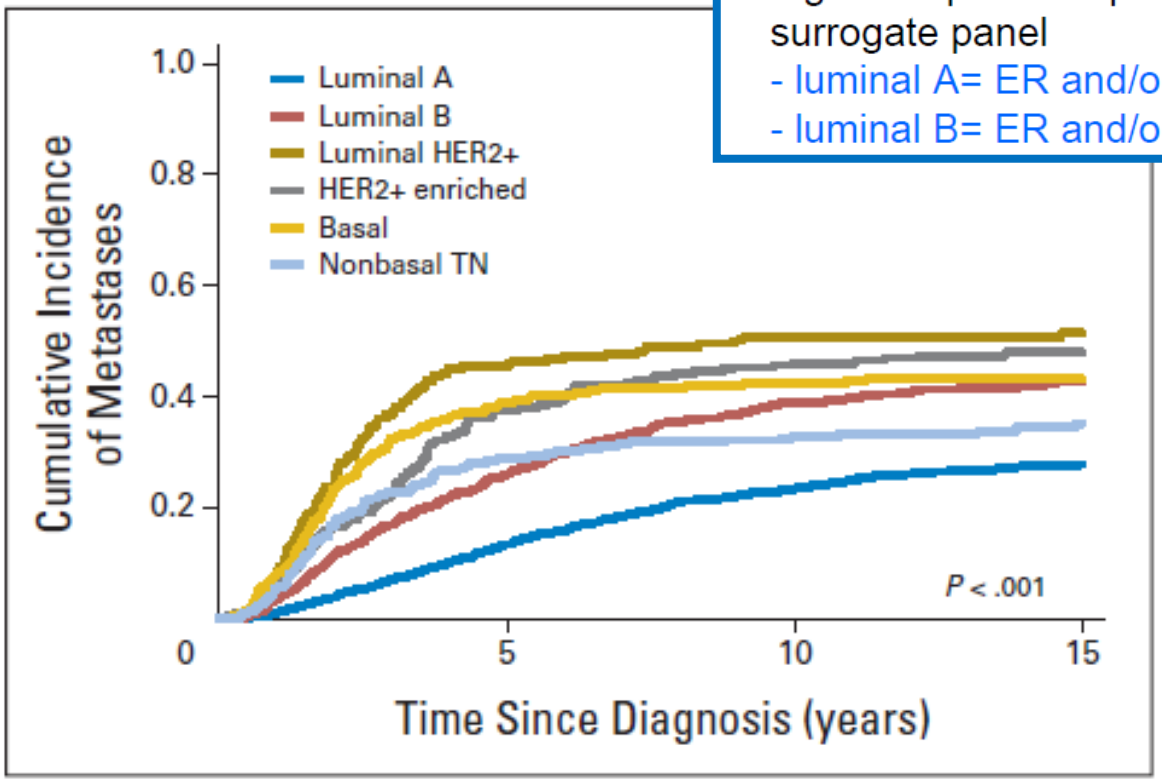
Goldhirsch A et al., Annals of Oncology 2013

Metastatic Behavior of Breast Cancer Subtypes

Hagen Kennecke, Rinat Yerushalmi, Ryan Woods, Maggie Chon U. Cheang, David Voduc, Caroline H. Speers, Torsten O. Nielsen, and Karen Gelmon

Effect of breast cancer subtype on relapse.

- 3726 patients with early-stage breast cancer diagnosed between 1986 and 1992 with archival tissue available
- Breast cancer molecular subtypes classified according to a gene expression profile-validated immunohistochemical surrogate panel
  - luminal A= ER and/or PgR + and Ki67<14%
  - luminal B= ER and/or PgR + and Ki67≥14%



Kennecke H et al., JCO 2010

Metastatic Behavior of Breast Cancer Subtypes

Hagen Kennecke, Rinat Yerushalmi, Ryan Woods, Maggie Chon U. Cheang, David Voduc, Caroline H. Speers, Torsten O. Nielsen, and Karen Gelmon

Effect of breast cancer subtype on site of metastasis.

Subtype	No. of Patients	Brain		Liver		Lung		Bone		Distant Nodal		Pleural/ Peritoneal		Other		Unknown	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Luminal A	458	35	7.6	131	28.6	109	23.8	305	66.6	73	15.9	129	28.2	62	13.5	36	7.9
Luminal B	378	41	10.8	121	32.0	115	30.4	270	71.4	88	23.3	133	35.2	73	19.3	13	3.4
HER2 positive, ER/PR positive	117	18	15.4	52	44.4	43	36.8	76	65.0	26	22.2	40	34.2	16	13.7	6	5.1
HER2 positive, ER/PR negative	136	39	28.7	62	45.6	64	47.1	81	59.6	34	25.0	43	31.6	23	16.9	6	4.4
Basal-like	159	40	25.2	34	21.4	68	42.8	62	39.0	63	39.6	47	29.6	38	23.9	11	6.9
TN nonbasal	109	24	22.0	35	32.1	39	35.8	47	43.1	39	35.8	31	28.4	28	25.7	6	5.5
P		< .001		< .001		< .001		< .001		< .001		.3214		.0056		.1338	

Kennecke H et al., JCO 2010

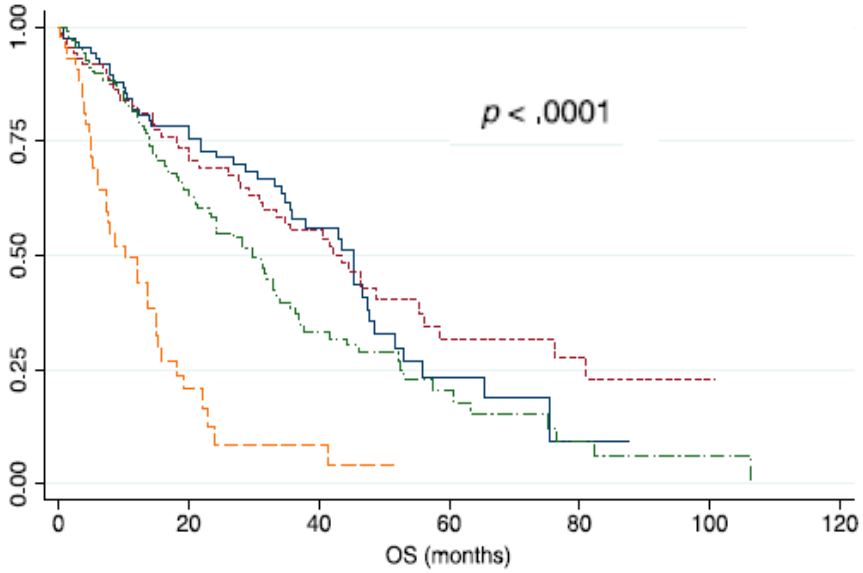
The Oncologist®

Breast Cancer

Measures of Outcome in Metastatic Breast Cancer: Insights From a Real-World Scenario

MARTA BONOTTO,[a] LORENZO GERRATANA,[a,c] ELENA POLETTO,[a] PAMELA DRIOL,[d] MANUELA GIANGRECO,[c] STEFANIA RUSSO,[a] ALESSANDRO M. MINISINI,[a] CLAUDIA ANDREETTA,[a] MAURO MANSUTTI,[a] FEDERICA E. PISA,[b] GIANPIERO FASOLA,[a] FABIO PUGLISI[a,c]

[a]Department of Oncology and [b]Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, Udine, Italy; [c]Department of Medical and Biological Sciences, University of Udine, Udine, Italy; [d]General Hospital, Gorizia, Italy

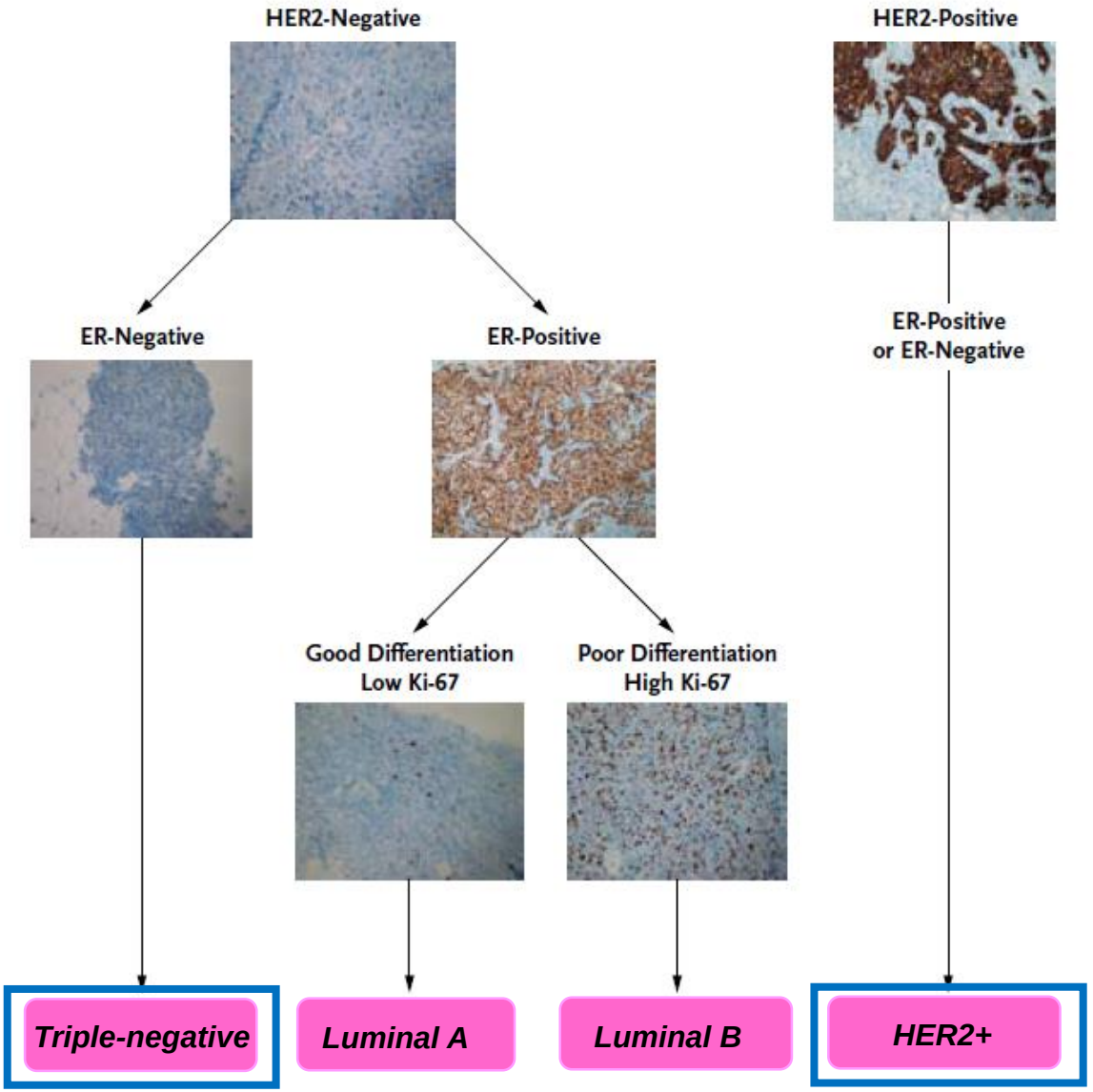


472 pts treated from 2004 to 2012

Outcome	*n*	Median (months)	IQR (25th–75th percentile)
OS			
Luminal A	88	45.3	21.9–56
Luminal B	138	29.7	13.9–52.4
HER2 positive	89	43.5	18.3–81.1
Triple negative	44	10.2	4.9–18.2

Bonotto M et al., The Oncologist 2014

Breast cancer subtypes:



Sotiriou C et al., NEJM 2009

Metastatic Breast Cancer:

HER-2 positive

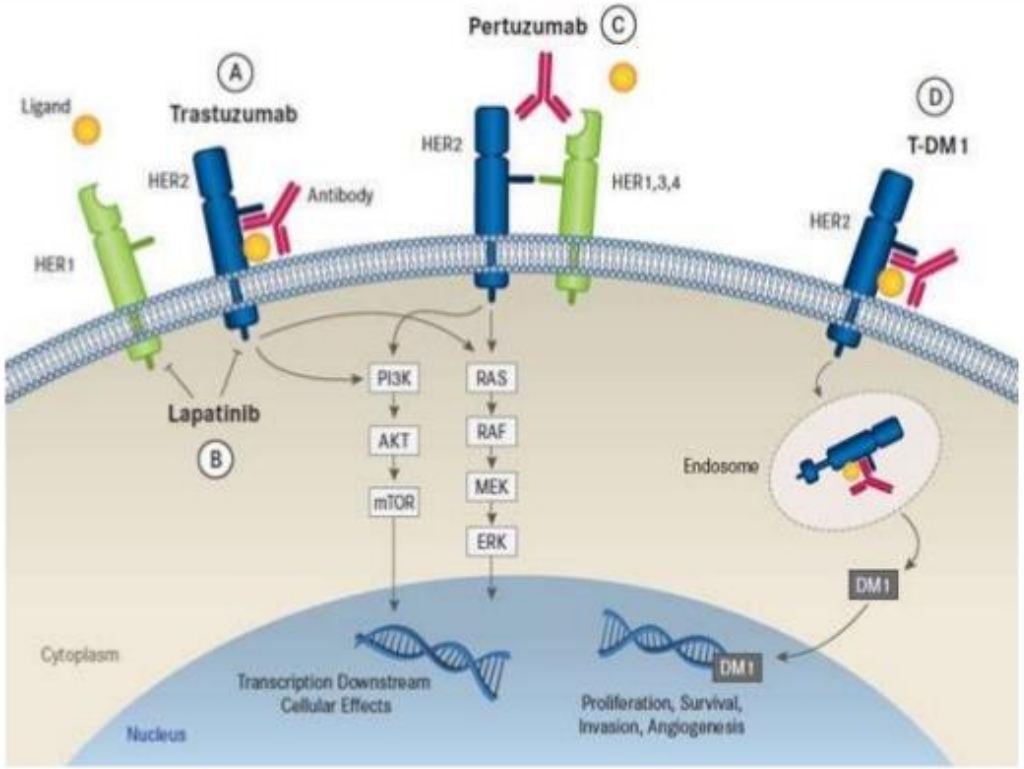
Targeting HER2

A. Trastuzumab: Blocks domain IV HER2 (1998)

B. Pertuzumab: Blocks domain II HER2 (2007)

C. Lapatinib : Blocks Intracellular ATP pocket of HER1 & HER2 (2012)

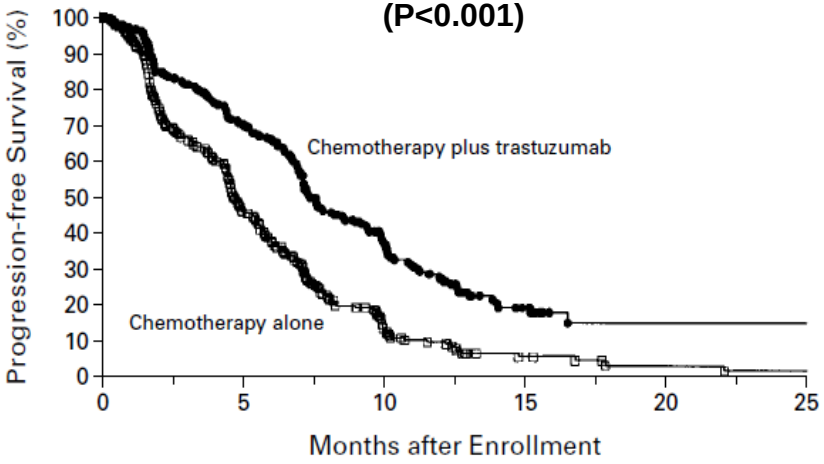
D. Ado-Trastuzumab emsantine (T-DM1) : monoclonal Ab – Cytotoxic drug (2013)



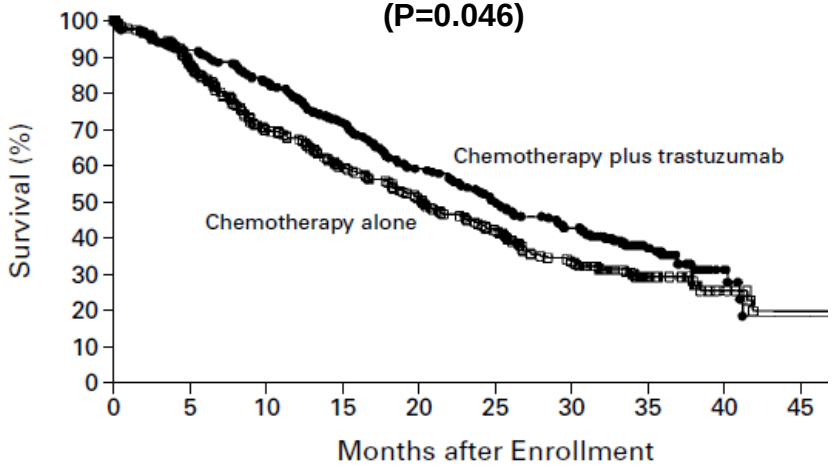
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

mPFS 7.4 vs 4.6 months (P<0.001)



mOS 25.1 vs 20.3 months (P=0.046)

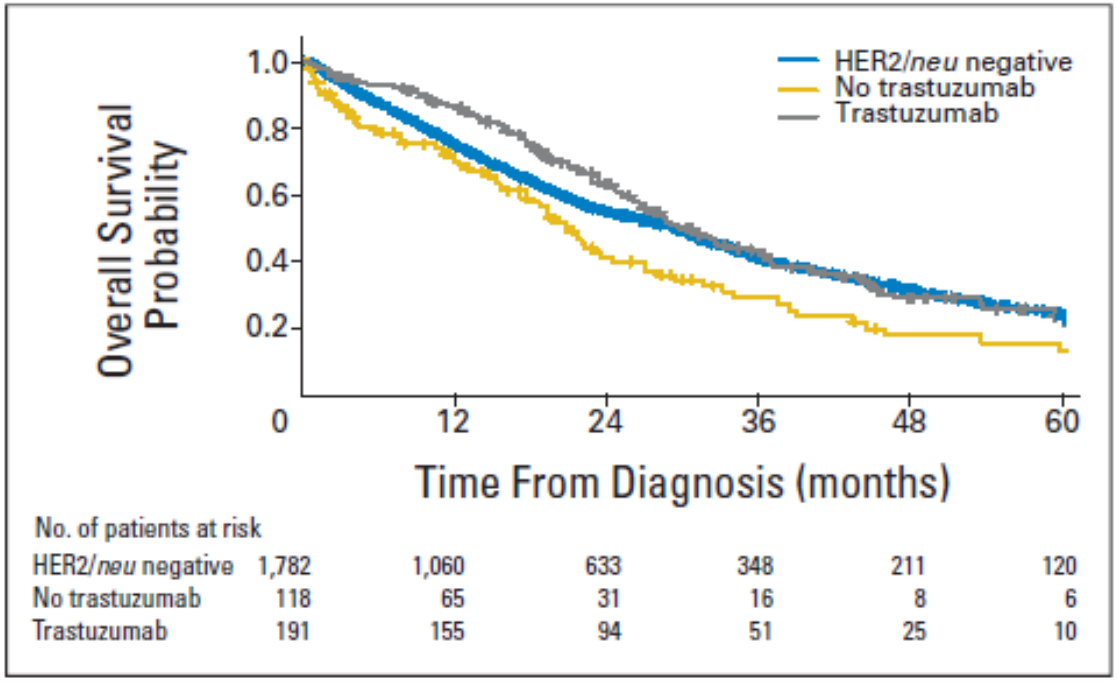


Trastuzumab increases the clinical benefit of first-line chemotherapy in MBC HER2+.

Slamon D et al., NEJM 2001

Prognosis of Women With Metastatic Breast Cancer by *HER2* Status and Trastuzumab Treatment: An Institutional-Based Review

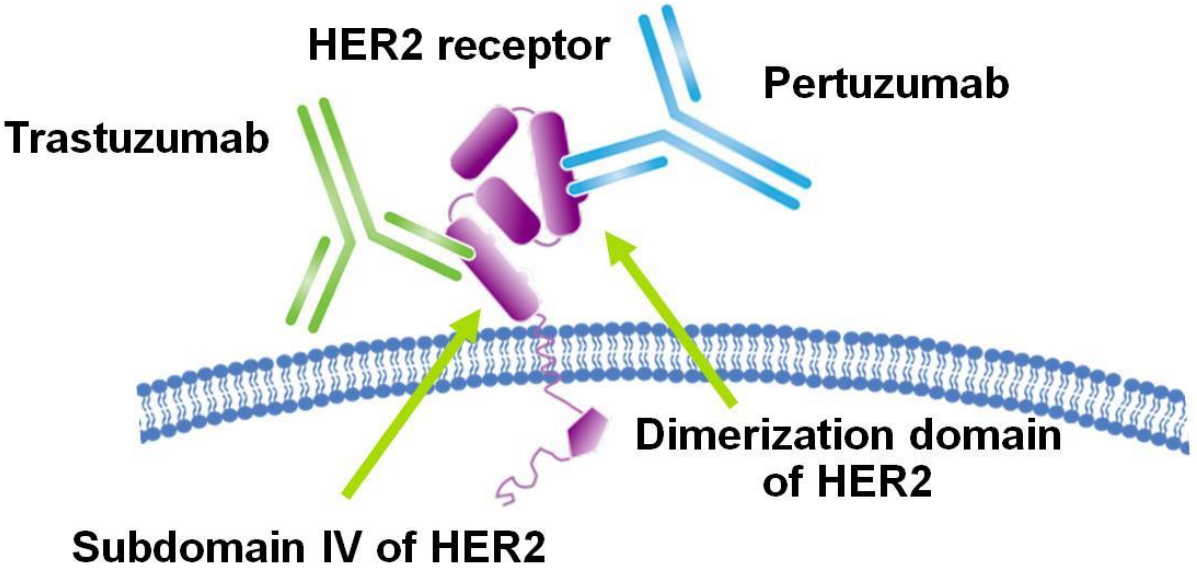
Shaheenah Dawood, Kristine Broglio, Aman U. Buzdar, Gabriel N. Hortobagyi, and Sharon H. Giordano



Patients with HER2-positive MBC now have comparable outcomes with HER2-negative MBC.

Dawood S et al., JCO 2010

Pertuzumab and Trastuzumab Bind to Different Regions on HER2

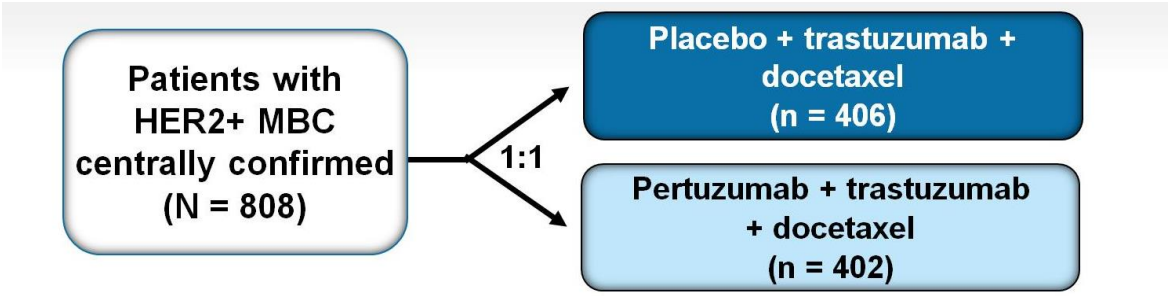


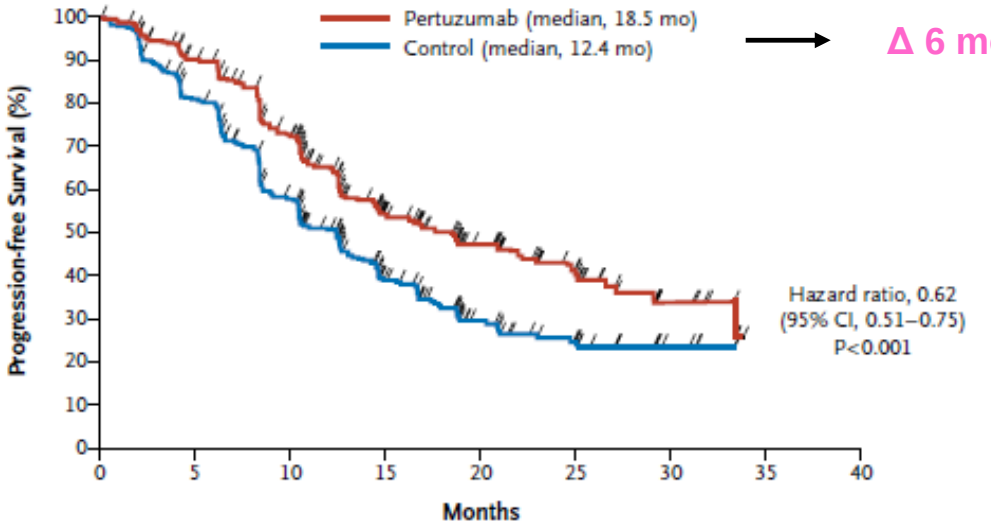
Trastuzumab	Pertuzumab
Suppresses HER2 activity	Inhibits HER2-forming dimer pairs
Does not inhibit HER2 heterodimerization	More complete HER2 blockade
Flags cells for destruction by the immune system (ADCC)	Flags cells for destruction by the immune system

Park Y et al., World J Clin Oncol 2012

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

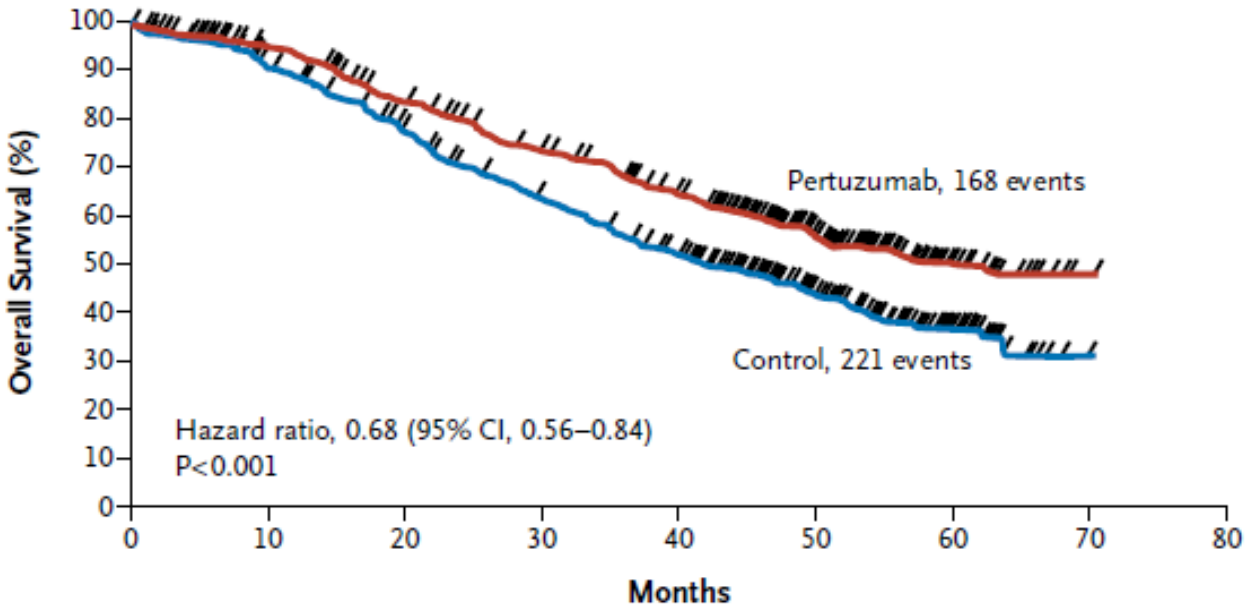




Δ 6 months

Baselga J et al., NEJM 2012

Final OS analysis of CLEOPATRA trial sets a new paradigm of treatment of HER2-positive MBC.



Median OS was 56.5 months in the group receiving pertuzumab combination as compared with 40.8 months in the group receiving the placebo combination (HR 0.68; p<0.001) → ***Δ 15.7 months***.

Swain SM et al., NEJM 2015

Adverse Event	Placebo plus Trastuzumab plus Docetaxel (N=397)	Pertuzumab plus Trastuzumab plus Docetaxel (N=407)
	number (percent)	
Most common events, all grades†		
Diarrhea	184 (46.3)	272 (66.8)
Alopecia	240 (60.5)	248 (60.9)
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	137 (33.7)
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	79 (19.9)	113 (27.8)
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	30 (7.6)	56 (13.8)
Dry skin	17 (4.3)	43 (10.6)
Grade 3 or higher events‡		
Neutropenia	182 (45.8)	199 (48.9)
Febrile neutropenia	30 (7.6)	56 (13.8)
Leukopenia	58 (14.6)	50 (12.3)
Diarrhea	20 (5.0)	32 (7.9)
Peripheral neuropathy	7 (1.8)	11 (2.7)
Anemia	14 (3.5)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Fatigue	13 (3.3)	9 (2.2)
Granulocytopenia	9 (2.3)	6 (1.5)
Left ventricular systolic dysfunction	11 (2.8)	5 (1.2)
Dyspnea	8 (2.0)	4 (1.0)

Baselga J et al., NEJM 2012

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Indicazioni terapeutiche AIFA:

Pertuzumab è indicato in associazione con trastuzumab e docetaxel nelle donne con carcinoma mammario HER2-positivo, inoperabile, metastatico o localmente avanzato, non trattate in precedenza con terapia anti-HER2 o chemioterapia per la malattia metastatica.

Therapy of MBC after progression on first-line anti-HER2 treatment:

Chemotherapy ± anti-HER2 therapy

- Capecitabine ± lapatinib (EGF100151)
- Capecitabine ± trastuzumab (GBG26)

Dual inhibition of HER2

- Lapatinib vs lapatinib/trastuzumab (EGF104900)

Antibody drug conjugate therapy

- T-DM1 vs capecitabine/lapatinib (EMILIA)

1. Continuing anti-HER2 therapy after progression on first-line anti-HER2 therapy: randomized trials.

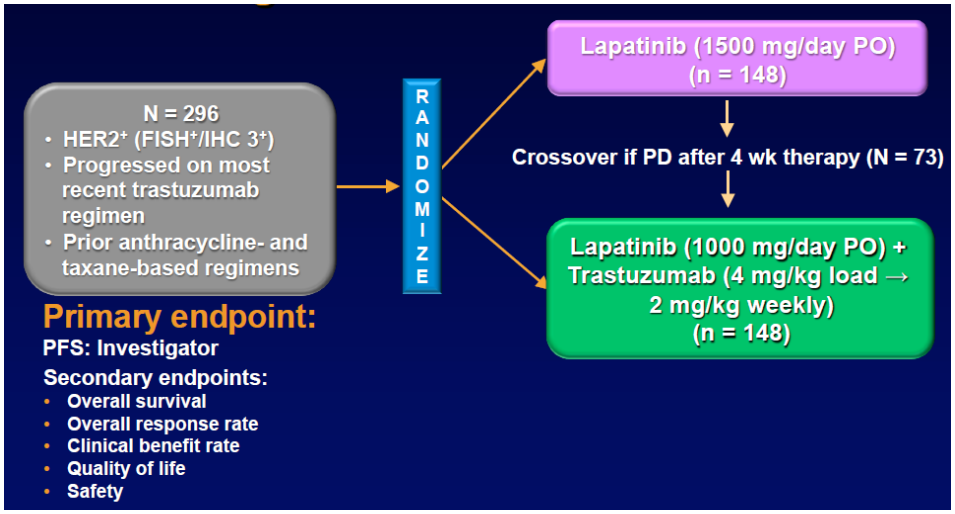
	Cameron D, et al[a]; Geyer CE, et al[b]; EGF100151	von Minckwitz, et al[c] GBG26/BIG3-05
Phase	3	3
No. of patients	399	156
Second-line HER2 therapy	Lapatinib vs placebo	Trastuzumab vs none
Concurrent chemotherapy	Capecitabine	Capecitabine
Median PFS	8.4 vs 4.4 mo HR = 0.49, *P* <.001	8.2 vs 5.6 mo HR = 0.69, *P* =.0338
Median OS	75 wk vs 64.7 wk HR = 0.87, *P* =.210	24.9 vs 20.6 mo HR = 0.94, *P* =.73

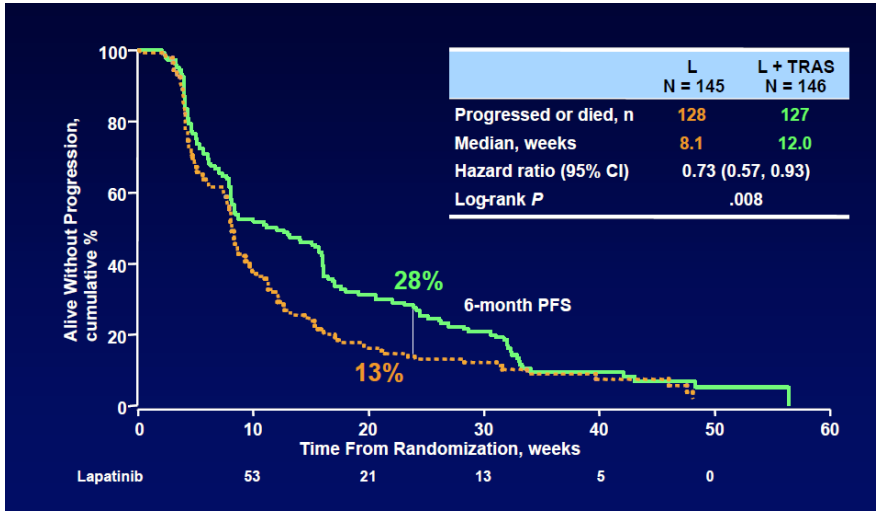
Geyer C et al., NEJM 2006; Cameron D et al., The Oncologist 2010; Mundhenke C et al. Eur J Cancer 2011.

2. Dual inhibition of HER2.

Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer

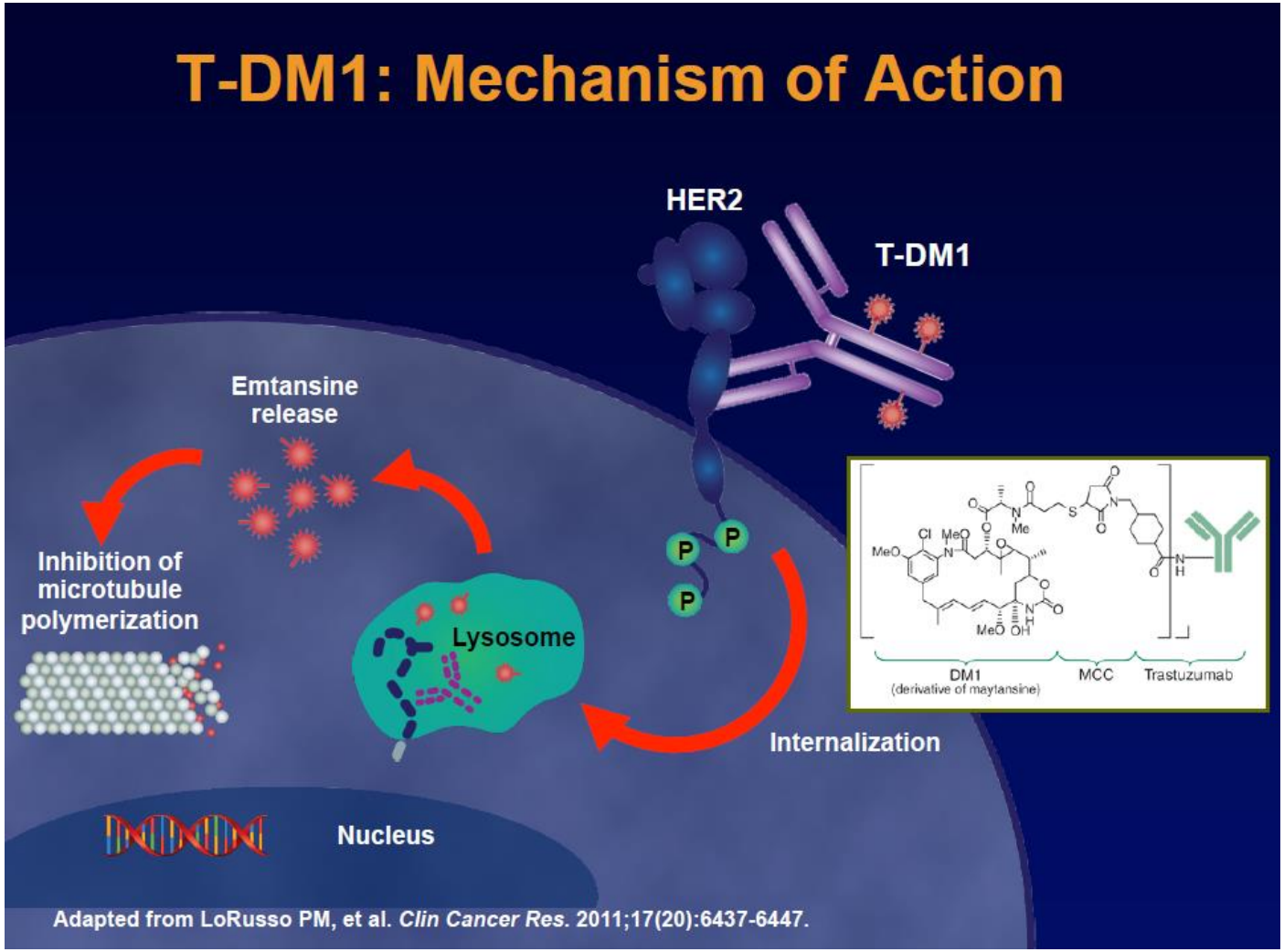
Kimberly L. Blackwell, Harold J. Burstein, Anna Maria Storniolo, Hope Rugo, George Sledge, Maria Koehler, Catherine Ellis, Michelle Casey, Svetislava Vukelja, Joachim Bischoff, Jose Baselga, and Joyce O'Shaughnessy





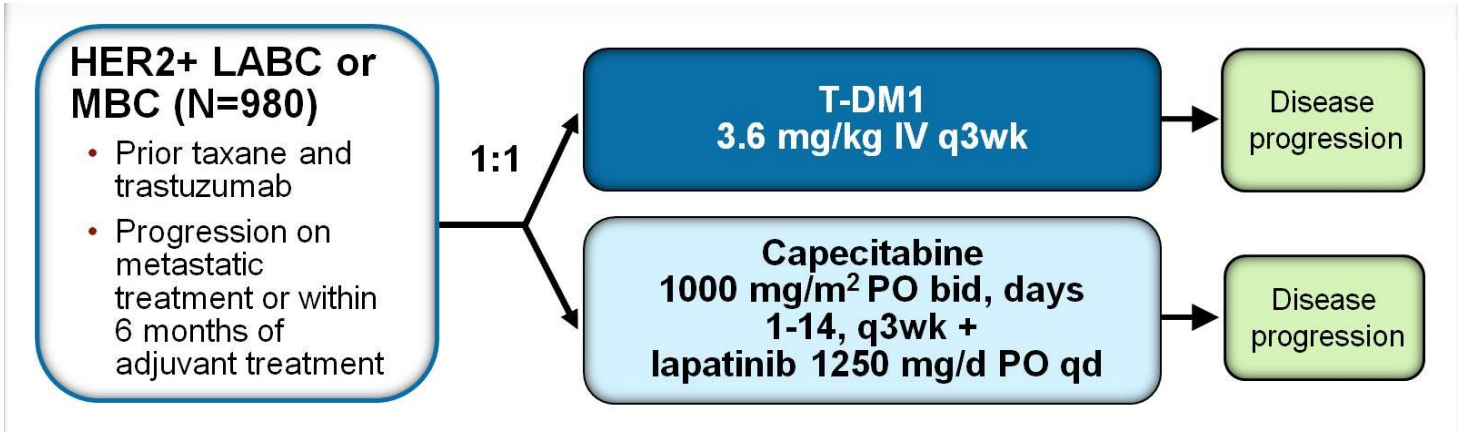
Blackwell K et al., JCO 2010

3. Antibody drug conjugate therapy.



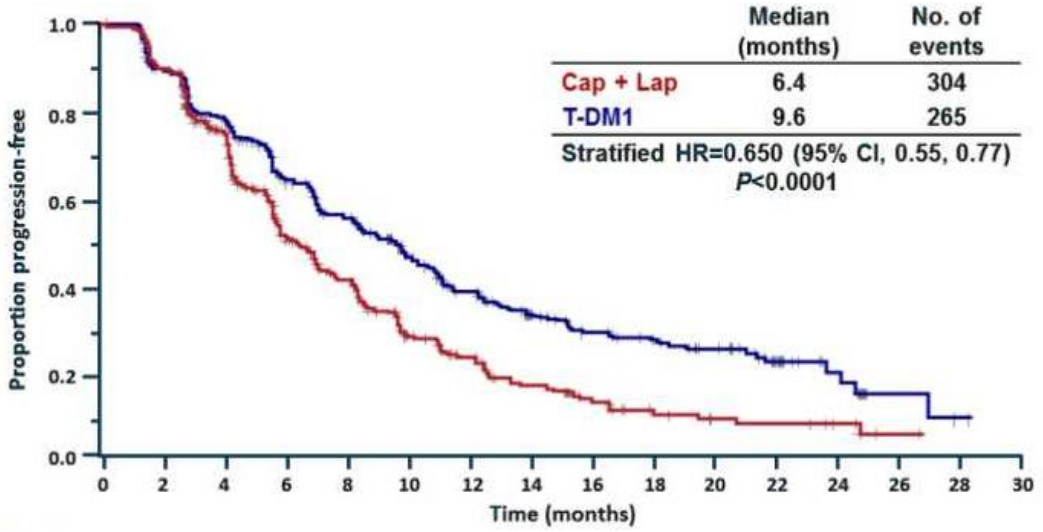
Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group



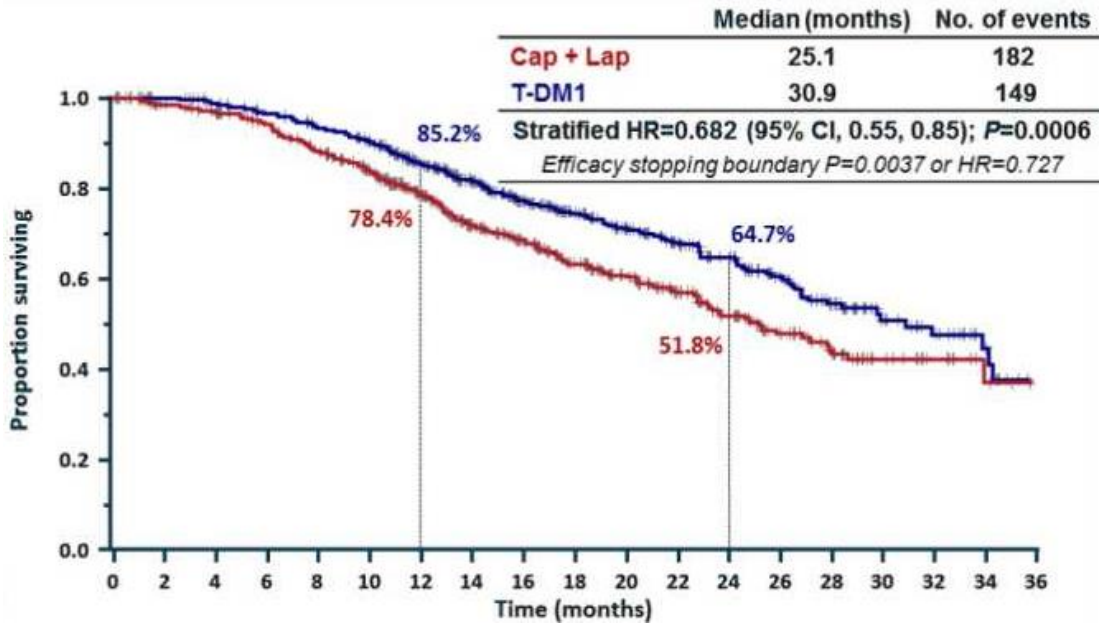
Verma S et al., NEJM 2012

PFS



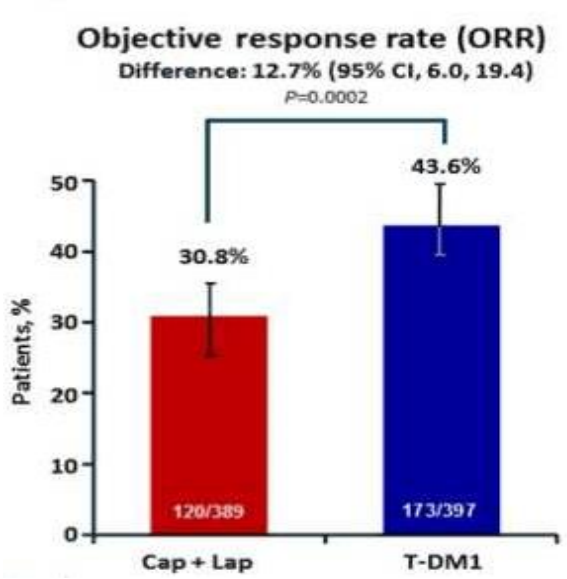
Δ 3,2 months

OS



Δ 5,8 months

Verma S et al., NEJM 2012



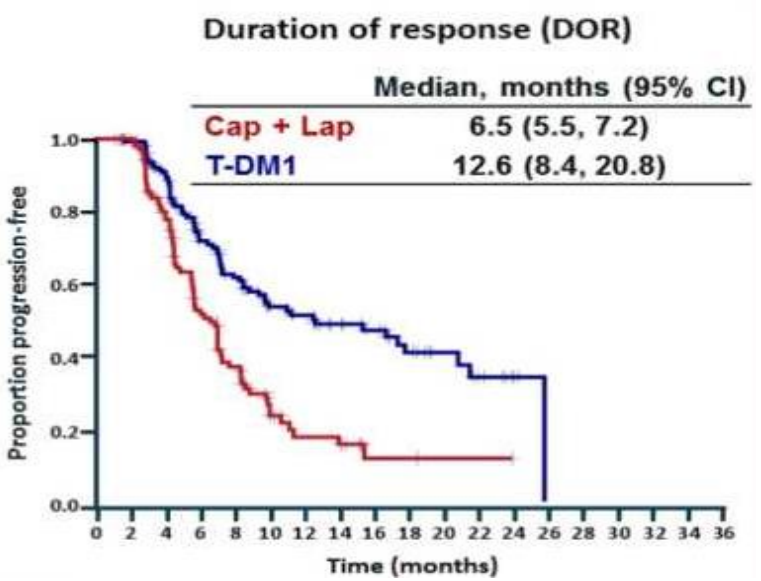


Table 2. Objective-Response Rate and Duration of Response, as Assessed by the Independent Review Committee.*

Variable	Lapatinib plus Capecitabine (N=389)	T-DM1 (N=397)	Difference	P Value
Complete or partial response				
No. of patients	120	173		
Percent (95% CI)	30.8 (26.3–35.7)	43.6 (38.6–48.6)	12.7 (6.0–19.4)	<0.001
Complete response — no. (%)	2 (0.5)	4 (1.0)		
Partial response — no. (%)	118 (30.3)	169 (42.6)		
Duration of complete or partial response — mo				
Median	6.5	12.6		
95% CI	5.5–7.2	8.4–20.8		

Verma S et al., NEJM 2012

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Events of Grade 3 or Above	Events of Any Grade	Events of Grade 3 or Above
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

Verma S et al., NEJM 2012

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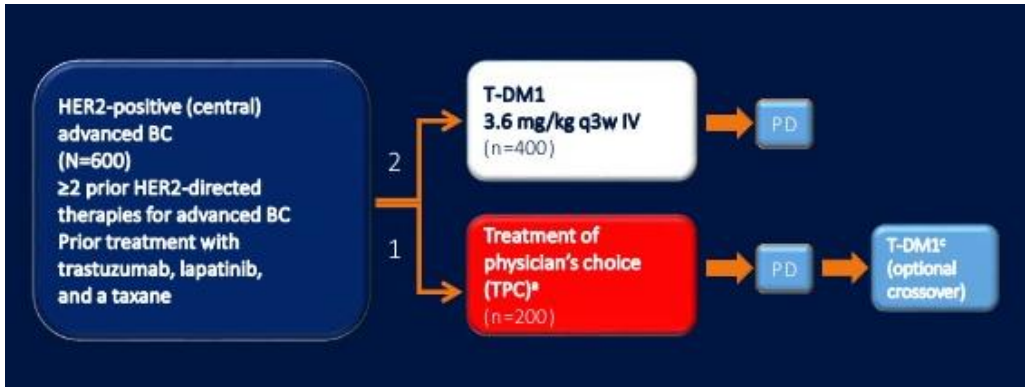
Indicazioni terapeutiche AIFA:

T-DM1, in monoterapia, è indicato per il trattamento delle donne con carcinoma mammario HER2-positivo, inoperabile, metastatico o localmente avanzato, sottoposte in precedenza a trattamento con trastuzumab e un taxano, somministrati separatamente o in combinazione.

Le pazienti devono essere state sottoposte in precedenza a terapia per la malattia localmente avanzata o metastatica o aver sviluppato recidiva di malattia durante o entro 6 mesi dal completamento della terapia adiuvante.

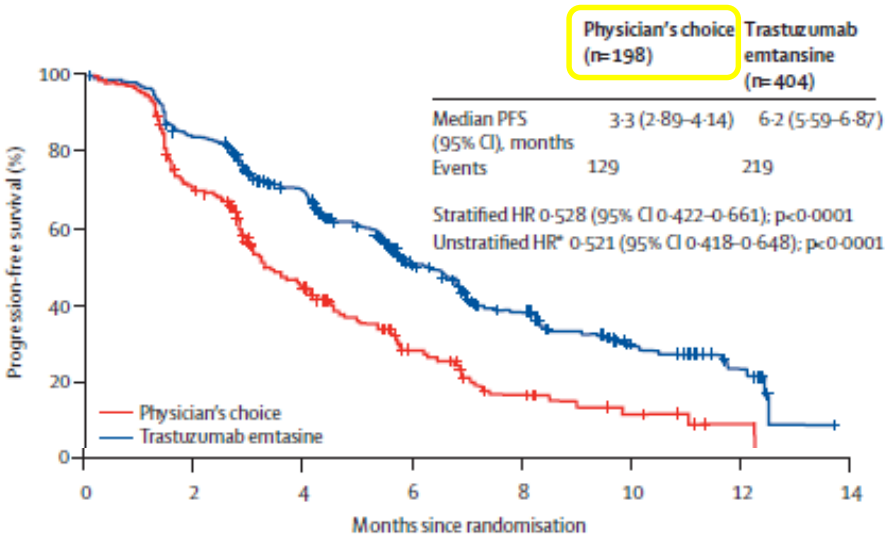
Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial

*Ian E Krop, Sung-Bae Kim, Antonio González-Martín, Patricia M LoRusso, Jean-Marc Ferrero, Melanie Smitt, Ron Yu, Abraham C F Leung, Hans Wildiers, on behalf of the TH3RESA study collaborators**

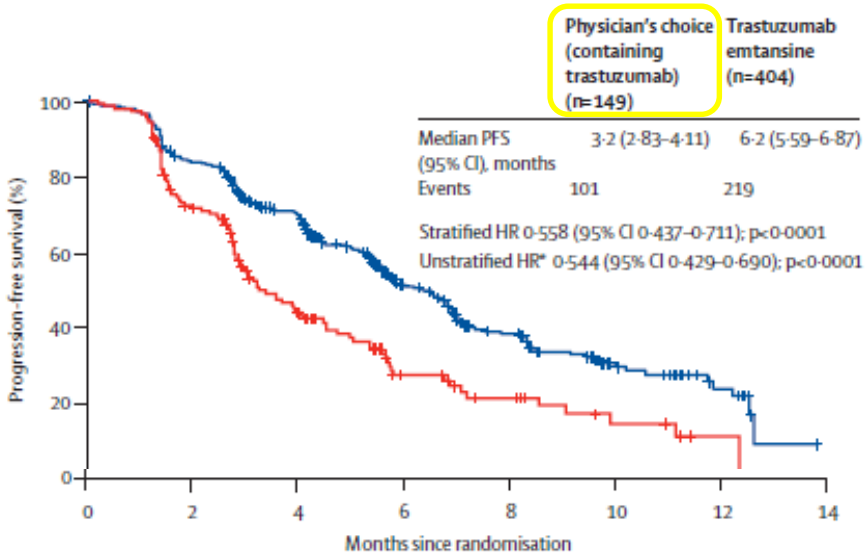


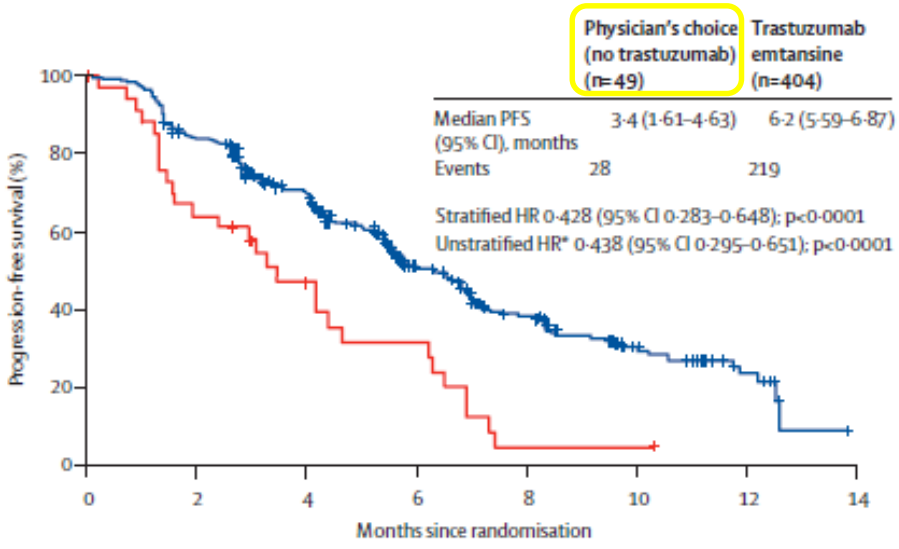
	Physician's choice (n=185)
Treatment category	
Single-agent trastuzumab emtansine	1 (<1%)*
Combination with HER2-directed agent	153 (83%)
Trastuzumab plus chemotherapy	126 (68%)
Trastuzumab plus lapatinib	19 (10%)
Trastuzumab plus hormonal therapy	3 (2%)
Lapatinib plus chemotherapy	5 (3%)
Single-agent chemotherapy	31 (17%)
Chemotherapy agents†	
Vinorelbine	59 (32%)
Gemcitabine	29 (16%)
Eribulin	16 (9%)
Paclitaxel	16 (9%)
Docetaxel	10 (5%)
Other	32 (17%)

Krop I et al., Lancet Oncol 2014



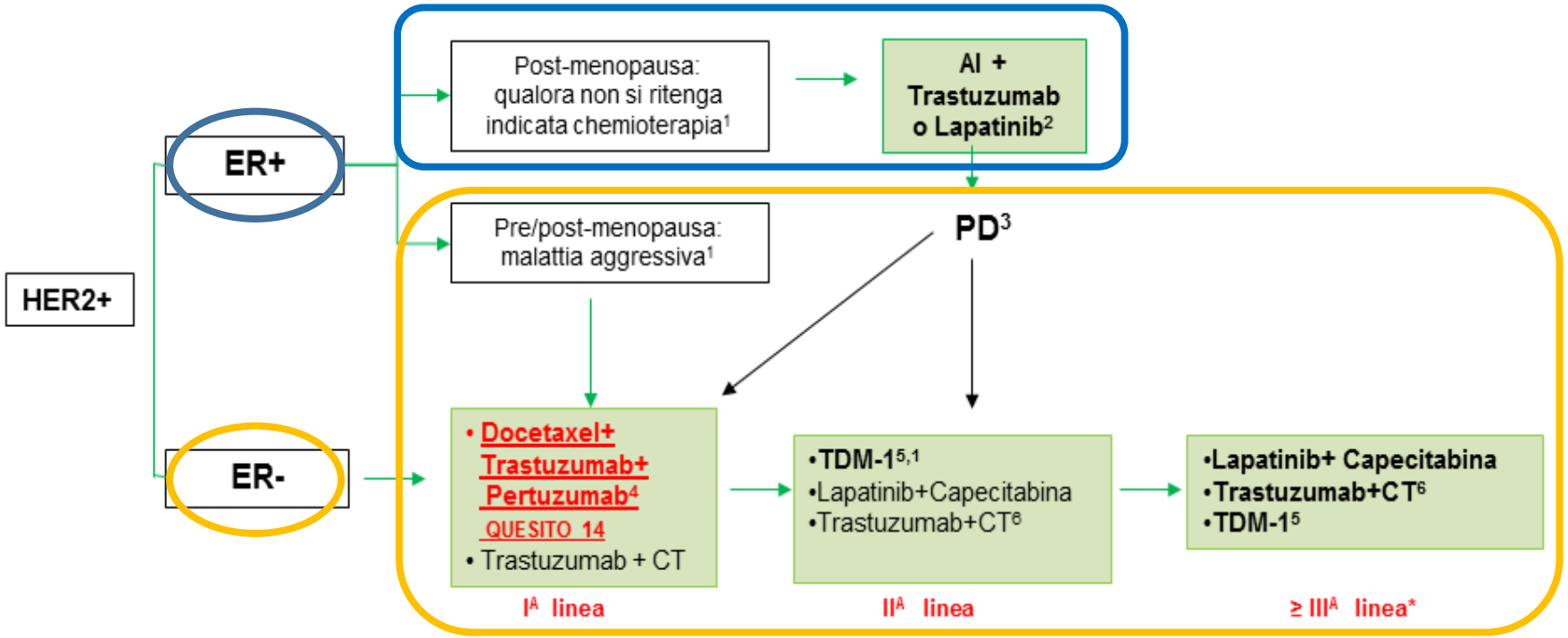
Δ ~3 months





Krop I et al., Lancet Oncol 2014

Terapia medica in base alle caratteristiche cliniche e biologiche:



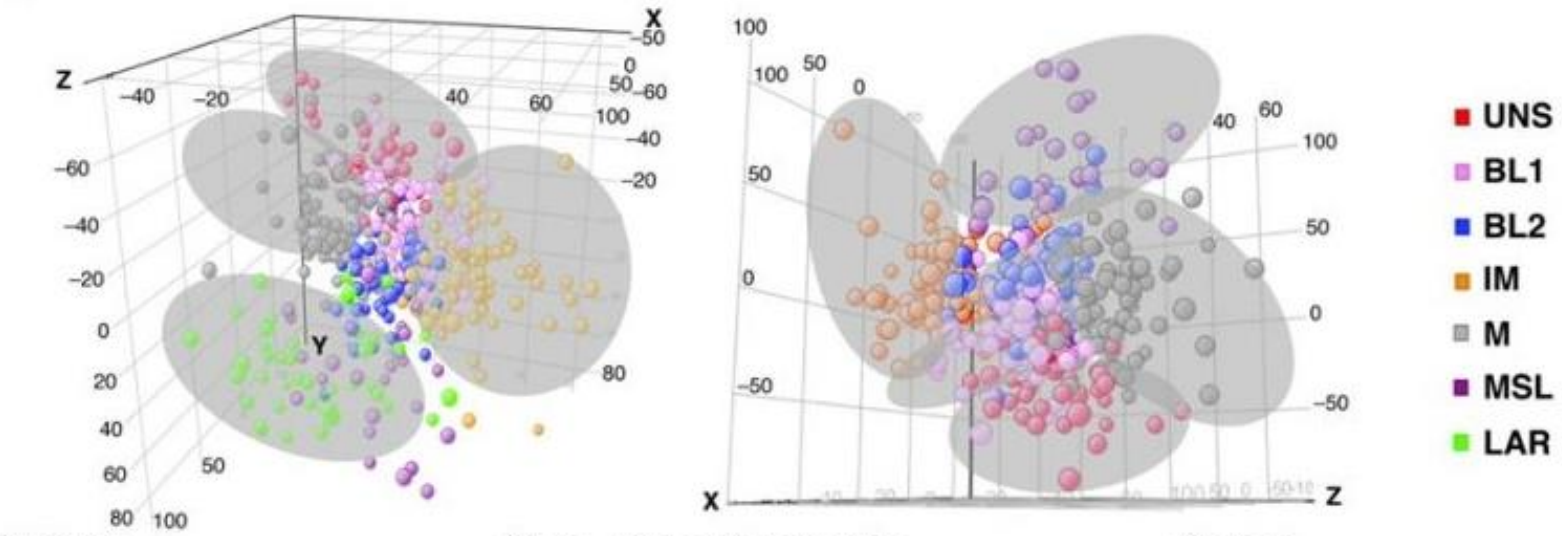
LINEE GUIDA AIOM 2017

Associazione Italiana di Oncologia Medica

Metastatic Breast Cancer:

Triple-negative

Clinical heterogeneity of TNBC:



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Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehmann B et al., J Clin Invest 2011

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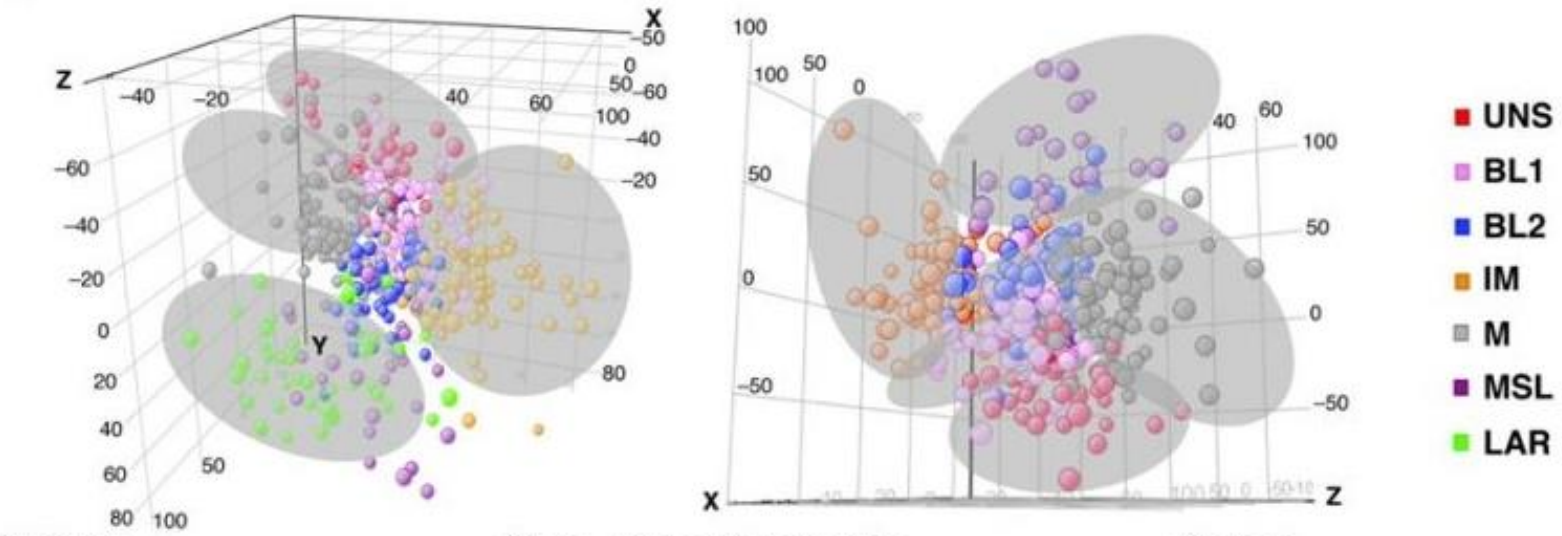

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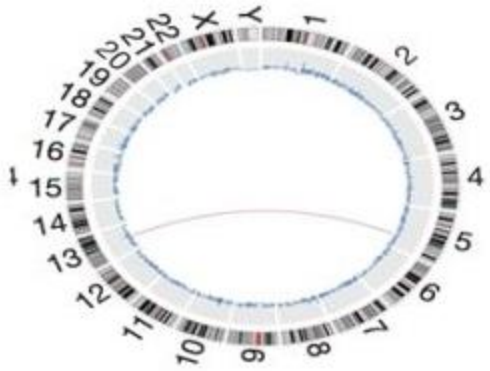
Lehmann B et al., J Clin Invest 2011

Basal like TNBC:

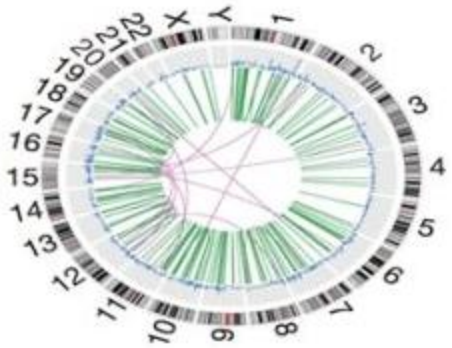
Triple negative breast cancer and BRCA-mutations

- **Clinical behavior**
- **Genomic instability**

PD3667a
ER+ PR+ ERBB2−

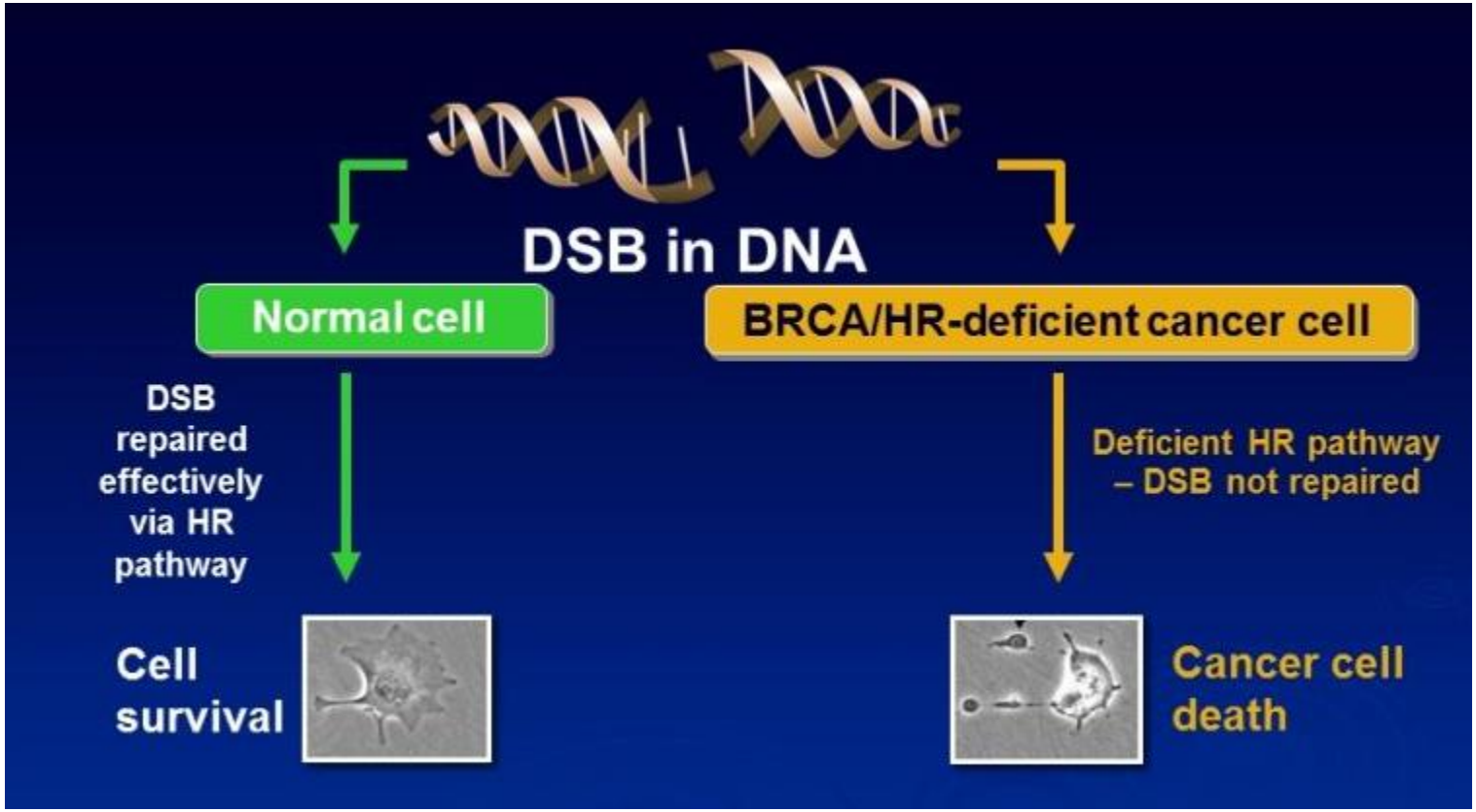


PD3664a
ER− PR− ERBB2−

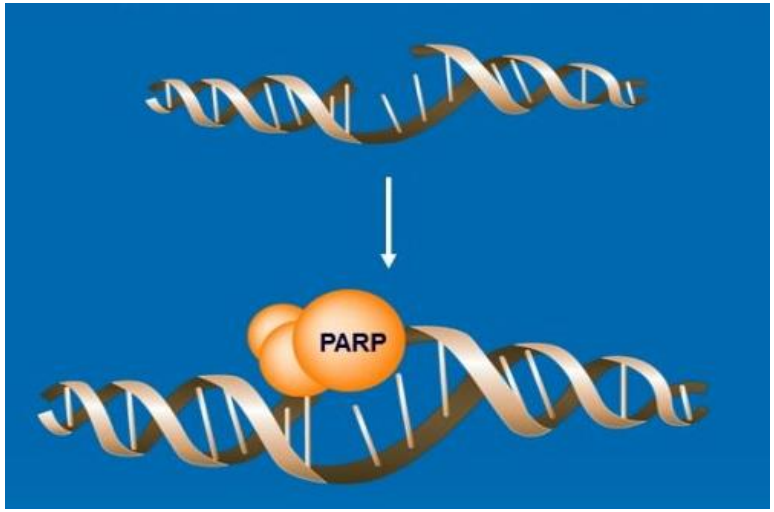


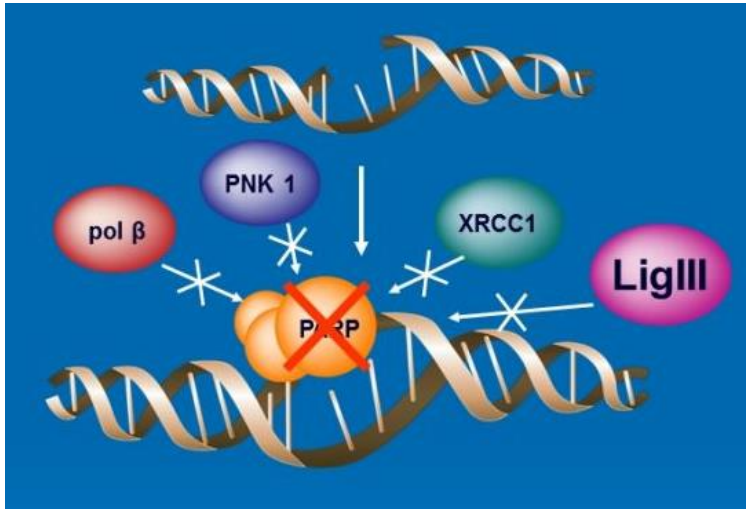
Stephens P et al., Nature 2009

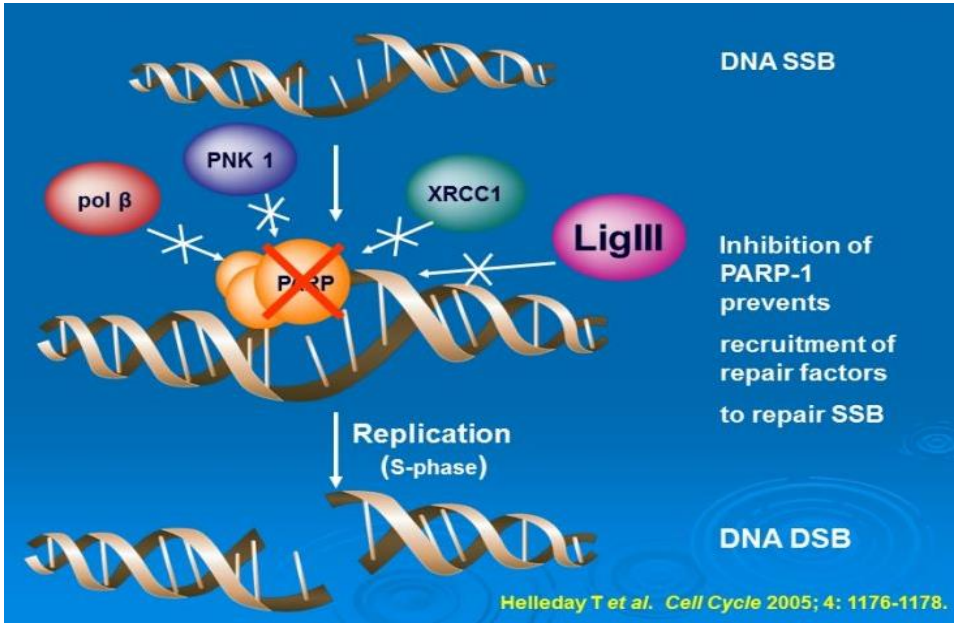
Synthetic lethality in BC:



Helleday T et al., Cell Cycle 2005

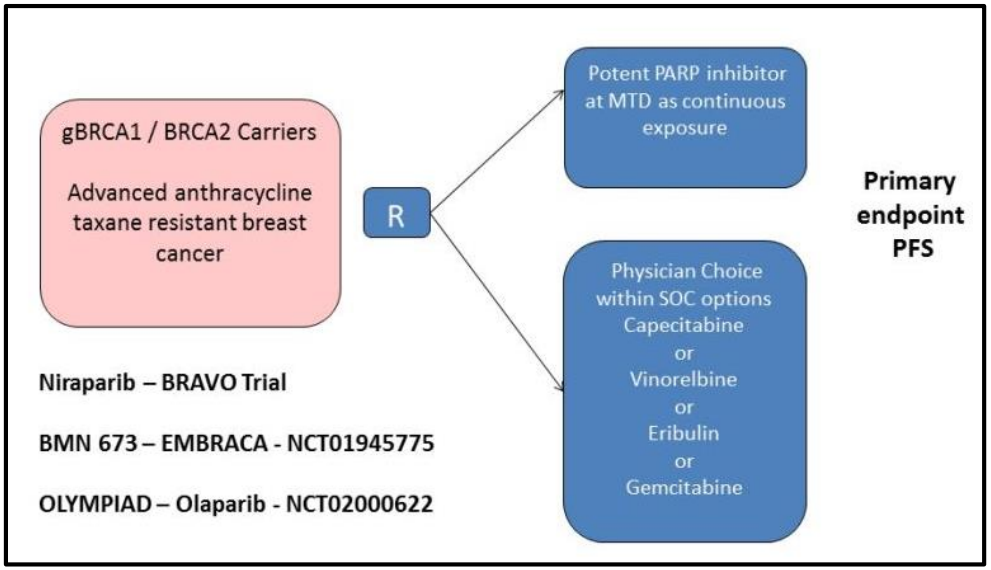

PARP


PNK 1
pol β
XRCC1
LigIII


DNA SSB
PNK 1
pol β
XRCC1
LigIII
Inhibition of PARP-1 prevents
recruitment of repair factors
to repair SSB
Replication
(S-phase)
DNA DSB
Helleday T et al. Cell Cycle 2005; 4: 1176-1178.

PARP inhibitors in metastatic TNBC:

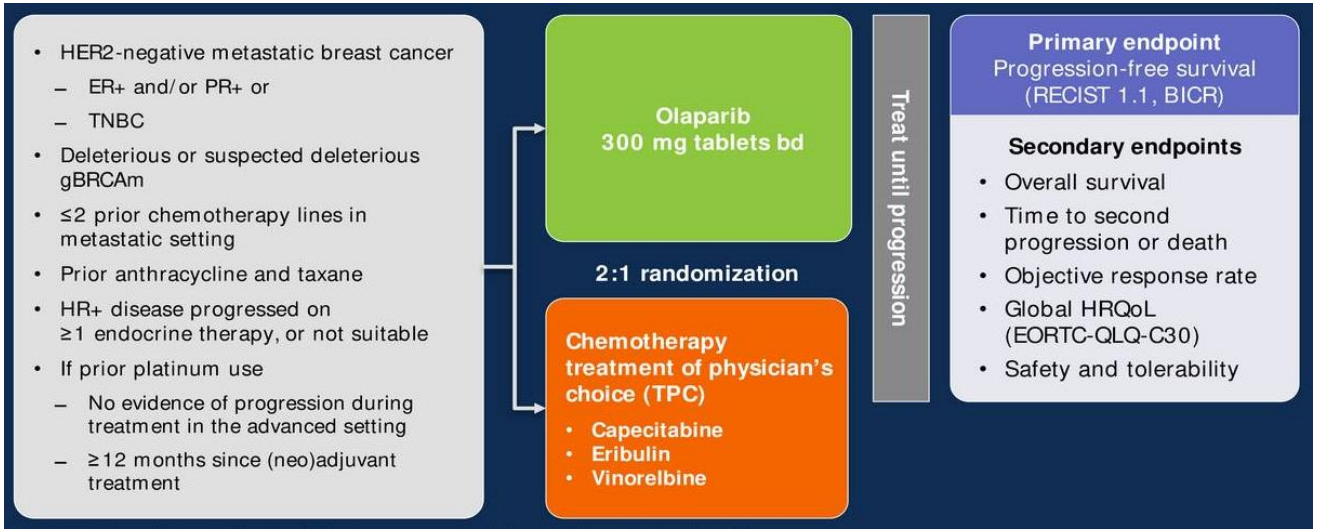
Agent	Pt Population	Trial	Primary Endpoint
Olaparib	*BRCA1* or *BRCA2* mutation	Olaparib vs physician's choice of chemotherapy (OlympiAD)[1]	PFS
Veliparib	*BRCA1* or *BRCA2* mutation (suspected/confirmed)	Veliparib + carboplatin/paclitaxel vs placebo + carboplatin/paclitaxel[2]	PFS
Talazoparib	*BRCA1* or *BRCA2* mutation	Talazoparib vs physician's choice of chemotherapy (EMBRACA)[3]	PFS
Niraparib	*BRCA1* or *BRCA2* mutation (pts with unknown status will be screened if appropriate)	Niraparib vs physician's choice of chemotherapy (BRAVO)[4]	PFS



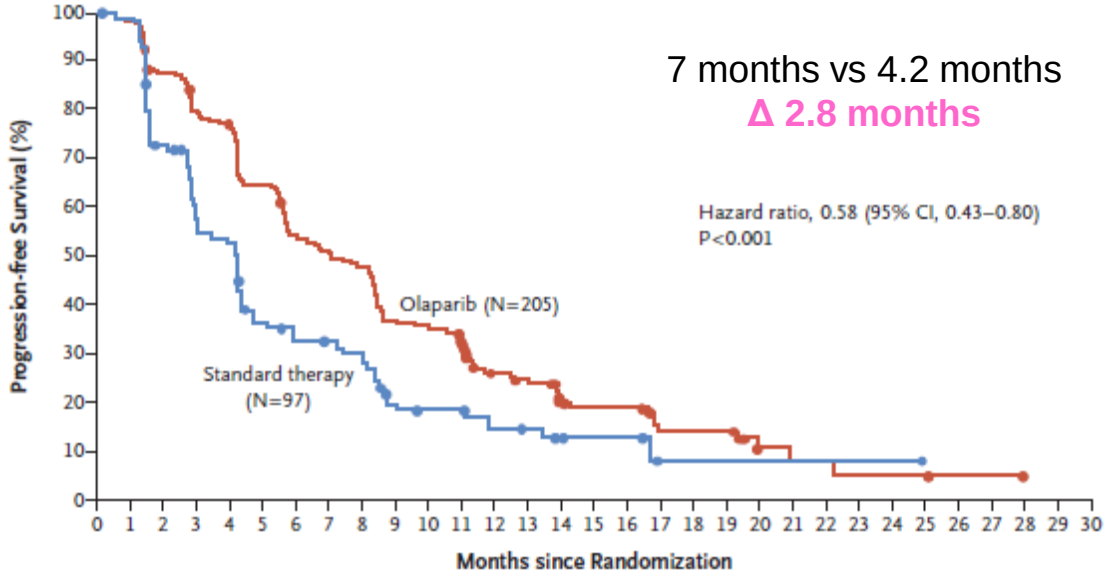
Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

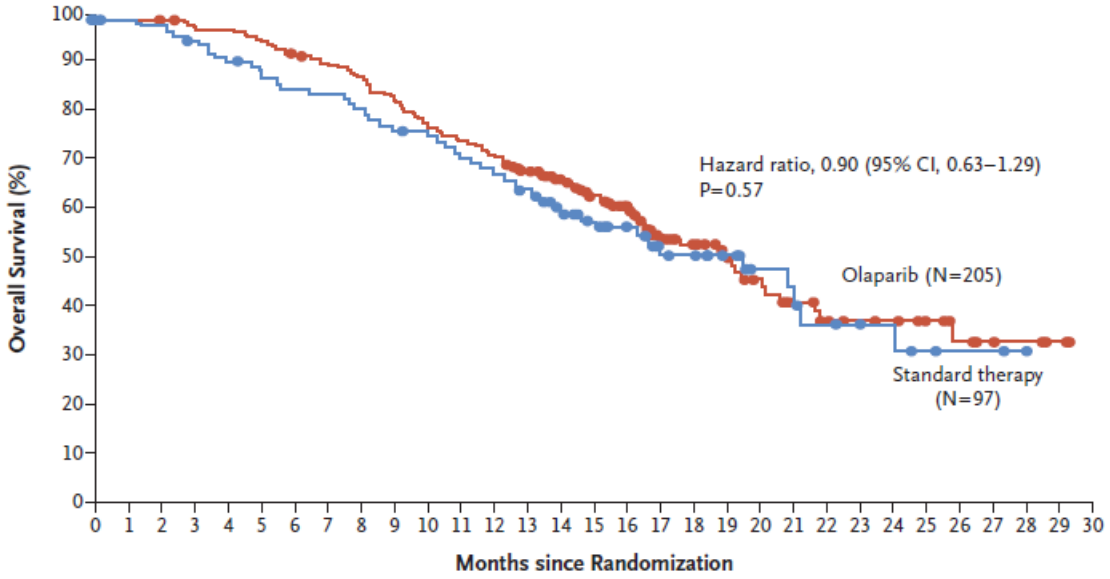
Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

OlympiAD trial



Robson M E et al., NEJM 2017





Robson M E et al., NEJM 2017

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

Robson M E et al., NEJM 2017

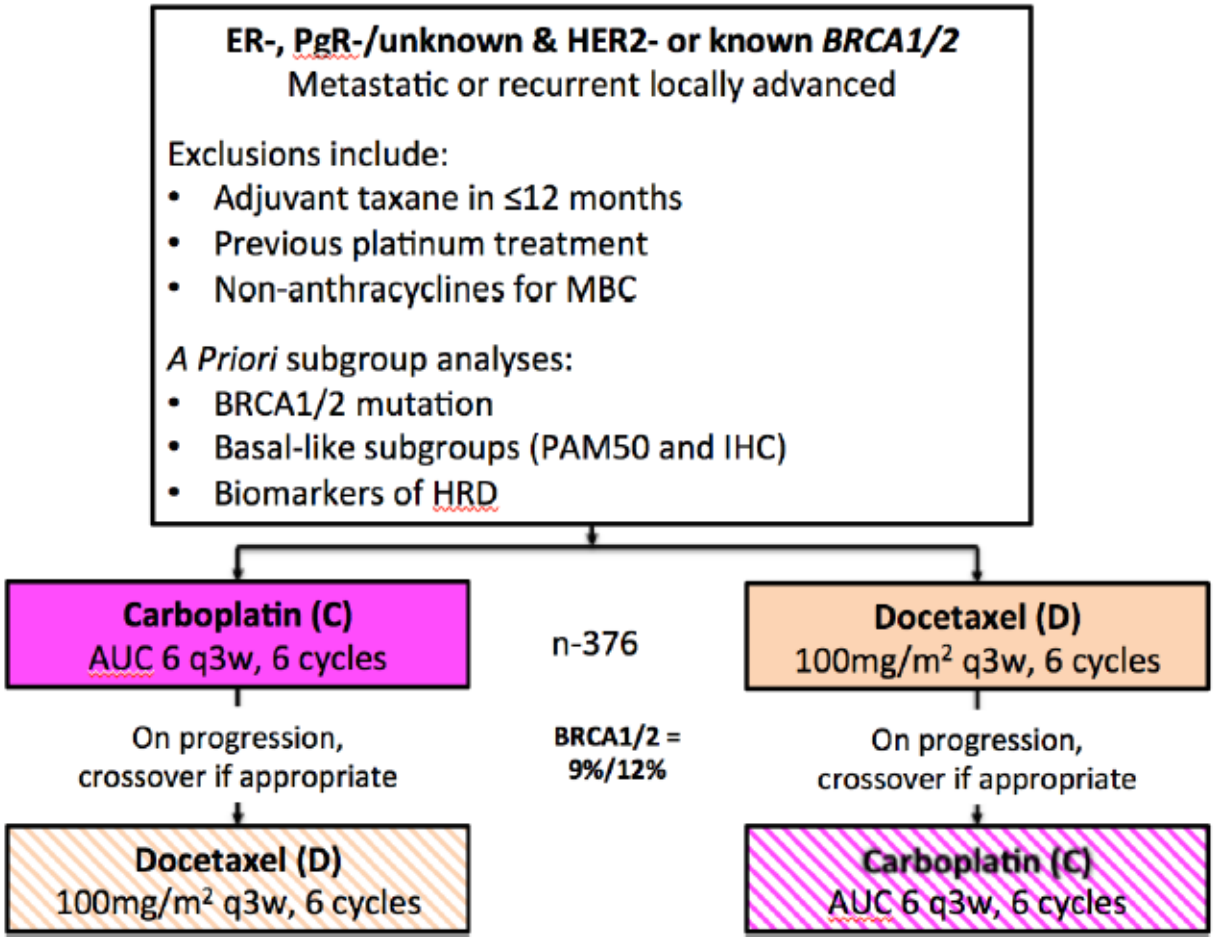
Platinum

- **Cisplatin first approved by the FDA in 1978**
  - Noted to have activity in metastatic breast cancer[1]
- **Family of platinum salts bind directly to DNA**
  - Results in formation of DNA-platinum adducts and consequently intra- and inter-strand DNA crosslinks that impede cell division
- **Recent renewed interest in investigating the role of platinum chemotherapy in breast cancer**
  - Hypothesis of greater susceptibility of TN and BRCA1/2 mutant BC to DNA damaging chemotherapeutic agents
  - Limited data in mTNBC; most important insights from neoadjuvant setting

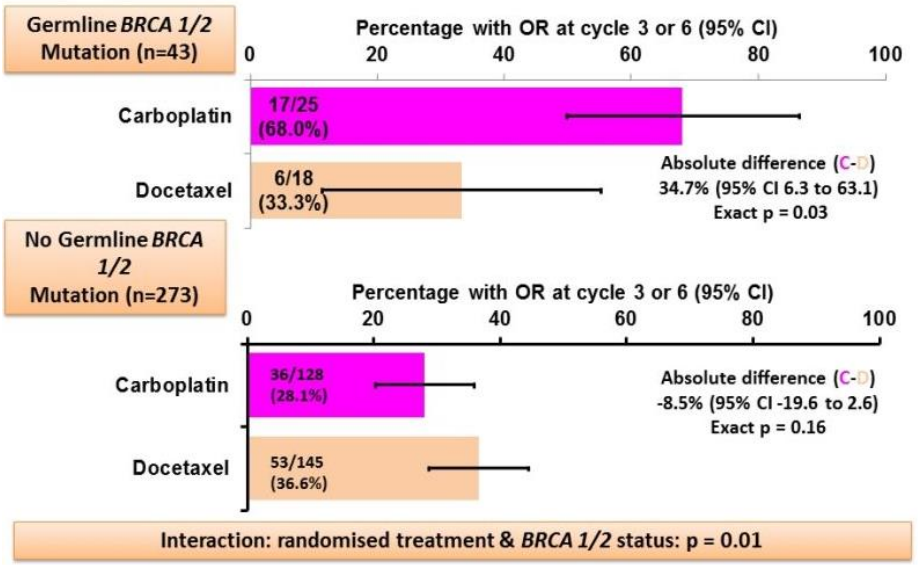
Presented By Melinda L. Telli, MD at 2013 Breast Cancer Symposium

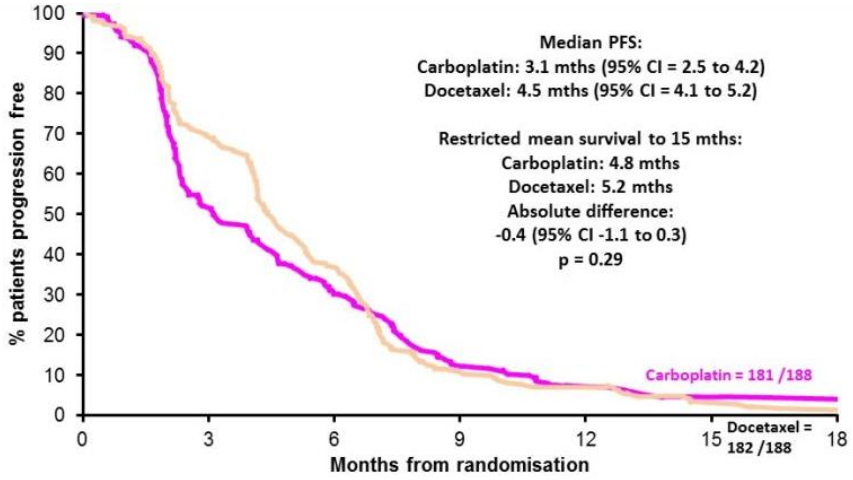
1st Line Therapy: Platinum Salts

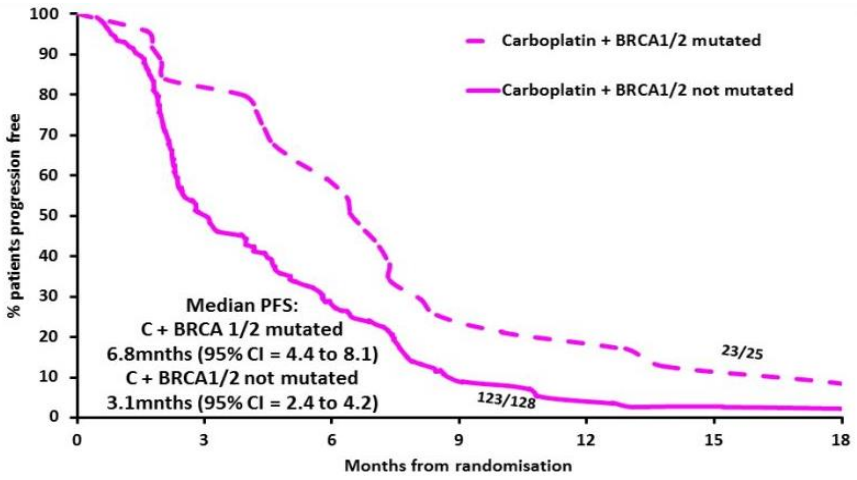
TNT Trial: CRUK/07/012



Tutt M et al., SABCS 2014

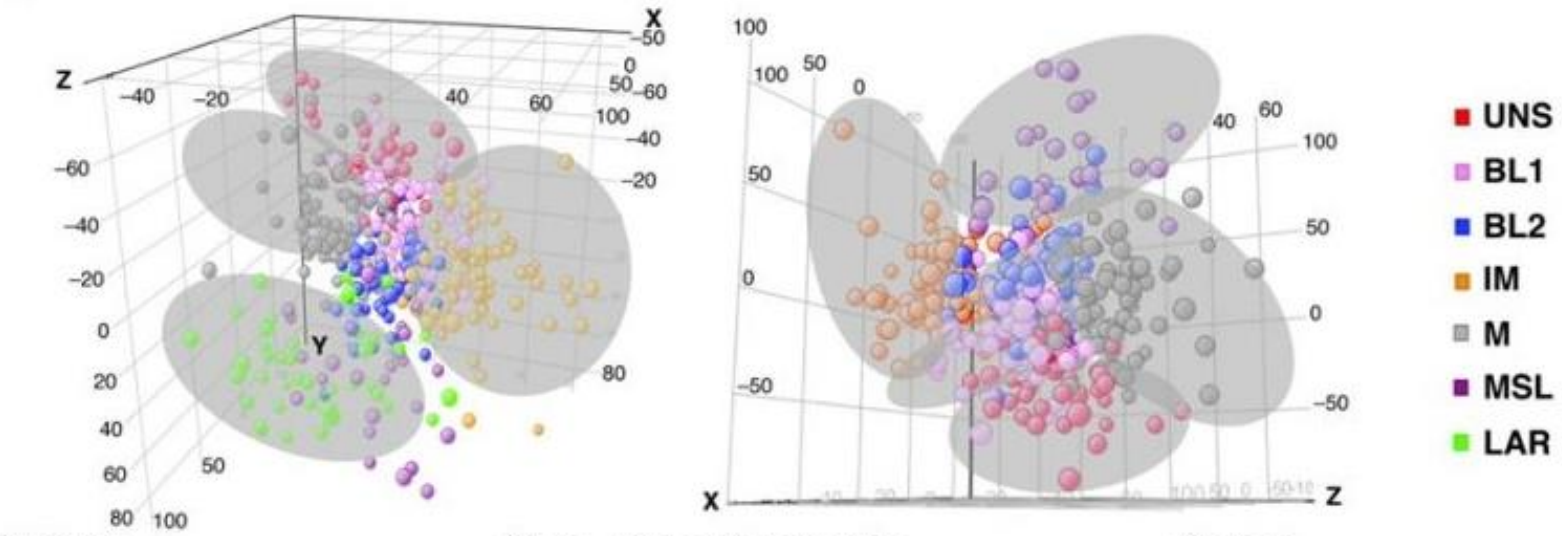






Tutt M et al., SABCS 2014

Clinical heterogeneity of TNBC:



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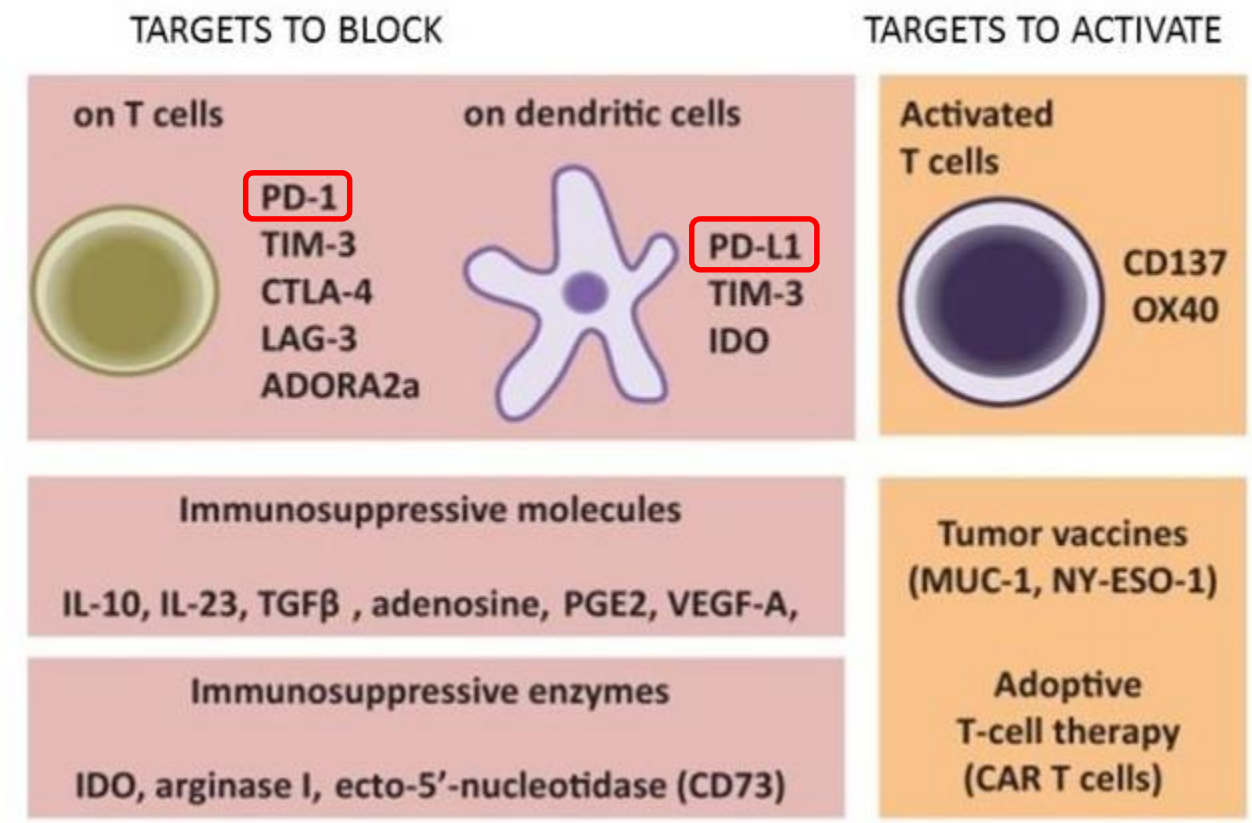
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehmann B et al., J Clin Invest 2011

Immunotherapy in TNBC:



Immune checkpoint inhibitors in metastatic TNBC PD-L1+/-:

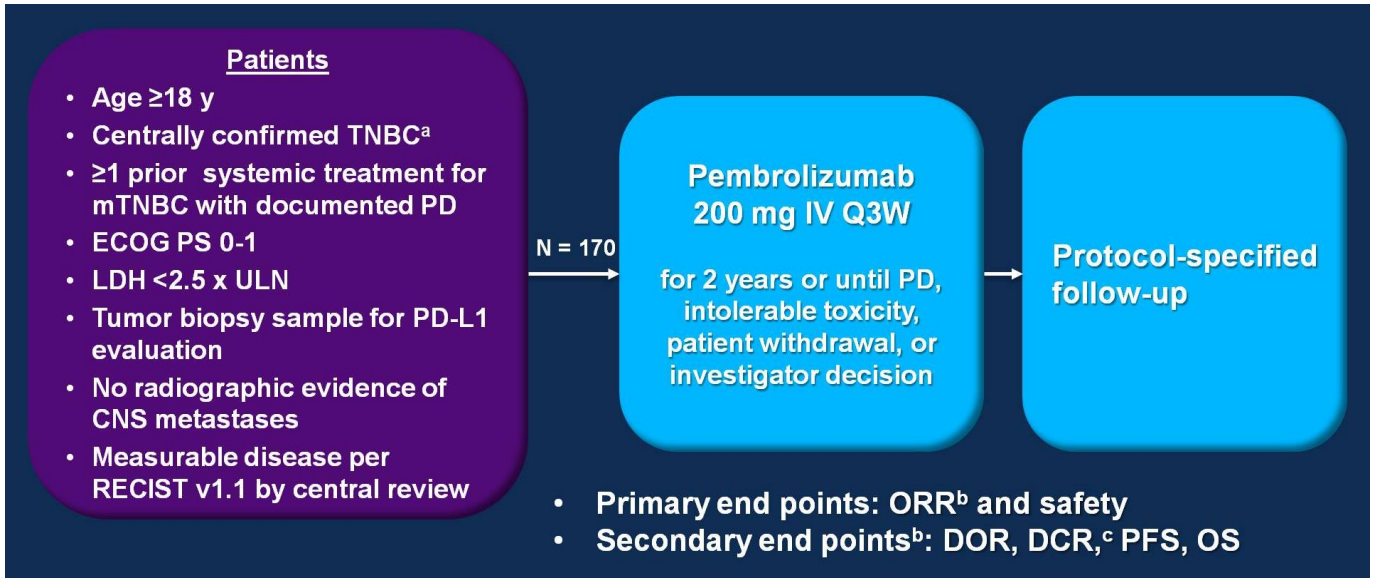
	Pembrolizumab	Atezolizumab	Avelumab
Phase	II	I	I
N	222	115	58
ORR	---	10%	5.2%**
ORR 1L	23.1%*	26%	---
ORR 2L+	4.7%	11%	---

*All PD-L1+

**50% received ≥ 2 previous lines of anticancer treatment

Phase 2 Study of Pembrolizumab Monotherapy for Previously Treated Metastatic Triple-Negative Breast Cancer: KEYNOTE-086 Cohort A

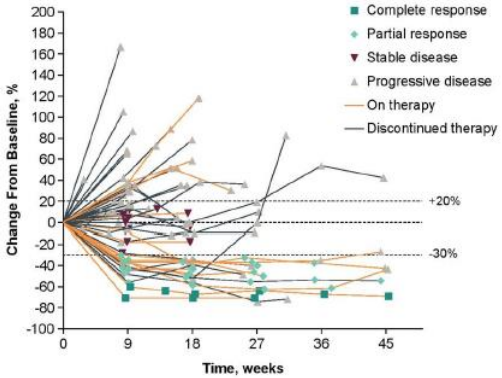
Sylvia Adams,[1] Peter Schmid,[2] Hope S. Rugo,[3] Eric P. Winer,[4] Delphine Loirat,[5] Ahmad Awada,[6] David W. Cescon,[7] Hiroji Iwata,[8] Mario Campone,[9] Rita Nanda,[10] Rina Hui,[11] Giuseppe Curigliano,[12] Deborah Toppmeyer,[13] Joyce O'Shaughnessy,[14] Sherene Loi,[15] Shani Paluch-Shimon,[16] Deborah Card,[17] Jing Zhao,[17] Vassiliki Karantza,[17] Javier Cortés[18]



Best Overall Response
(RECIST v1.1, Central Review)

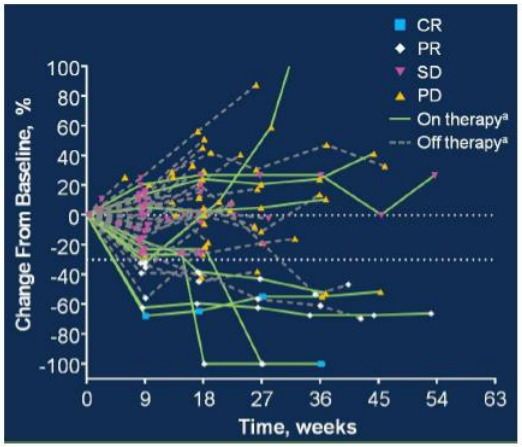
	Total Population[a] N = 170	PD-L1 Positive n = 105	PD-L1 Negative n = 64
ORR, n (%) [95% CI]	8 (4.7) [2.3-9.2]	5 (4.8) [1.8-10.9]	3 (4.7) [1.1-13.4]
DCR,[b] n (%) [95% CI]	13 (7.6) [4.4-12.7]	10 (9.5) [5.1-16.8]	3 (4.7) [1.1-13.4]
Best Overall Response, n (%)			
Complete response	1 (0.6)	1 (1.0)	0
Partial response	7 (4.1)	4 (3.8)	3 (4.7)
Stable disease	35 (20.6)	22 (21.0)	12 (18.8)
Progressive disease	103 (60.6)	66 (62.9)	37 (57.8)
Not evaluable[c]	5 (2.9)	2 (1.9)	3 (4.7)
Not able to be assessed[d]	19 (11.2)	10 (9.5)	9 (14.1)

KEYNOTE-086
Cohort B



Pembrolizumab single agent in TNBC PD-L1+, 1st line

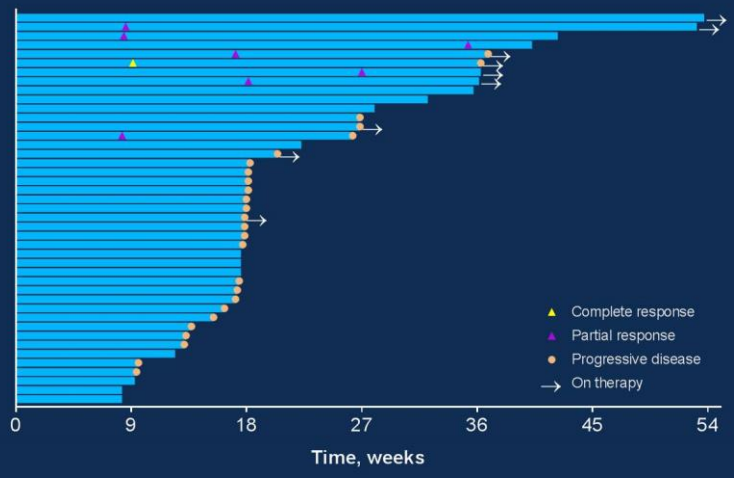
KEYNOTE-086
Cohort A



Pembrolizumab single agent in TNBC PD-L1+/-, 2+ line

ASCO Annual Meeting 2017

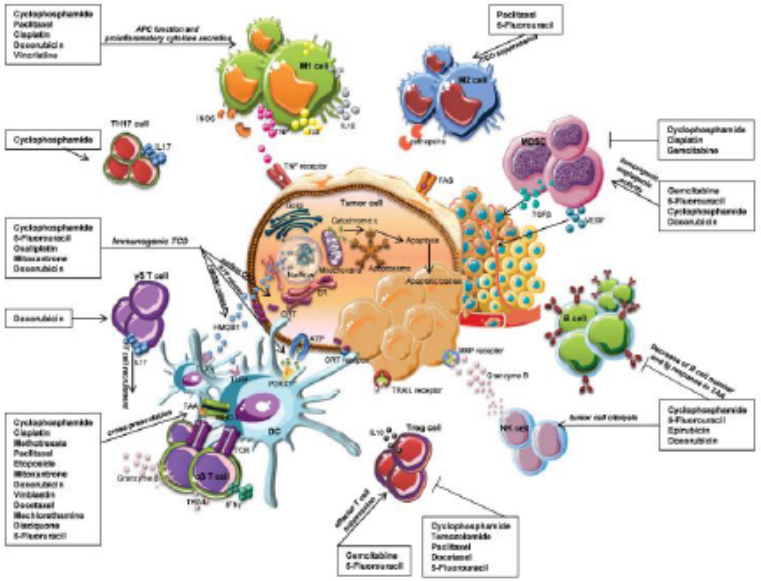
Time to Response and Duration of Response and Stable Disease (RECIST v1.1, Central Review)

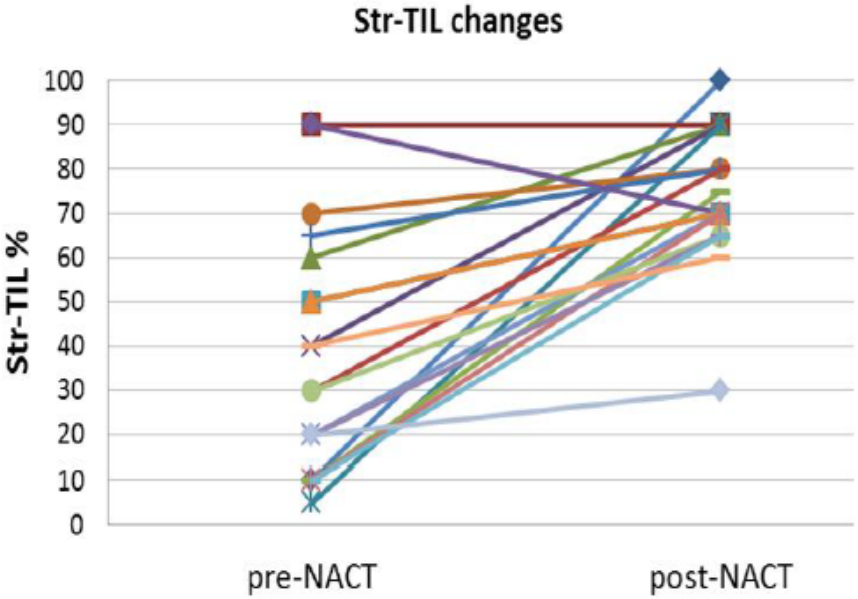


- Median TTR: 3.0 mo (range, 1.9-8.1)
- No subsequent progression
  - 0/1 with CR
  - 5/7 with PR
  - 12/35 with SD
- Median DOR: 6.3 mo (range 1.2+ to 10.3+)

- Pembrolizumab monotherapy showed durable antitumor activity in a subset of patients with heavily pretreated mTNBC
  - Activity appeared independent of tumor PD-L1 expression
  - ORR was numerically lower in patients with poor prognostic factors
  - Survival is promising, particularly in patients with CR, PR, or SD
- Activity may be greater in patients with less heavily pretreated disease
- Analyses of non–PD-L1 biomarkers, including TILs, are ongoing
- Treatment was well tolerated
- Randomized studies of pembrolizumab monotherapy and pembrolizumab-based combination therapy are ongoing for TNBC

Chemotherapy as a trigger for immune activation





Bracci L, et al. *Cell Death Differ 2014*

Dieci MV, et al. *Ann Oncol*. 2014

Courtesely by PF Conte

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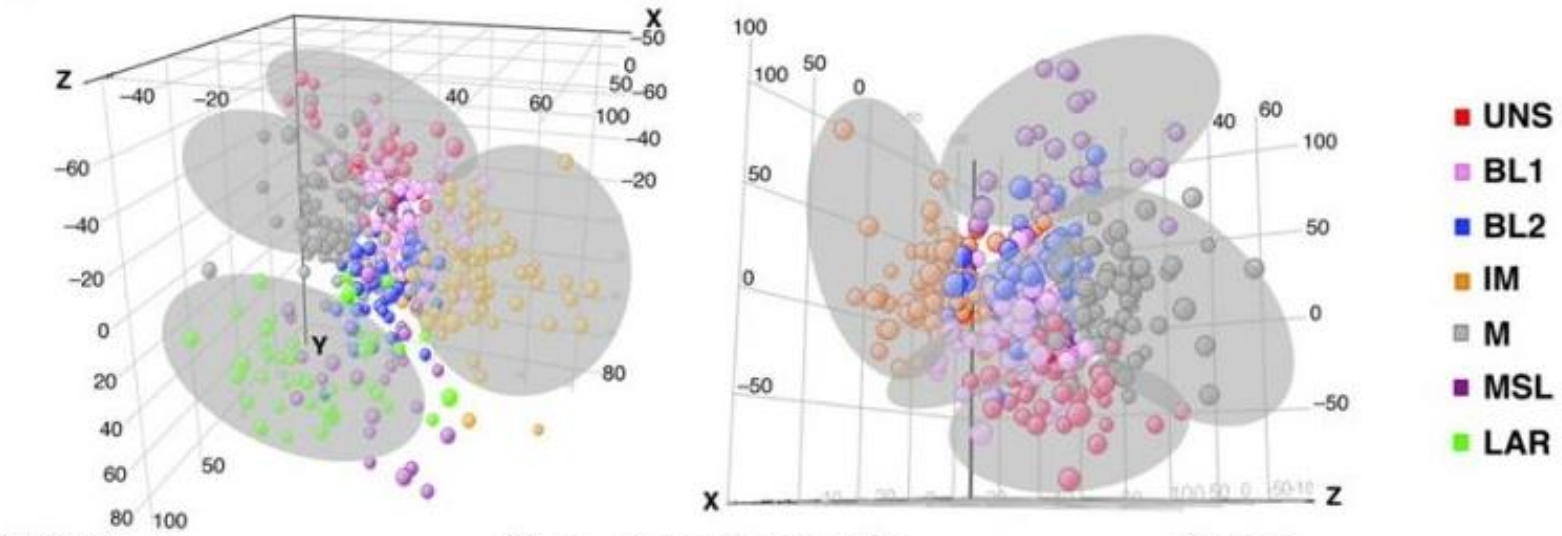

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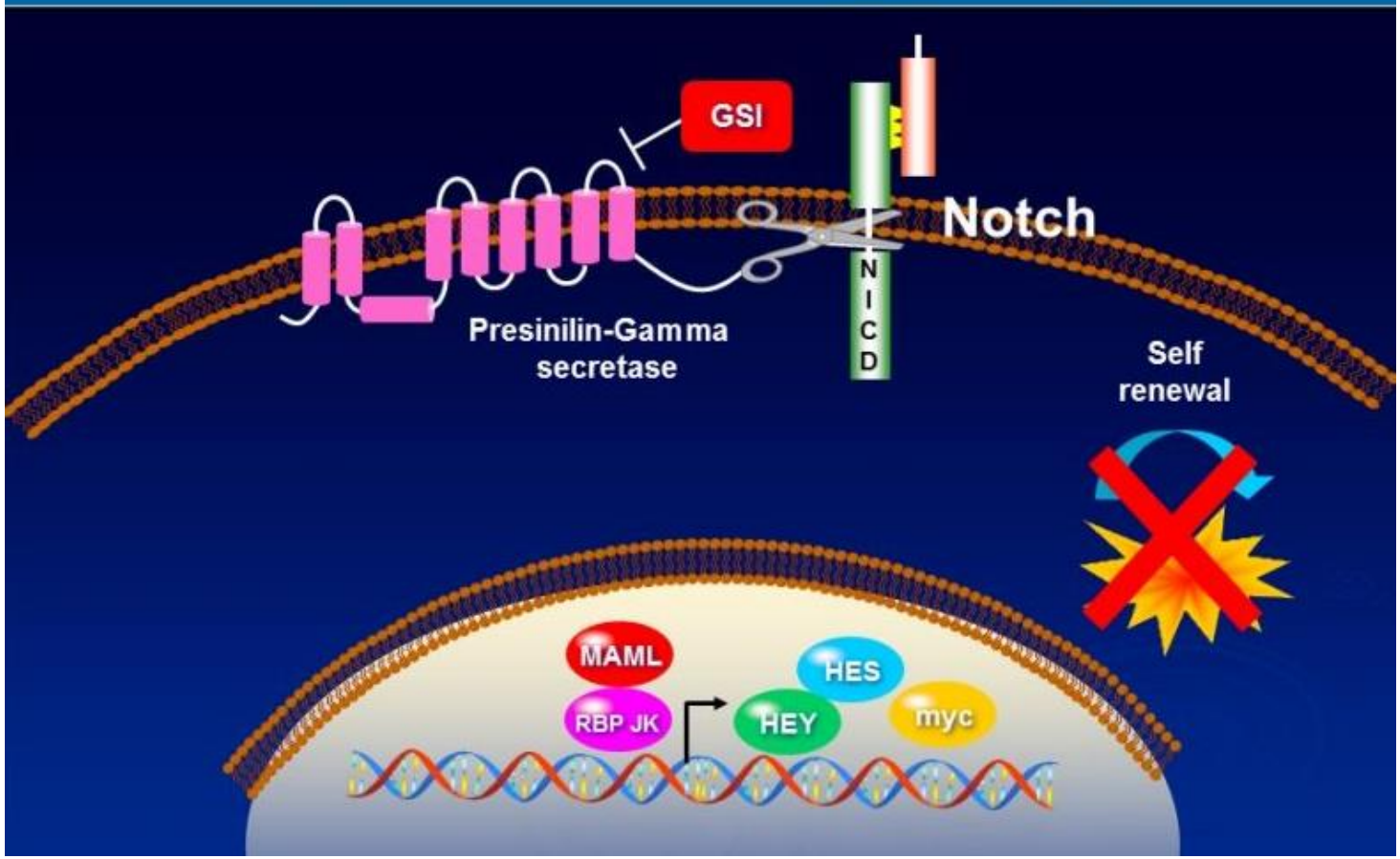
Lehmann B et al., J Clin Invest 2011

Gamma Secretase Inhibitors (GSI) block the notch pathway



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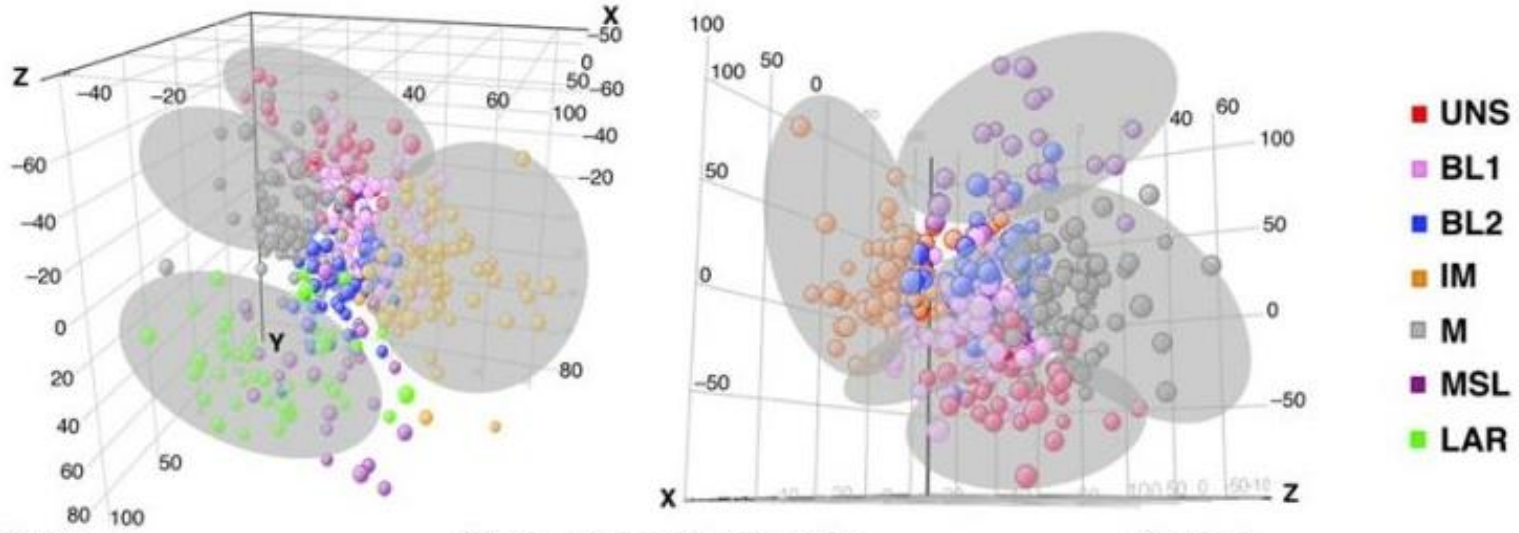

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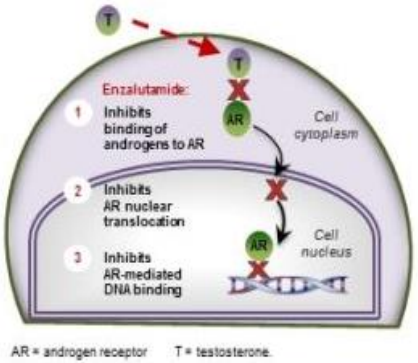
Lehmann B et al., J Clin Invest 2011
Lehmann B et al., J Clin Invest 2011

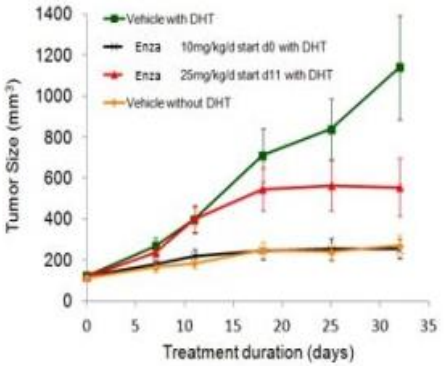
Enzalutamide shows early promise in AR+ metastatic TNBC:

Enzalutamide Inhibits AR Signaling in 3 Different Ways



AR = androgen receptor T = testosterone.

Preclinical Activity of Enzalutamide in an AR+ TNBC Cell Line (MDA-MB-453)



Eligibility

- "AR positive" advanced TNBC*
- ECOG-PS ≤ 1
- Any number of prior therapies permissible
- Evaluable bone-only disease allowed
- No CNS metastases
- Sufficient tissue to enable biomarker discovery

Endpoints

Primary
- CBR16

Other Key Endpoints
- CBR24
- Response rate
- PFS
- OS
- Safety
- AR biomarker discovery

Treatment

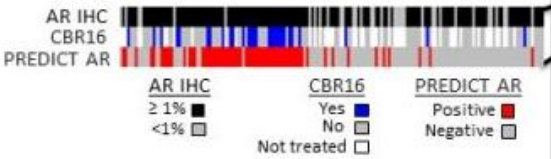
Enzalutamide 160 mg/day orally

Stage 1
≥ 3 of 26 Evaluable have CBR16 "Go" to Stage 2

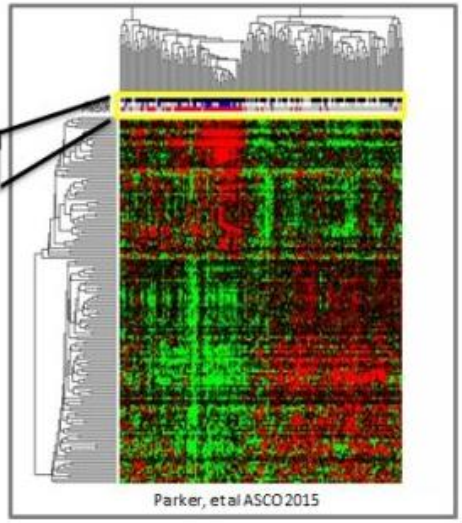
Stage 2
≥ 9 of 62 Evaluable have CBR16 Rejection of H_0

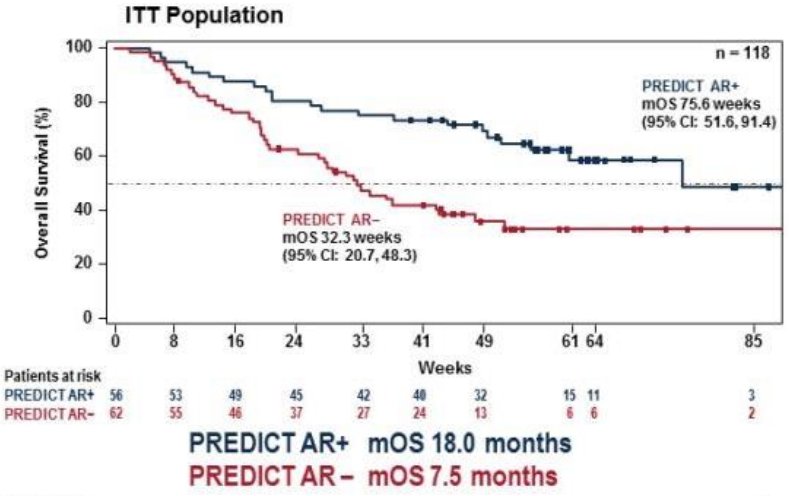
Traina TA et al., ASCO Annual Meeting 2017

- Hierarchical clustering according to biology



- Responders clustered within a recognized and distinct pattern that includes AR[1-5]
  - 521 genes significantly different in responders at 1% false discovery rate
- A diagnostic test (PREDICT AR) was created and validated





PREDICT AR+ mOS 18.0 months

PREDICT AR – mOS 7.5 months

Traina TA et al., ASCO Annual Meeting 2017

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Grazie a tutti per l'attenzione

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