IEO
Istituto Europeo di Oncologia

Systemic therapy of triple negative advanced breast cancer

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Division of Early Drug Development

IBCSG

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

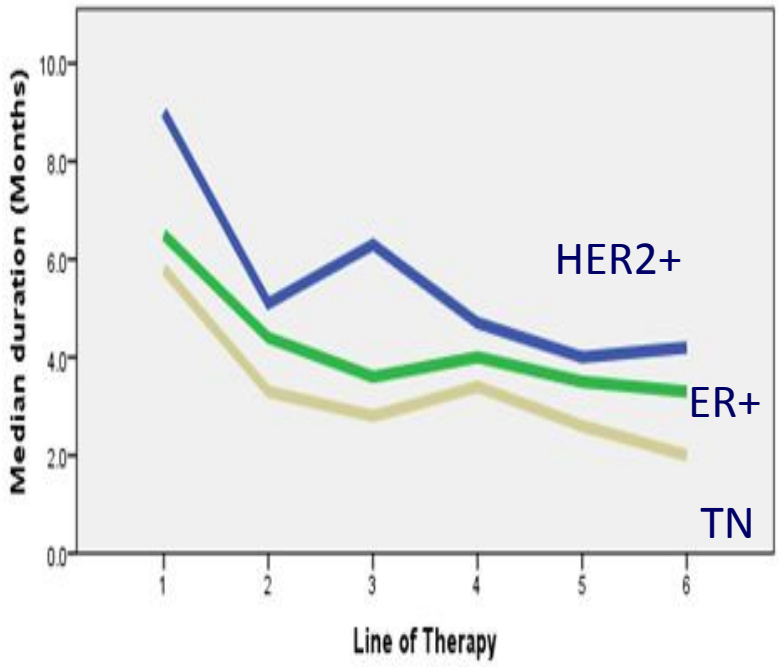
BIG against breast cancer

Outline

- State of the Art in the management of TN advanced breast cancer
- Dealing with heterogeneity of TN breast cancer
- Targeting subtypes and clinical trials
- Targeting pathways and immune-system

TNBC in the real life

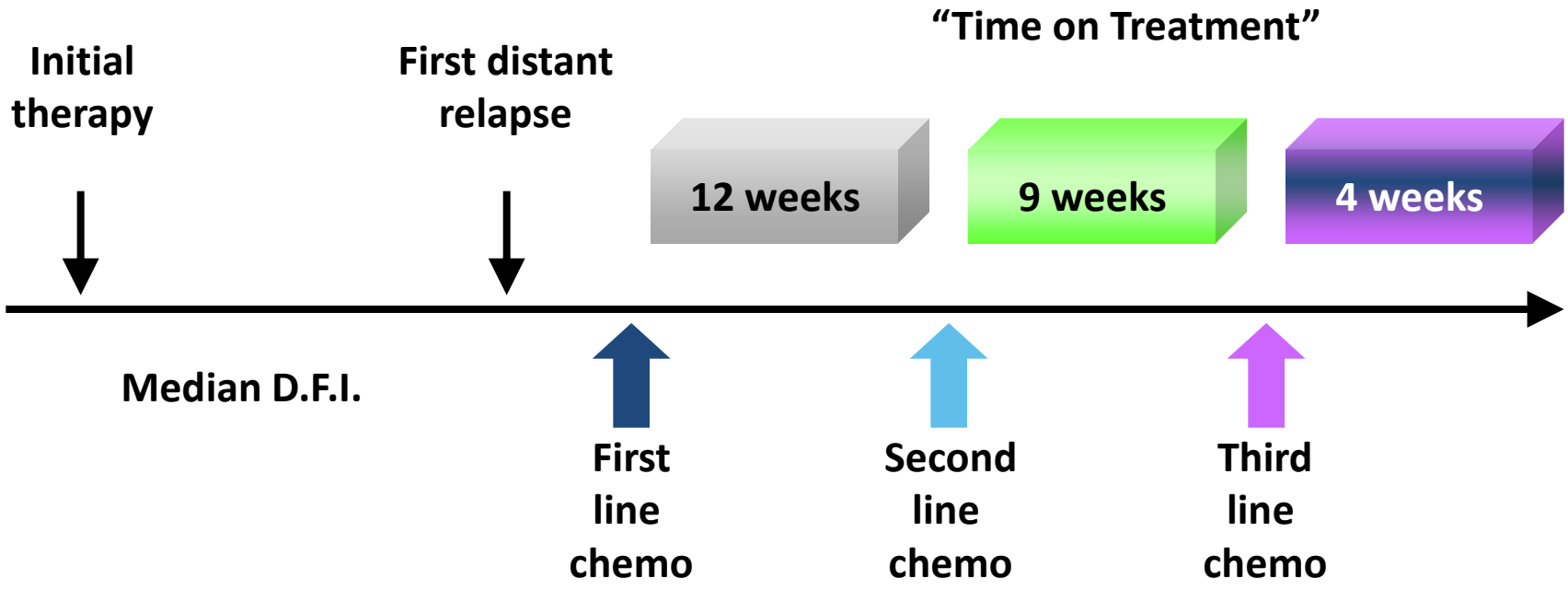
Line of CT	Total	TNBC	ER+	HER2+
1	205	45 (100%)	102 (100%)	58 (100%)
2	159	36 (80%)	79 (77%)	44 (76%)
3	122	26 (58%)	56 (55%)	69 (52%)
4	81	13 (29%)	38 (37%)	30 (52%)
5	56	8 (18%)	24 (24%)	24 (40%)
6	34	6 (13%)	9 (9%)	19 (33%)



Patients with TN Disease Received Fewer Treatments and Stayed on Each Treatment Regimen For A Shorter Interval

Seah et al, ASCO 2012

Median PFS to Chemotherapy in TNBC



Taxanes for TNBC

Retrospective subgroup analyses
Placebo arm data

Trial	Phase	N	Setting	Taxane	Outcome in TNBC
CALGB 9342[1]	III	44	First- or second-line metastatic	Paclitaxel weekly and q3w	ORR = 26% TTF = 2.8 months OS = 8.6 months
ECOG 2100[2]	III	110	First-line metastatic	Paclitaxel weekly	ORR = 11.7%[4] PFS = 5.3 months
AVADO[3]	III	52	First-line metastatic	Docetaxel q3w	ORR = 23.1%[4] PFS = 6.1 months

1. Harris, et al. Br Cancer Res 2006; 2. O'Shaughnessy, et al. SABCS 2009 3. Glaspy, et al. EBCC 2010; 4. Roche data on file

Capecitabine for TNBC

Retrospective subgroup analyses
Placebo arm data

Trial	Phase	N	Setting	Treatment	Outcome in TNBC
Pooled analysis[1]	III	208	Third-line or greater metastatic	Capecitabine	ORR = 15% PFS = 1.7 months
RIBBON-1[2]	III	50	First-line metastatic	Capecitabine + placebo	PFS = 4.2 months

1. Rugo, et al. SABCS 2008 2. Glaspy, et al. EBCC 2010

Platinum salts for TNBC

Study	Agent	Multiple doses	N	First Line	ORR(%)	PFS
BALI-1	Cisplatin	75 mg/m^2 q3w	48	73%	6 (10.3%)	1.5 m
BSI-201	Carbo - Gem	AUC 2 d1, 8 q3w 1000 mg/m^2 d1, 8	62	59%	20 (32%)	3.3 m
TBCRC 001	Carbo – Cetuximab	AUC 2 d1, 8, 15 q4w	71	46%	13 (18%)	2.0 m

Targeting Triple Negative

- Bevacizumab beyond progression
  - TANIA
    (*von Minckwitz et al, Lancet Oncol 2014)*
- Manteinance with capecitabine and bevacizumab following response to Bevacizumab
- IMELDA (*Gligorov et al, Lancet Oncol 2014)*

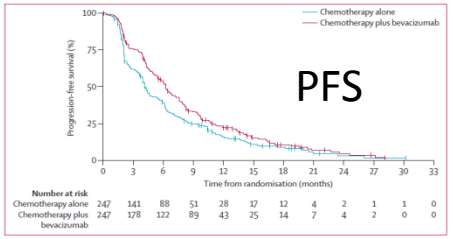
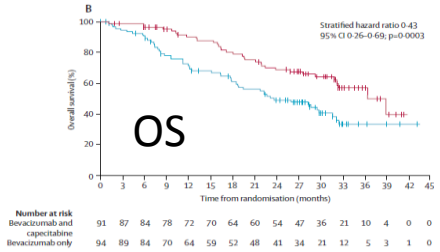


Figure 2: Second-line progression-free survival



Ideal drug

Efficacy (ORR, pFS)

Safety profile

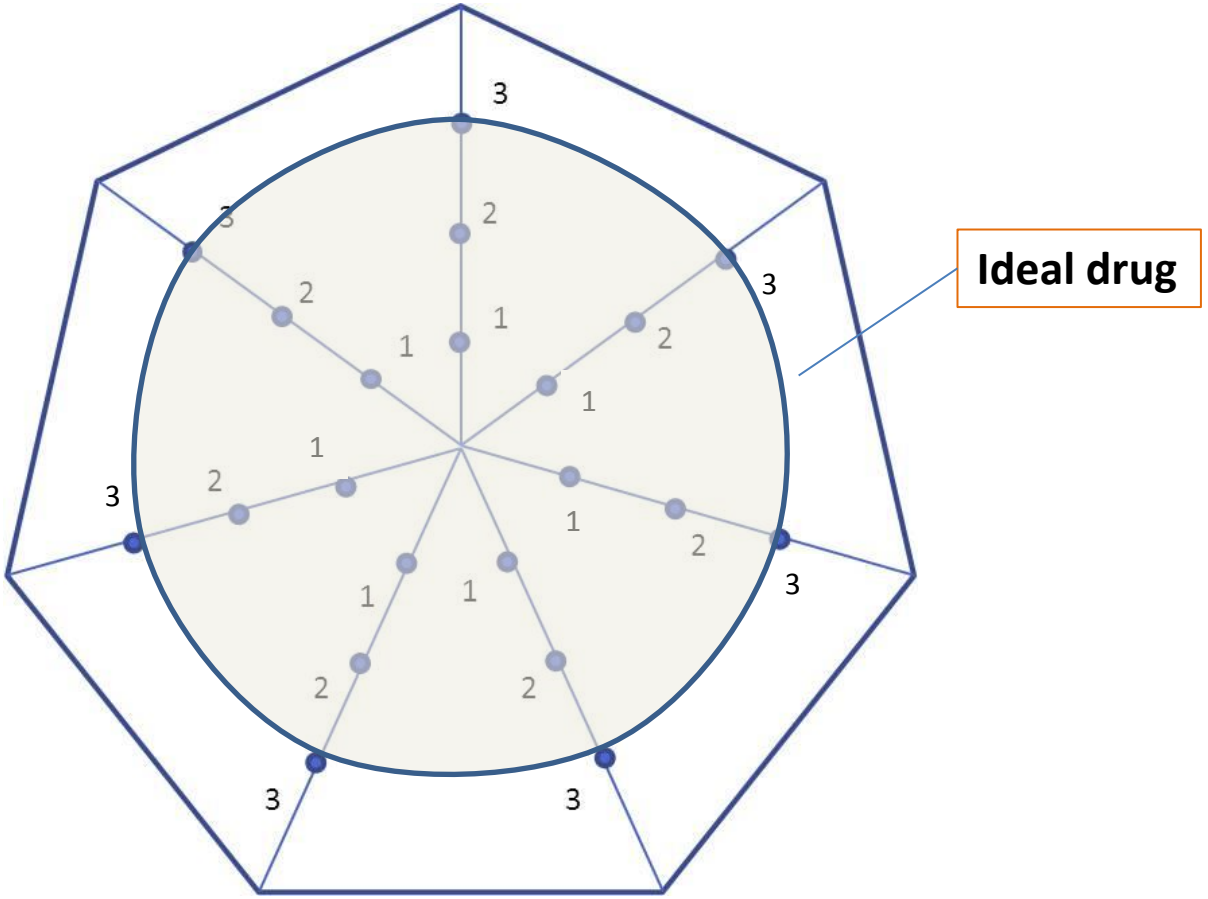
Impact on QoL

Comorbidity

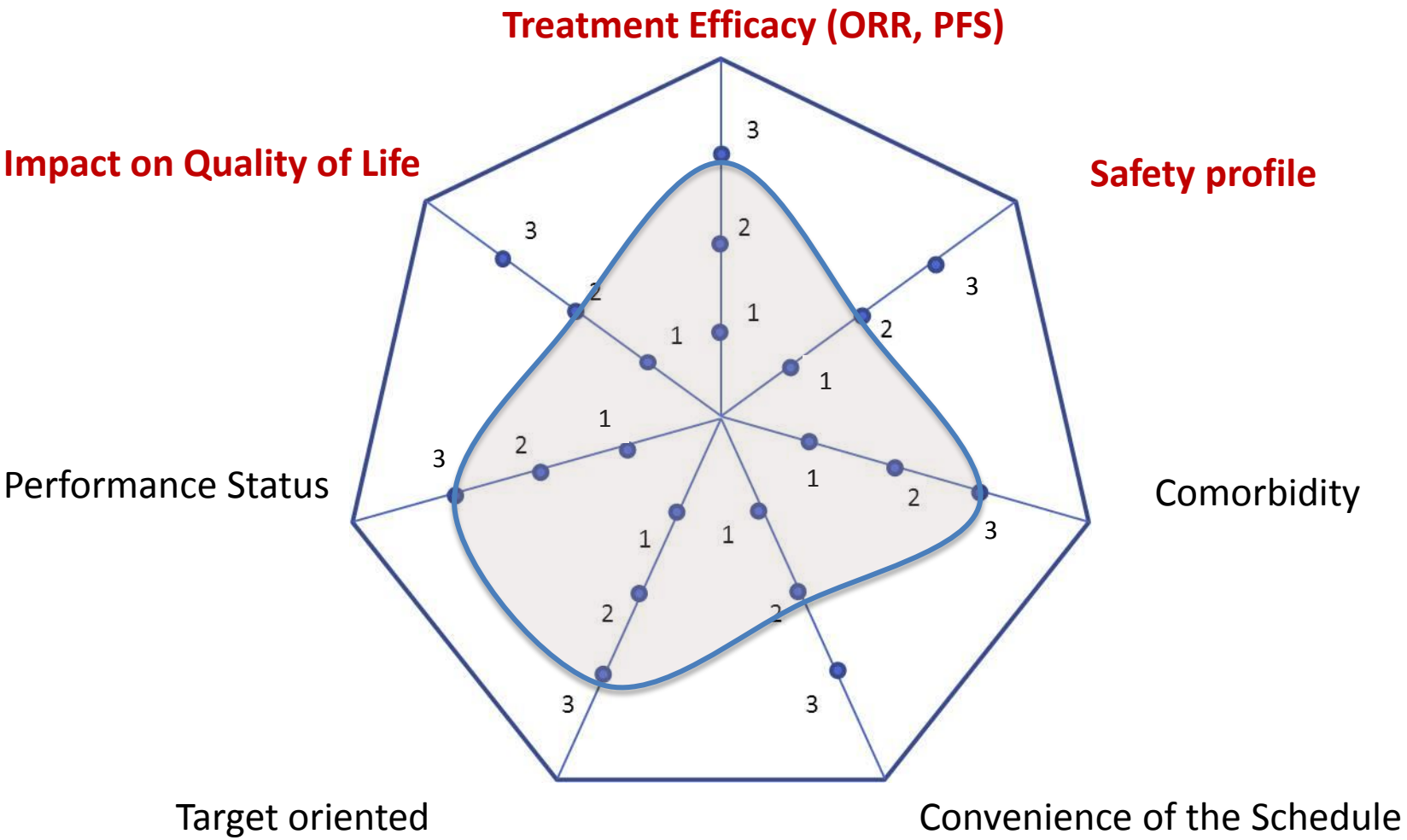
Performance status

Target oriented

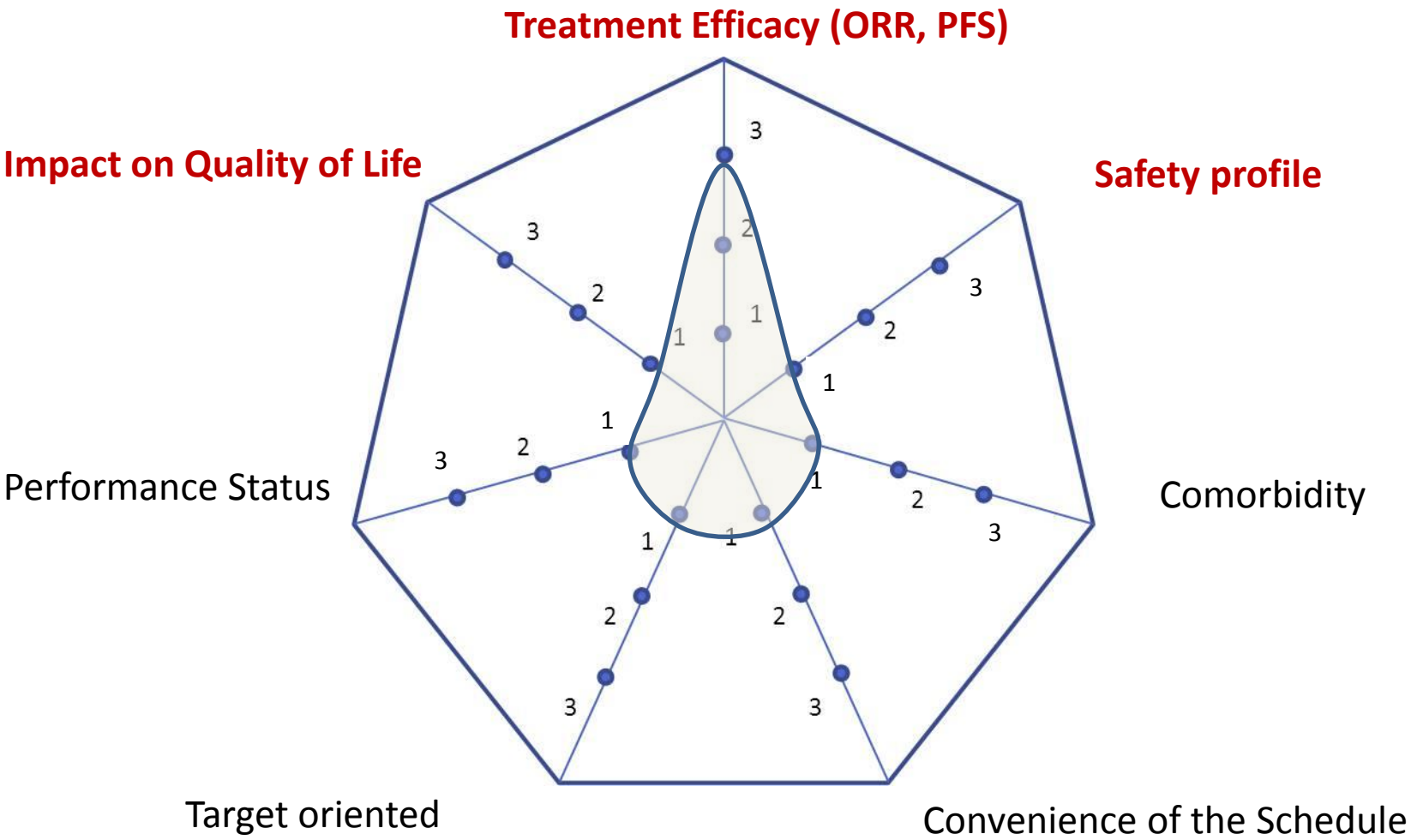
Schedule



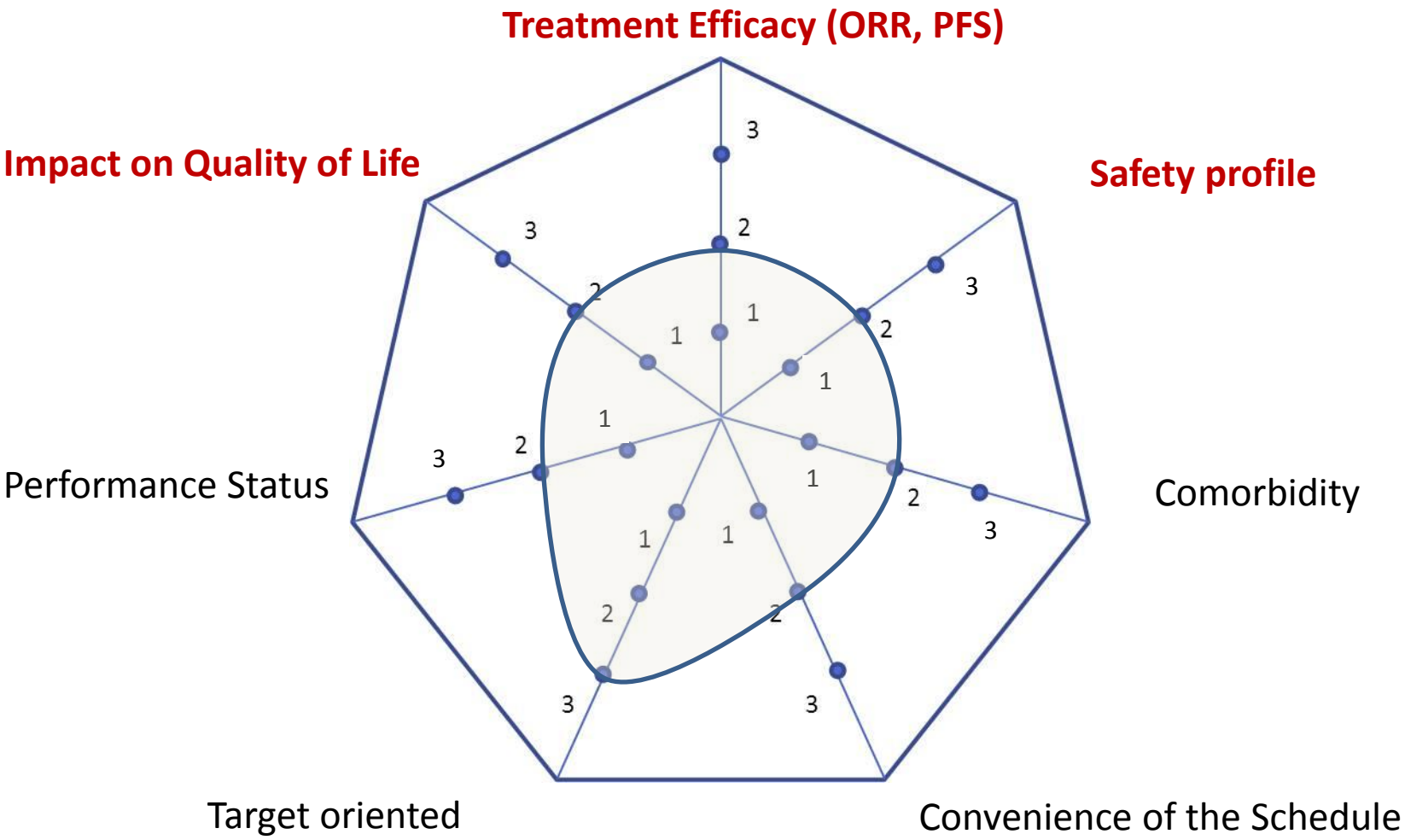
Real life therapy



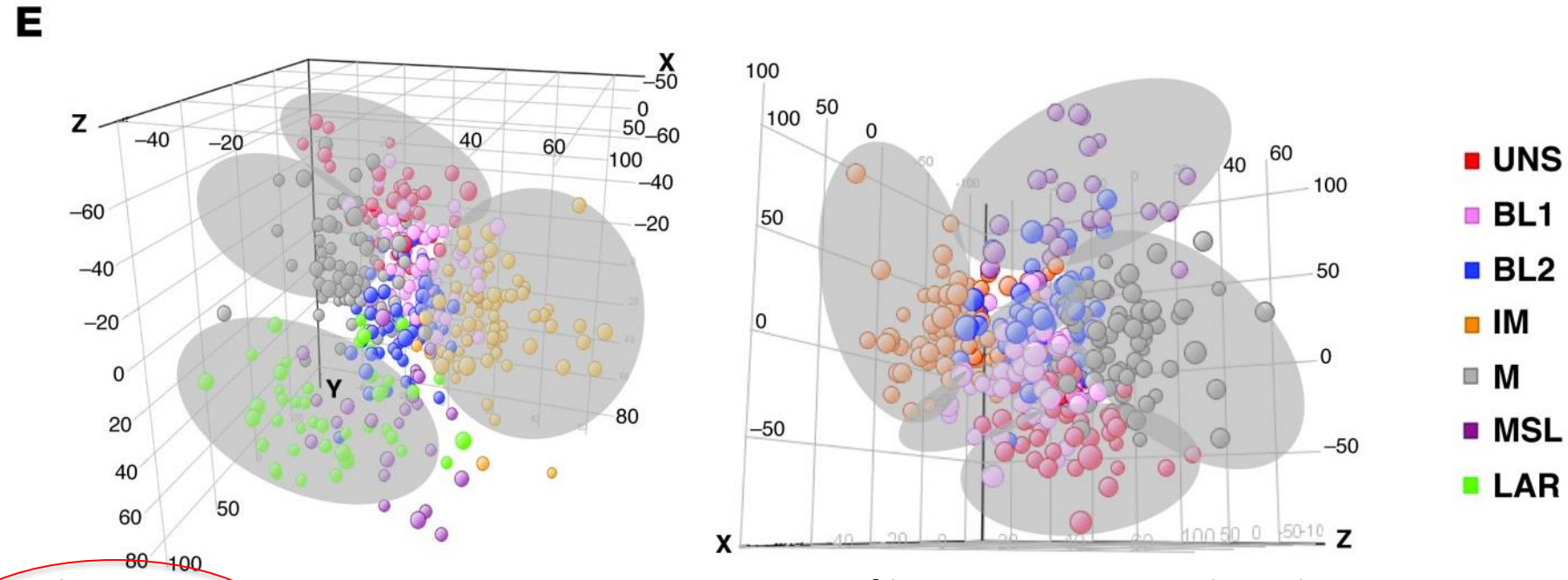
Real life therapy



Real life therapy



Clinical Heterogeneity of TNBC



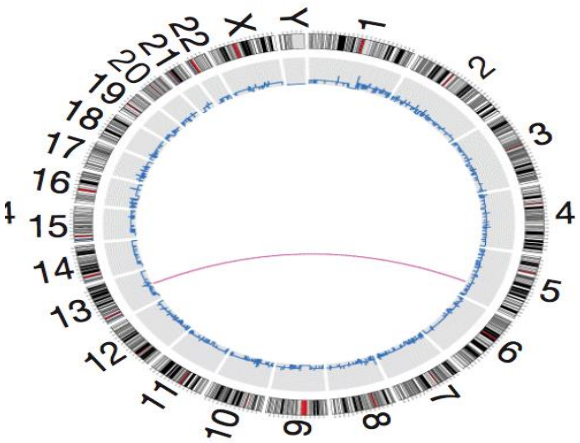
Subtype	Gene expression profile	Clinical
Basal-like 1	high Ki-67; DNA damage response	BRCA-associated
Basal-like 2	GF pathways	Higher pCR
Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

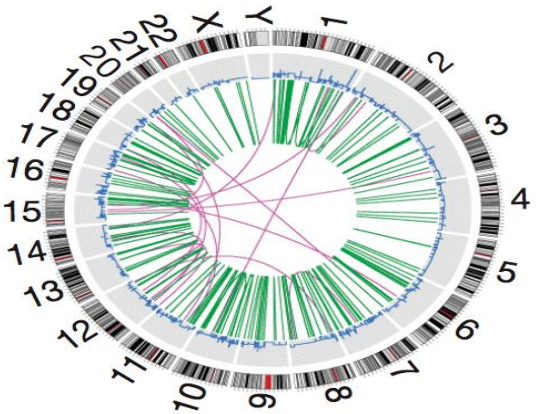
Basal like 1 TNBC

- **Triple negative breast cancer and BRCA-mutations**
  - **Clinical behavior**
  - **Genomic instability**

PD3667a
ER+ PR+ ERBB2−



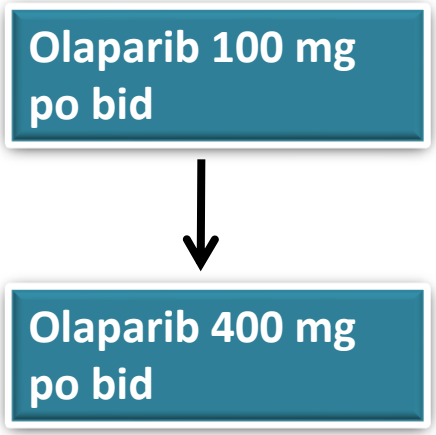
PD3664a
ER− PR− ERBB2−



Stephens et al *Nature* 2009
vol. 462 (7276) pp 1005

Basal like 1 TNBC

54 Stage IV **women**
- Inherited BRCA1/2



- **Primary endpoint = Objective response rate**
- **Secondary endpoints:**
  - **% tumor change**
  - **Progression-free survival**

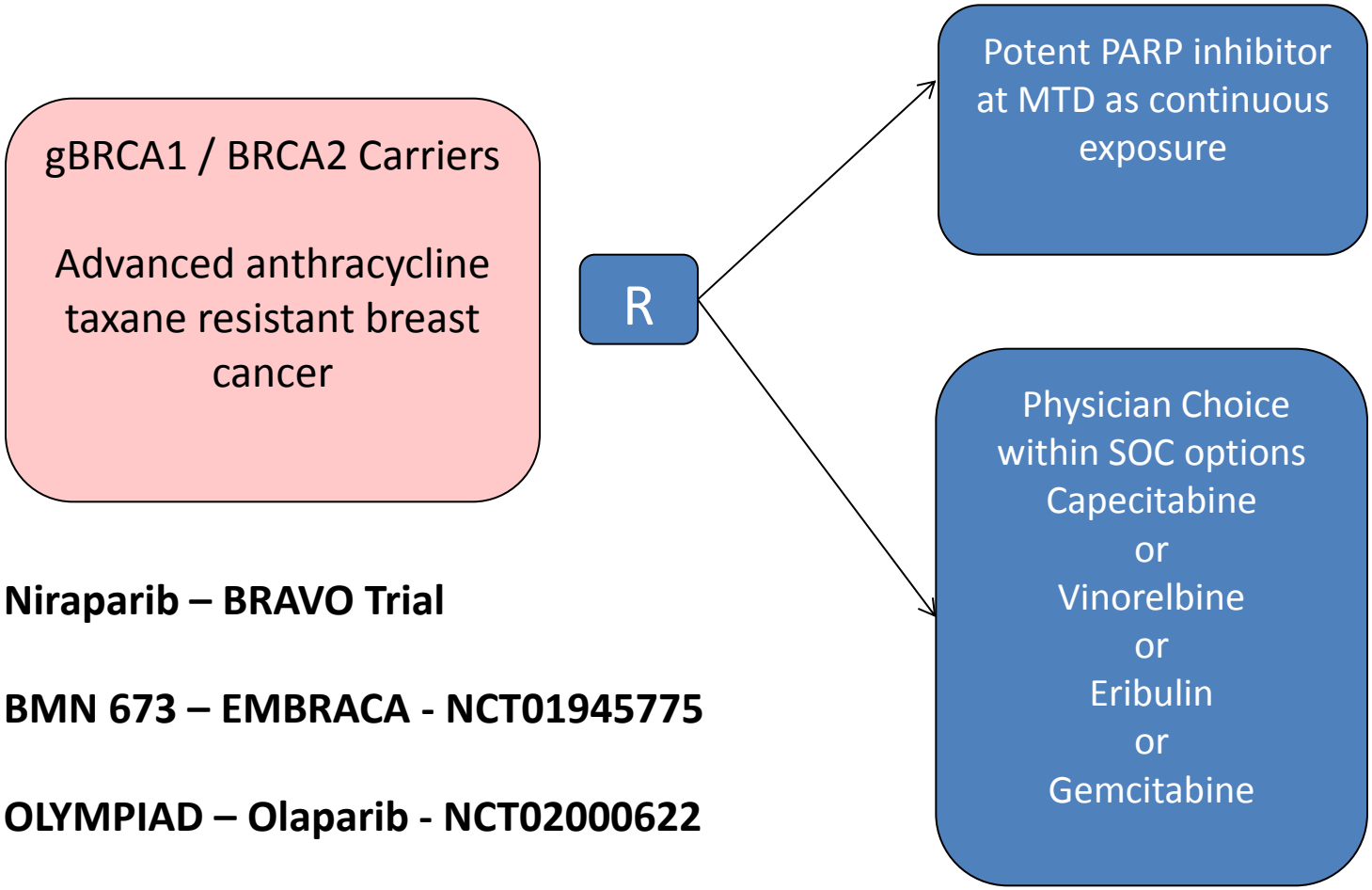
Demographics	400 bid (n=27)
Prior chemo	3 (1-5)
BRCA1	67%
Triple negative	50%

Efficacy (400 bid) (n=27)	n (%)
Overall response rate	11 (41)
CR	1 (4)
PR	10 (37)

- **30% reduced doses, 30% delayed doses for toxicity**

Tutt A et al, Lancet 2011

PARP inhibitors in metastatic TNBC



Primary endpoint PFS

Niraparib – BRAVO Trial

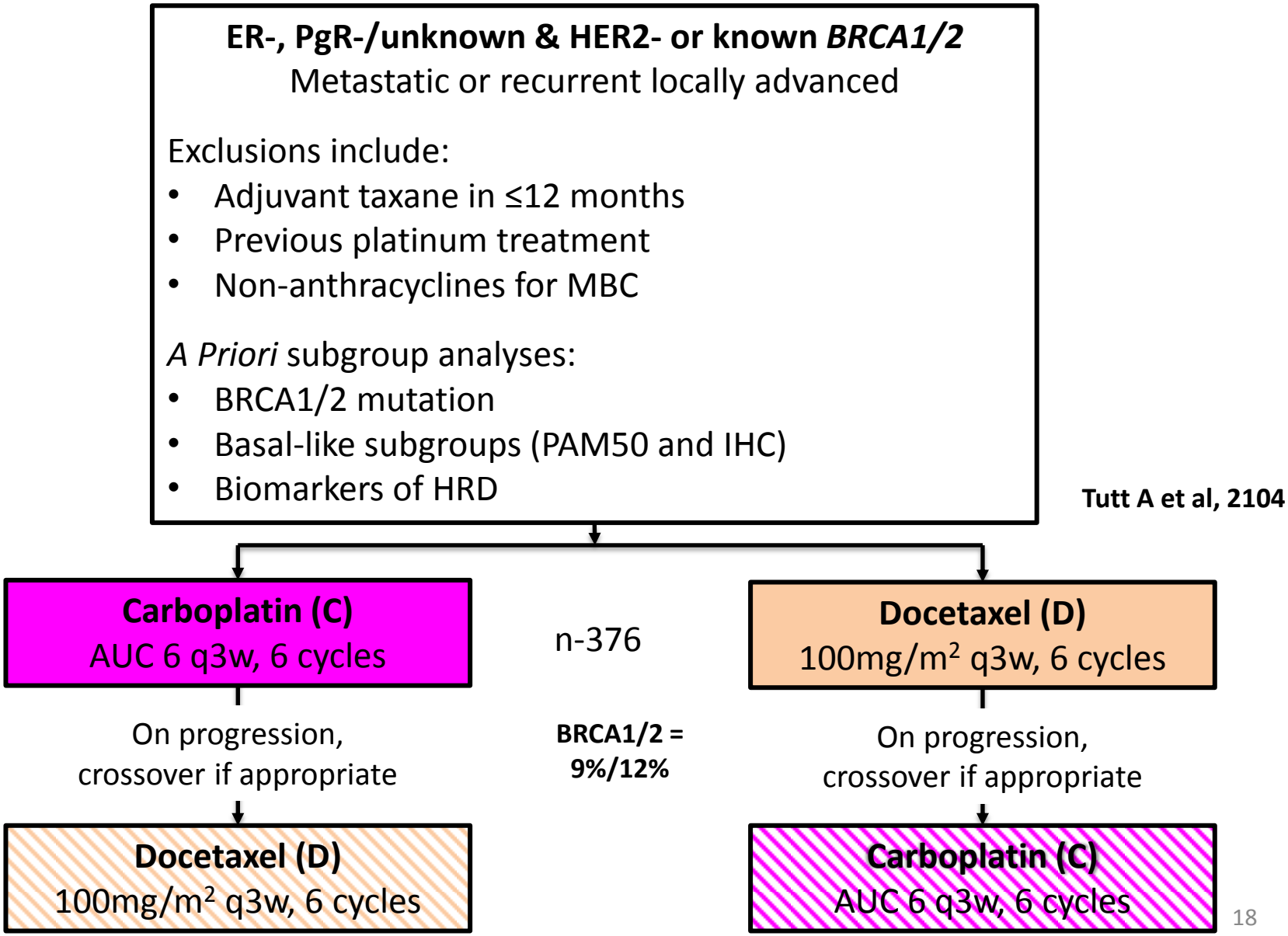
BMN 673 – EMBRACA - NCT01945775

OLYMPIAD – Olaparib - NCT02000622

PARP inhibition in basal like 1

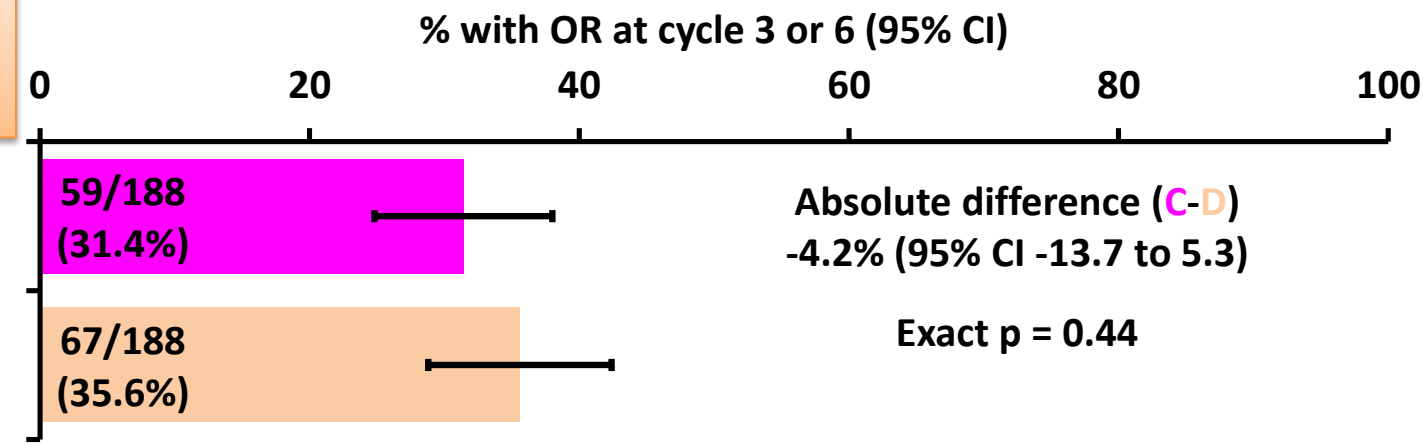
Agent	Company	Route	Current trials
Rucaparib	Clovis	IV/oral	BRCA+ Post neoadjuvant TNBC + cisplatin
Olaparib	AstraZeneca	Oral	BRCA+
Veliparib	Abbott	Oral	BRCA+, TNBC Temodal Paclitaxel CBDCA
Iniparib	BiPar/ Sanofi Aventis	IV	Dose escalation
LT673	Biomarin	Oral	-
INO-1001	Inotek/Genentech	IV	
MK4827	Merck	Oral	
CEP 9722	Cephalon	Oral	
E7016	Eisai/MGI Pharma	Oral	

Cisplatin in basal like 1

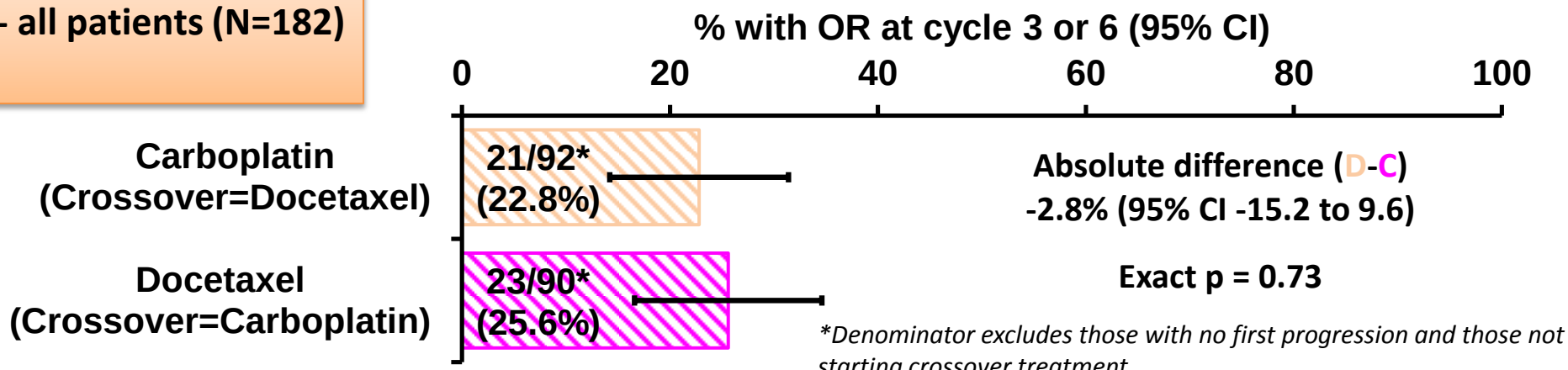


Cisplatin in basal like 1

Randomised treatment - all patients (N=376)



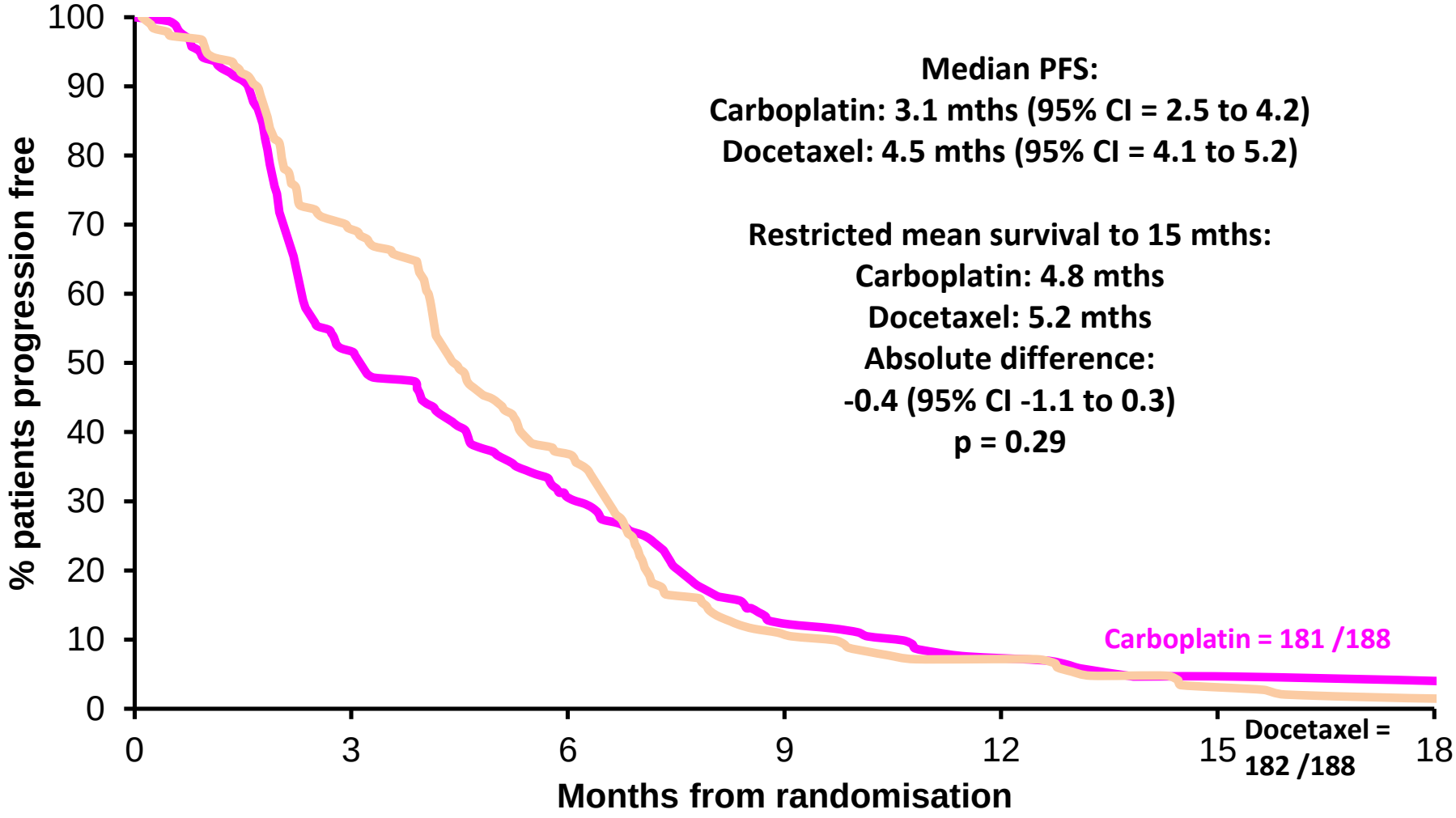
Crossover treatment - all patients (N=182)



**Denominator excludes those with no first progression and those not starting crossover treatment*

Tutt, SABCS 2014

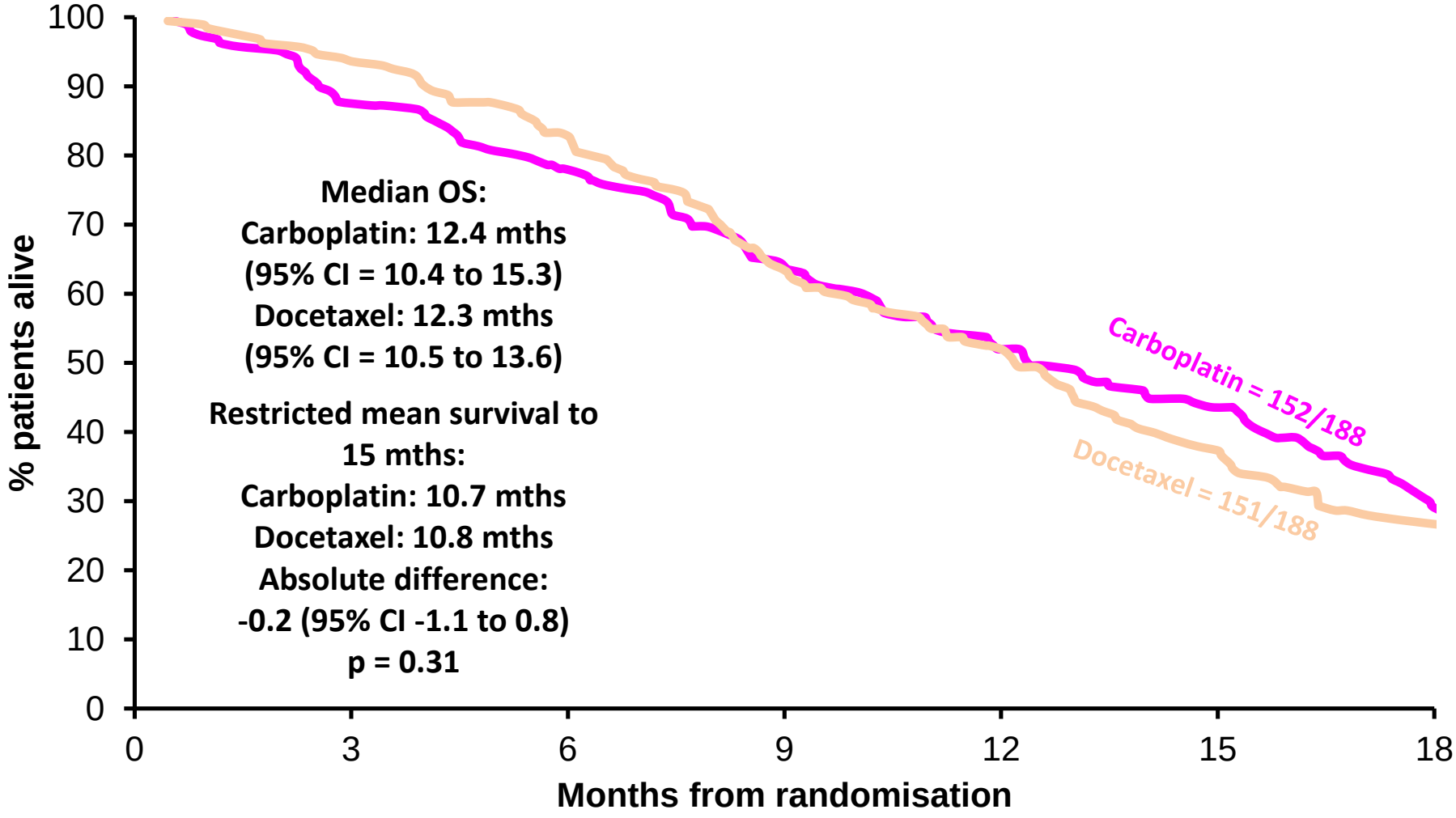
Cisplatin in basal like 1



Number of events/at risk

C:	*0/188*	*90/98*	*40/56*	*32/22*	*9/13*	*5/8*	*0/7*
D:	*0/188*	*57/130*	*60/69*	*48/20*	*7/13*	*6/5*	*2/3*

Cisplatin in basal like 1

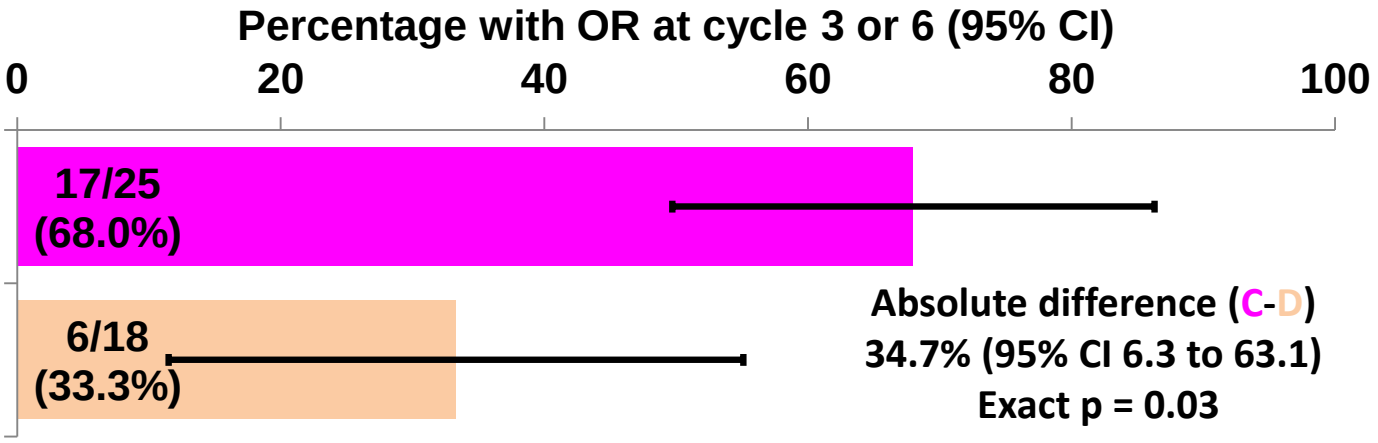


Number of events/at risk

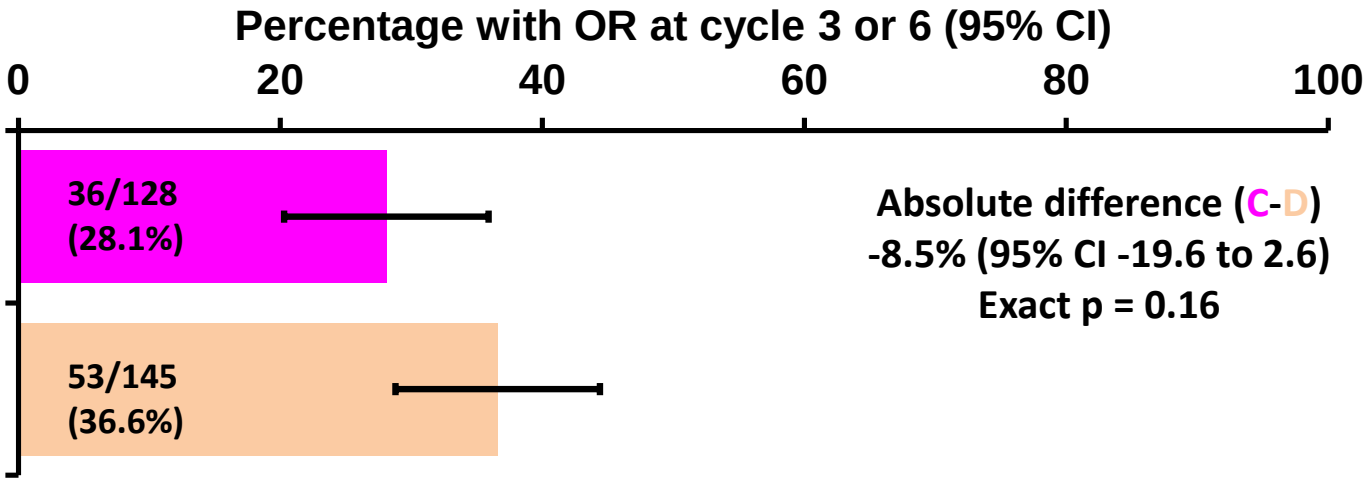
C:	*0/188*	*23/165*	*18/141*	*24/114*	*22/89*	*14/71*	*22/44*
D:	*0/188*	*11/176*	*20/151*	*35/110*	*19/85*	*23/58*	*16/39*

Cisplatin in basal like 1

Germline *BRCA 1/2* Mutation (n=43)

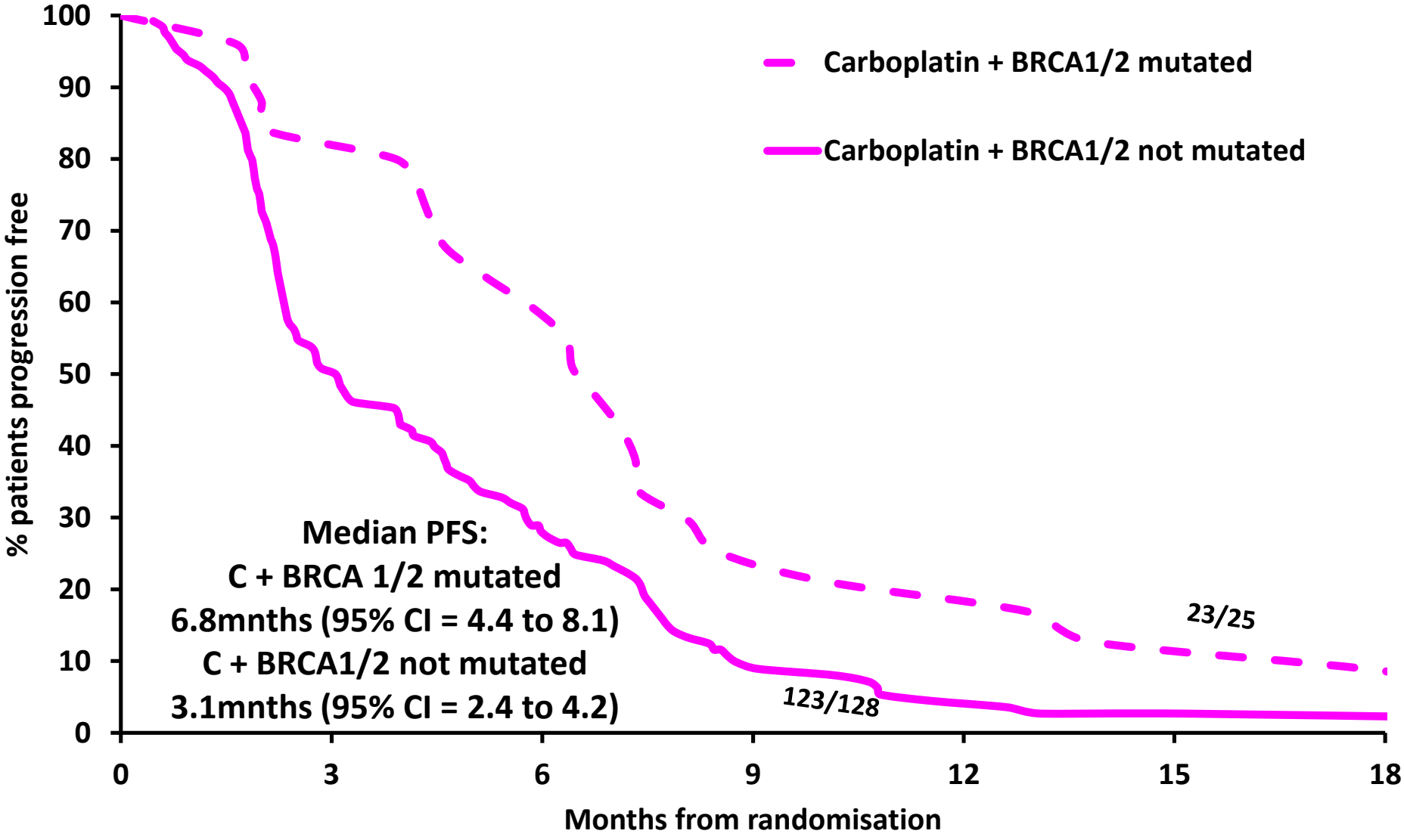


No Germline *BRCA 1/2* Mutation (n=273)



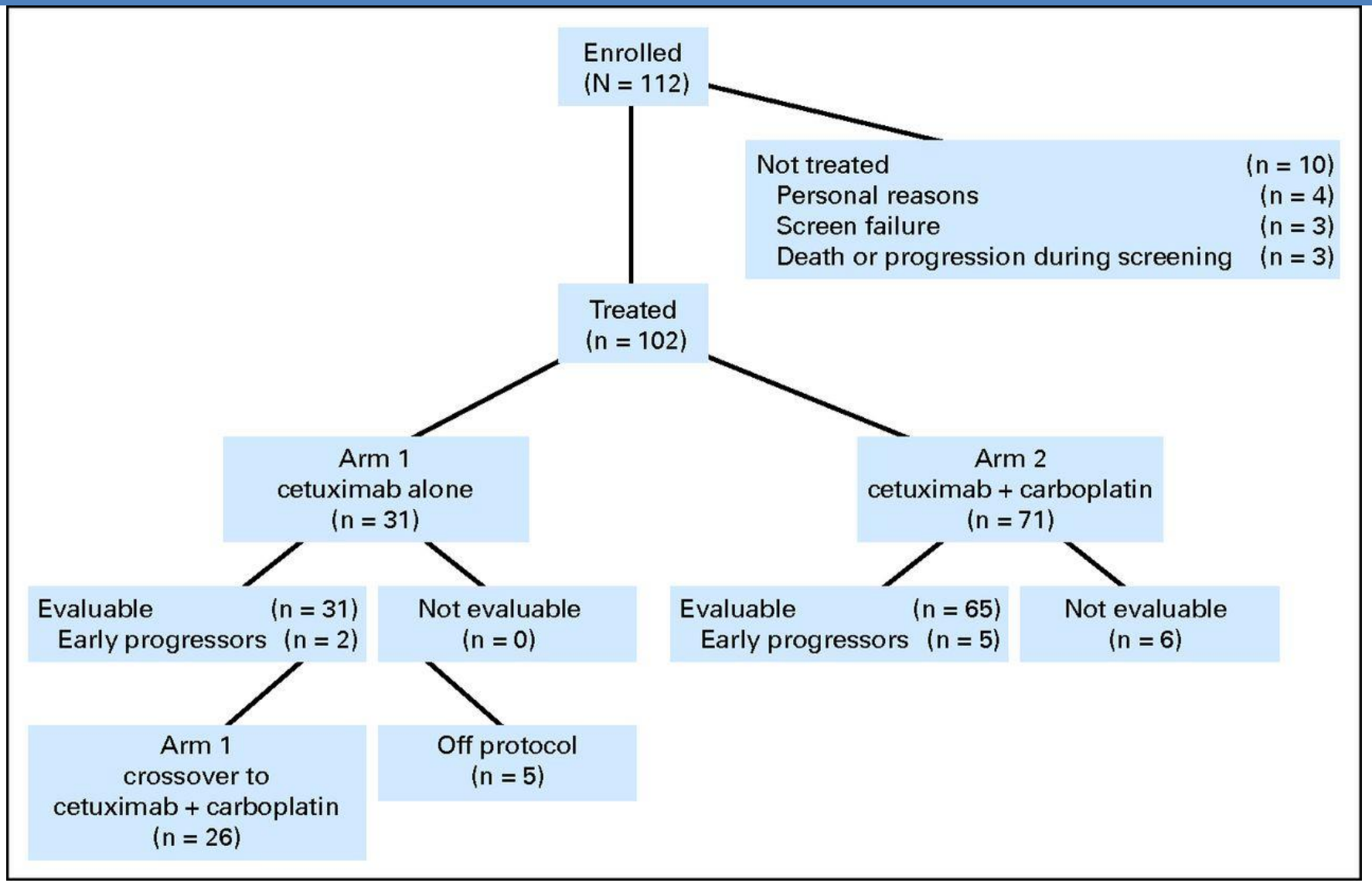
Interaction: randomised treatment & *BRCA 1/2* status: p = 0.01

Cisplatin in basal like 1



Tutt, SABCS 2014

Basal like 2:Growth factor signalling



Lisa A. Carey et al. JCO 2012;30:2615-2623

Basal like 2:Growth factor signalling

Table 2. Response Within Treatment Arms and to Combined Therapy in Basal-Like Disease

	Arm 1 (n = 31)		Arm 1B (n = 25)		Arm 2 (n = 71)		C + Cb* (n = 51)	
	C Only		C + Cb†		C + Cb		Basal-Like Tumors‡	
Response	No.	%	No.	%	No.	%	No.	%
CR	0	0	0	0	1	1	1	2
PR	2	6	4	16	11	16	7	14
SD	3	10	7	28	15	21	8	16
> 6 months	1	3	3	12	10	14	7	14
PD	26	84	12	48	38	54	32	63
NE	0	0	2	8	6	8	3	6

Abbreviations: C, cetuximab; Cb, carboplatin; CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

*Combined Arms 1B and 2.

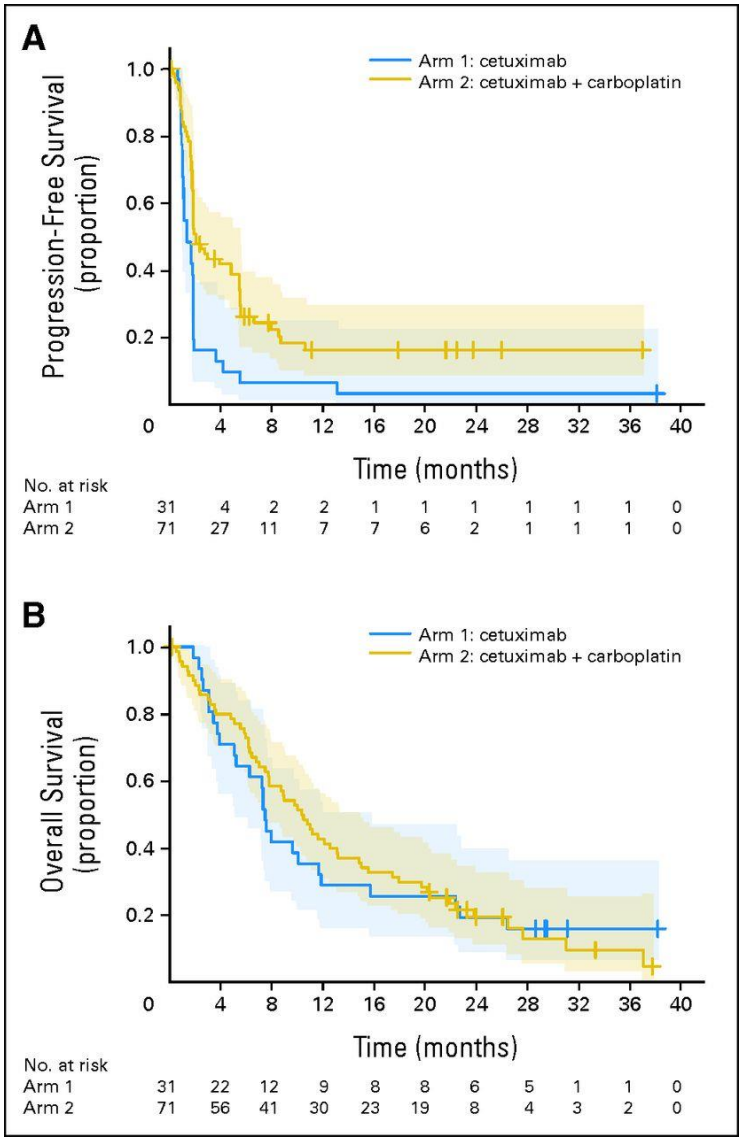
†After progression while receiving C.

‡Limited to those with confirmed basal-like disease by quantitative real-time polymerase chain reaction–based intrinsic subtype assay.

Lisa A. Carey et al. JCO 2012;30:2615-2623

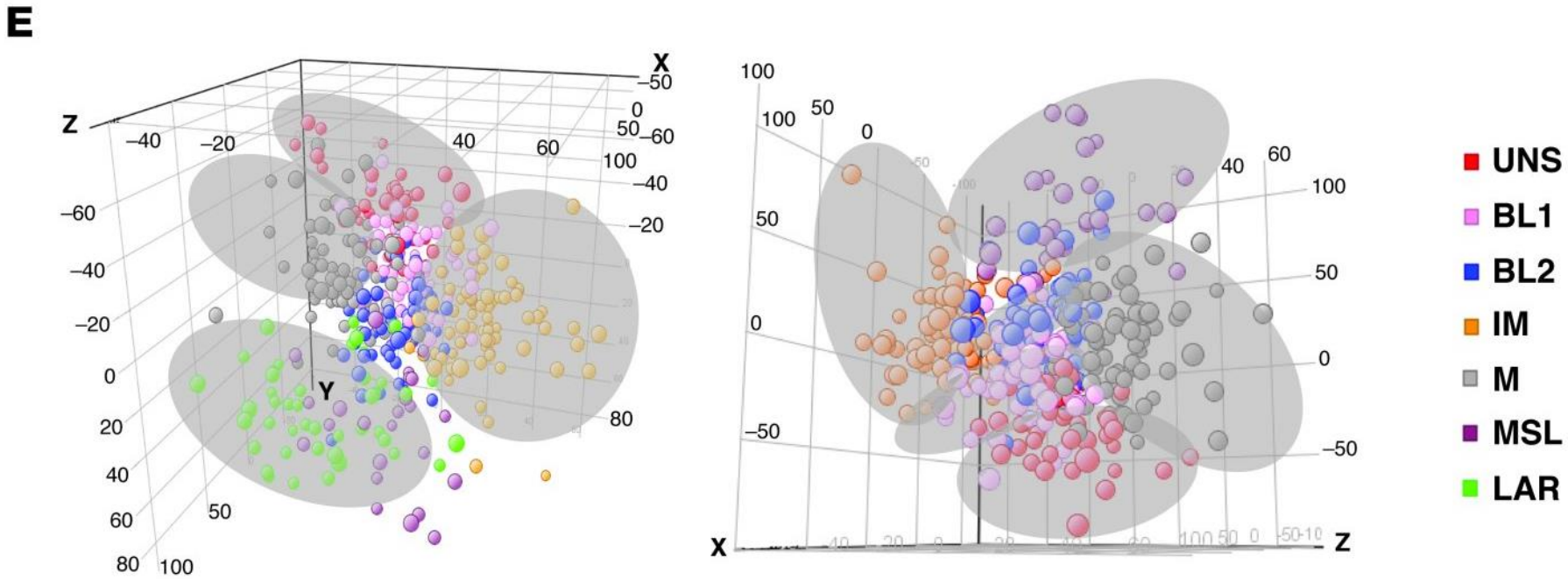
Basal like 2:Growth factor signalling

The combination of cetuximab plus Carboplatin in metastatic TNBC produced responses in fewer than 20% of patients. EGFR pathway analysis showed that most TNBCs involved activation.



Lisa A. Carey et al. JCO 2012;30:2615-2623

Clinical Heterogeneity of TNBC



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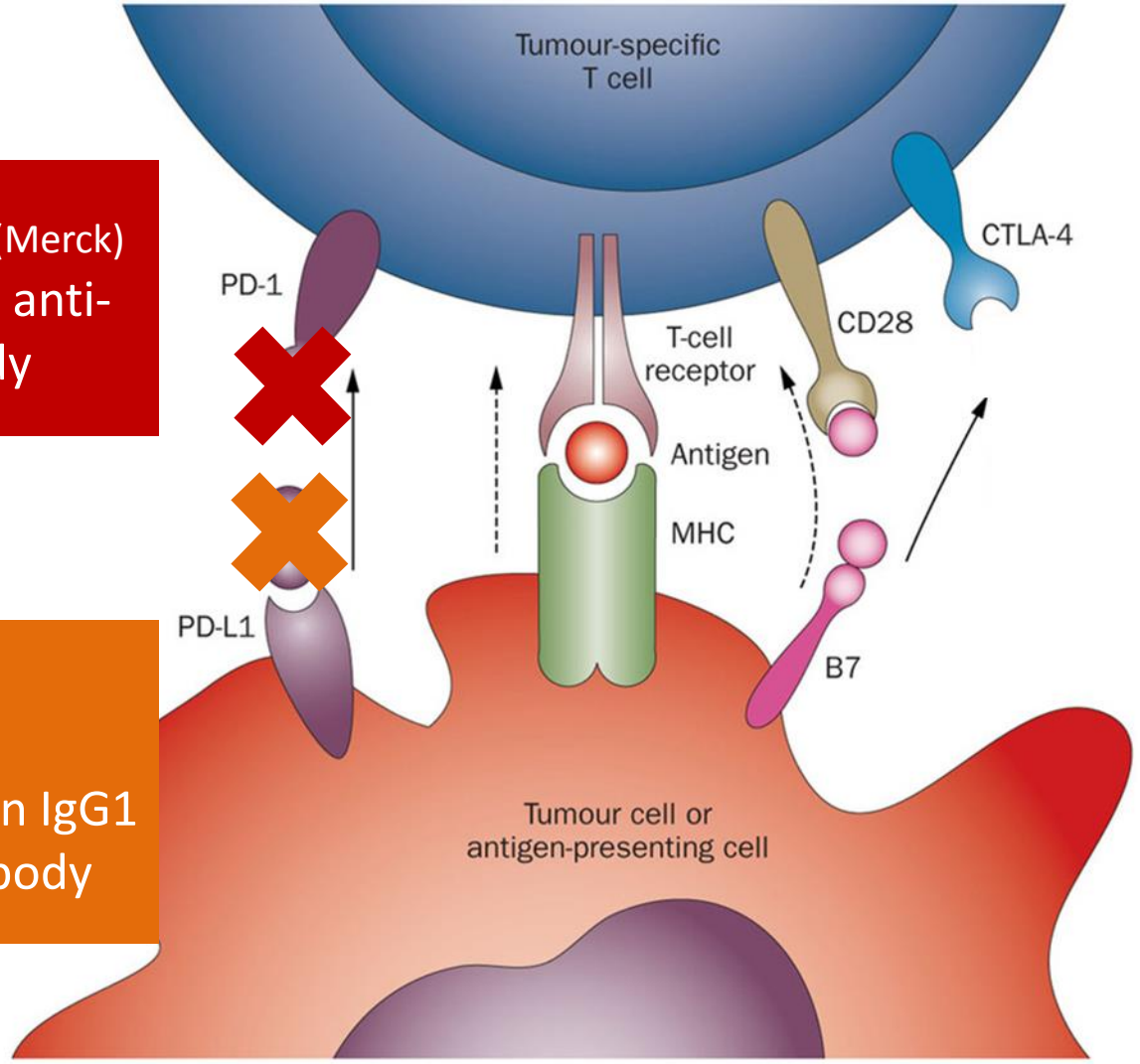
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

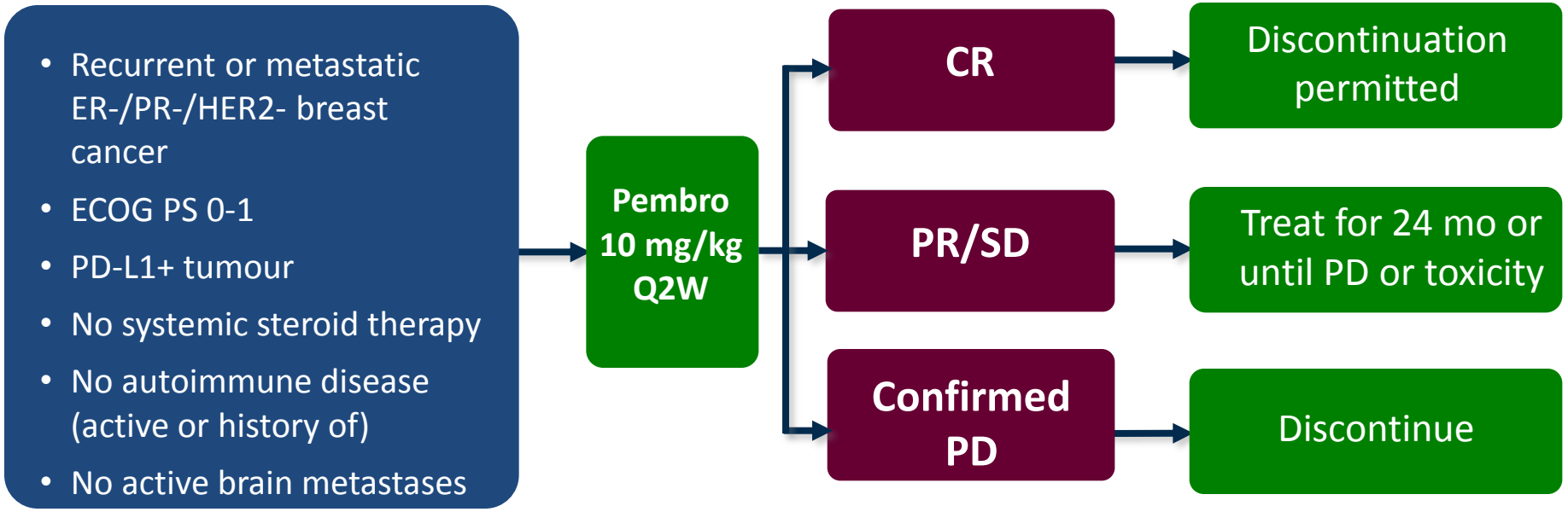
Evidence from clinical trials

Pembrolizumab (Merck)
Humanized IgG4 anti-PD-1 antibody

MPDL3280
(Genentech)
engineered human IgG1 anti-PD-L1 antibody



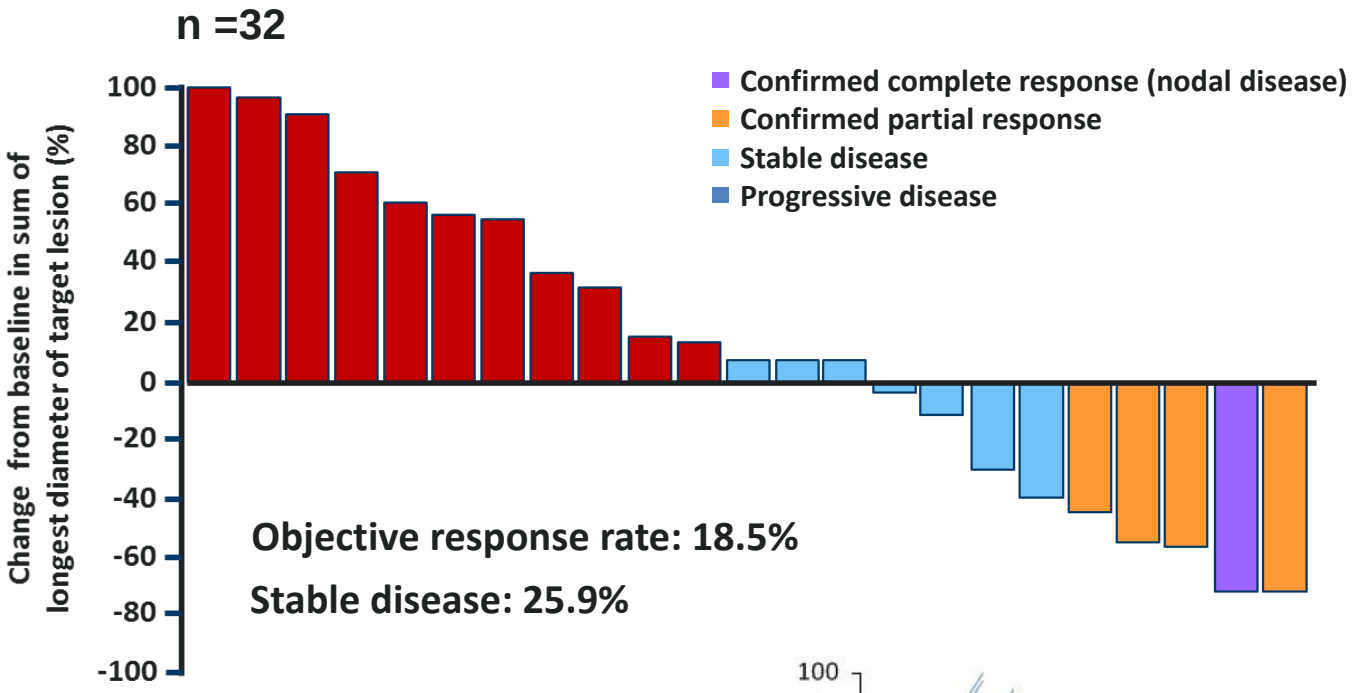
Pembrolizumab in TNBC

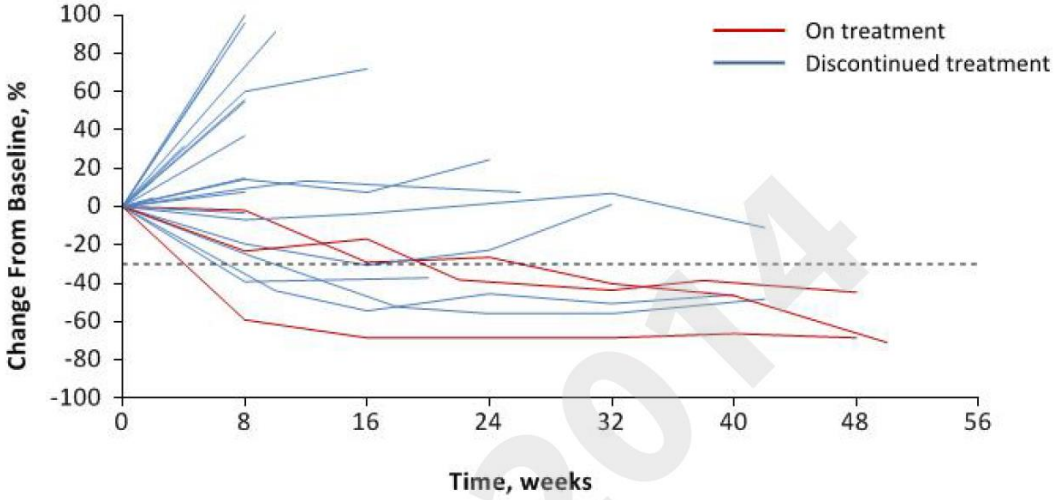


- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

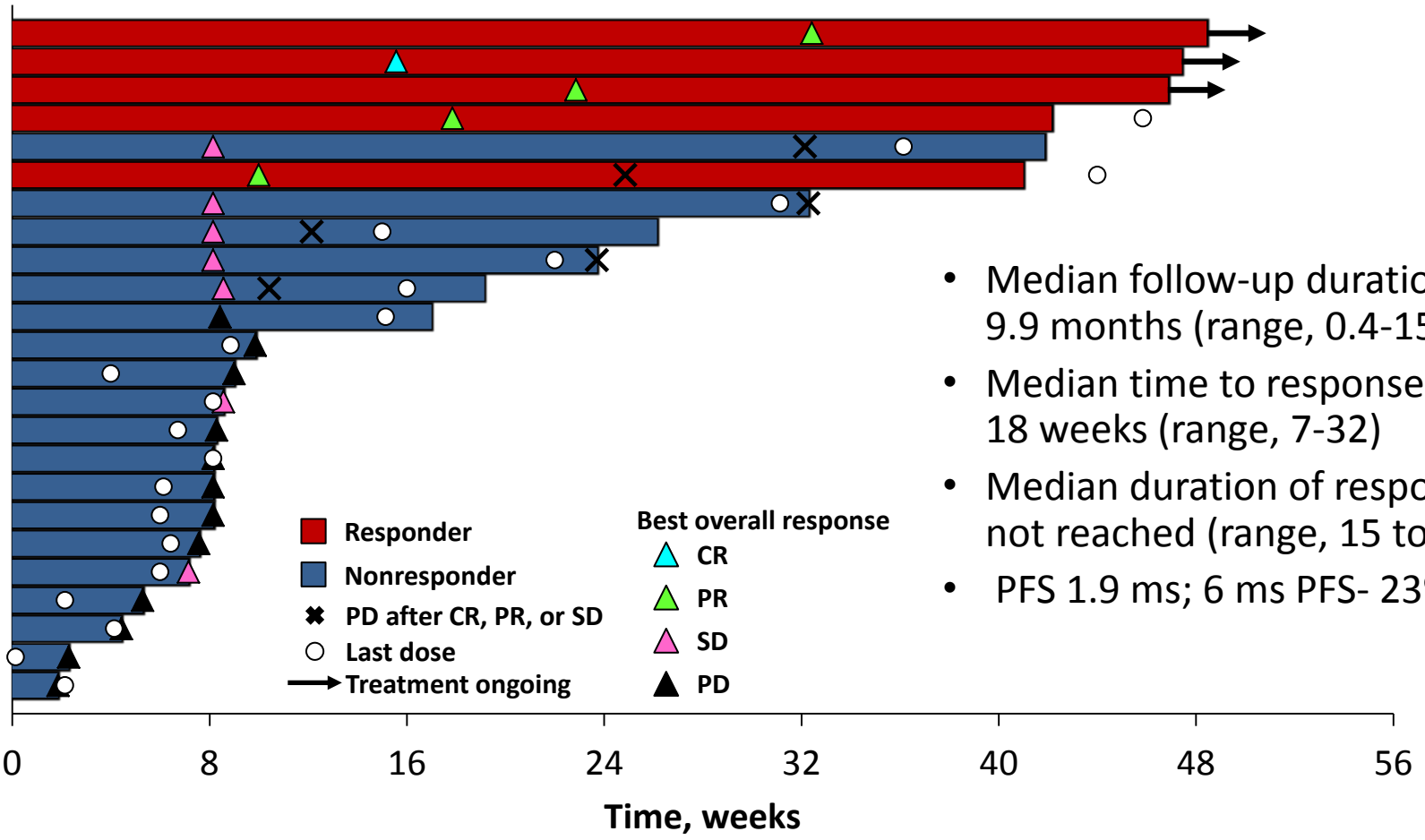
Pembrolizumab in TNBC





Nanda, SABCS 2015

Pembrolizumab in TNBC



- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response[a]: not reached (range, 15 to 40+ weeks)
- PFS 1.9 ms; 6 ms PFS- 23%

[a]Kaplan-Meier estimate.
Analysis cut-off date: November 10, 2014.

Nanda, SABCS 2014

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

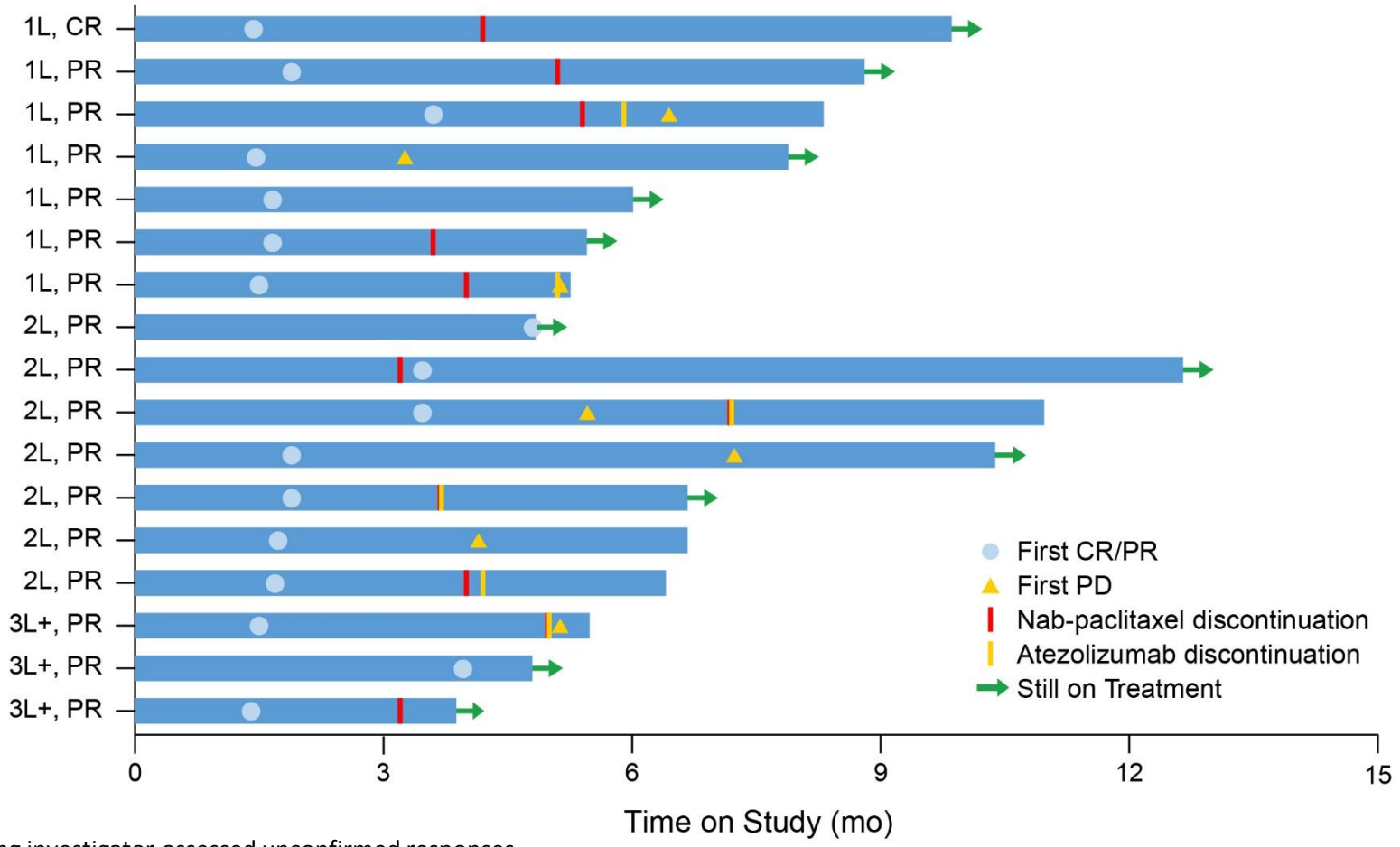
Best Overall Response	1L (n = 9)	2L (n = 8)	3L+ (n = 7)	All Patients N = 24
Confirmed ORR (95% CI)[a]	66.7% (29.9, 92.5)	25% (3.2, 65.1)	28.6% (3.7, 71.0)	41.7% (22.1, 63.4)
ORR (95% CI)[b]	88.9% (51.7, 99.7)	75.0% (34.9, 96.8)	42.9% (9.9, 81.6)	70.8% (48.9, 87.4)
CR	11.1%	0	0	4.2%
PR	77.8%	75.0%	42.9%	66.7%
SD	11.1%	25.0%	28.6%	20.8%
PD	0	0	28.6%	8.3%

Response rates were higher for patients who received atezolizumab/nab-paclitaxel treatment as 1L therapy compared to 2L+

[a] Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.
[b] Including investigator-assessed unconfirmed responses.
Efficacy-evaluable patients were dosed by June 1, 2015, and were evaluable for response by RECIST v1.1.
Minimum efficacy follow up was ≥ 3 months.

Adams S, et al. SABCS. 2015 [abstract 850477].

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC



Including investigator-assessed unconfirmed responses.

- 11 of 17 responses (65%) continued on treatment at time of data cut off

Adams S, et al. SABCS. 2015 [abstract 850477].

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

PD-L1 IHC IC Status	Patients N = 24	PD-L1 IHC TC Status	Patients N = 24
IC3 (≥ 10%)[a]	1	TC3 (≥ 50%)	1
IC2 (≥ 5% and < 10%)	3	TC2 (≥ 5% and < 50%)	0
IC1 (≥1% and < 5%)	5	TC1 (≥ 1% and < 5%)	2
IC0 (< 1%)	7	TC0 (< 1%)	13
Unknown	8	Unknown	8

[a] Percent of IC or TC staining positive for PD-L1.

- Expression of PD-L1 in TNBC is mostly restricted to IC

Adams S, et al. SABCS. 2015 [abstract 850477].

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

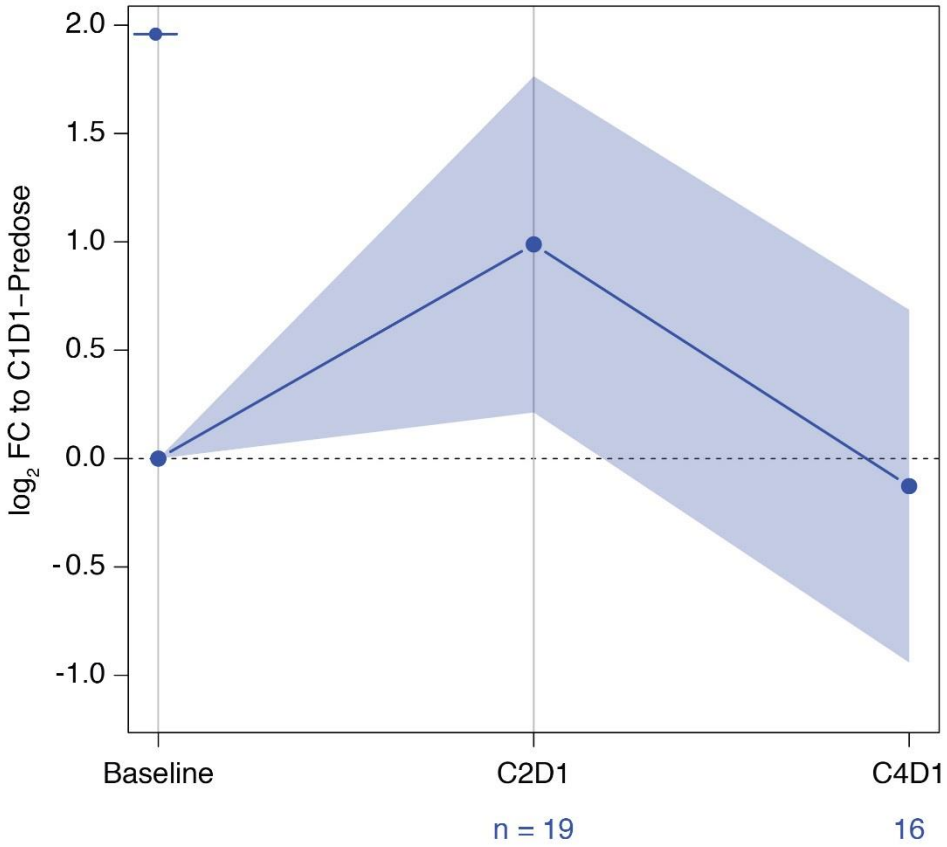
	IC0 (n = 7)	IC1/2/3 (n = 9)	Unknown (n = 8)
ORR (95% CI)	57.1% (18.4, 90.1)	77.8% (40.0, 97.2)	75% (34.9, 96.8)
CR	0	0	12.5%
PR	57.1%	77.8%	62.5%
SD	42.9%	22.2%	0
PD	0	0	25%

Including investigator-assessed unconfirmed responses.

- Responses were observed in both IC0 and IC1/2/3 patients

Adams S, et al. SABCS. 2015 [abstract 850477].

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC



- Proliferating activated CD8+ T cells transiently peaked at the end of the first cycle of atezolizumab treatment

Adams S, et al. SABCS. 2015 [abstract 850477].

Phase III Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- Randomized, double-blind, placebo-controlled Phase 3 trial of nab-paclitaxel ± atezolizumab as 1st line therapy in mTNBC (NCT02425891)

Study design

- Histologically documented locally advanced or metastatic TNBC
- No prior therapy for advanced disease
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Patients with significant CV or CNS disease (except asymptomatic brain metastases), autoimmune disease or prior checkpoint inhibitor therapy are excluded
- Target accrual: ~350 pts

R

1:1

Nab-paclitaxel
100 mg/m^2 QW 3/4
+
Atezolizumab
840 mg Q2W

Nab-paclitaxel
100 mg/m^2 QW 3/4
+
Placebo Q2W

Co-primary endpoints:

- PFS in all patients
- PFS according to PD-L1 expression

Secondary endpoints:

- OS
- ORR
- Response duration
- Safety/tolerability
- PK
- HR QoL

Stratification factors:

- Presence of liver metastases
- Prior taxane therapy
- PD-L1 expression status (centrally evaluated by IHC using the SP142 assay)

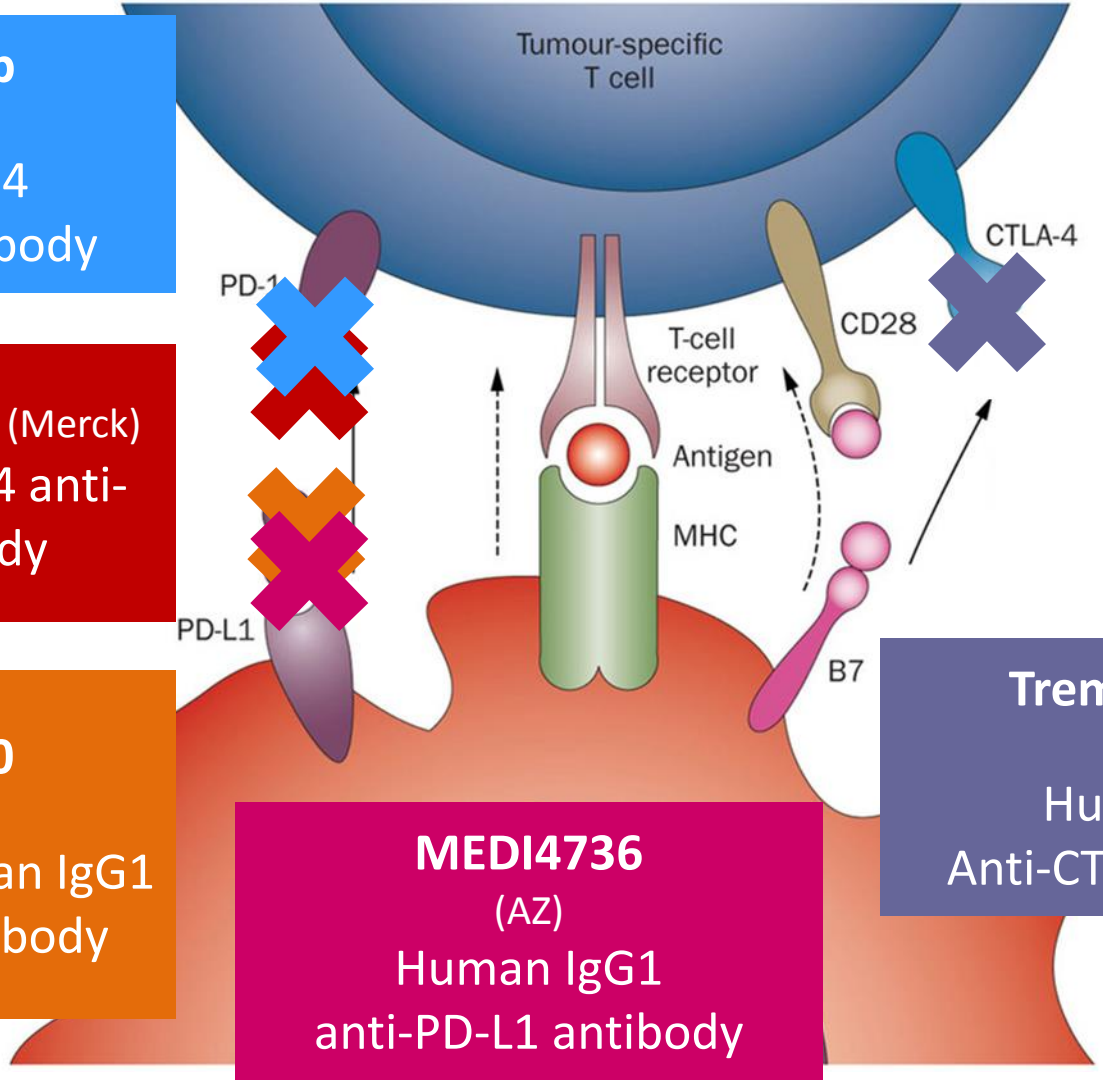
Emens et al. SABCS 2015 (abstract OT1-01-06)

Immunotherapy in TNBC

Nivolumab
(BMS)
Human IgG4
anti-PD-1 antibody

Pembrolizumab (Merck)
Humanized IgG4 anti-PD-1 antibody

MPDL3280
(Genentech)
engineered human IgG1
anti-PD-L1 antibody



MEDI4736
(AZ)
Human IgG1
anti-PD-L1 antibody

Tremelimumab
(AZ)
Human IgG2
Anti-CTLA-4 antibody

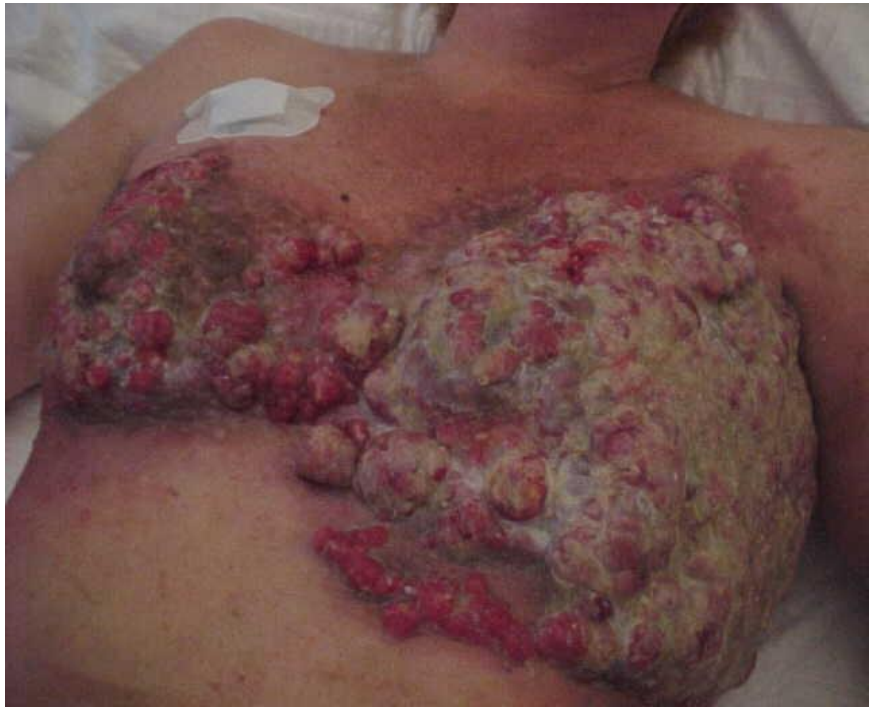
Immunotherapy in TNBC

	Phase	Setting	Subtype	PD-L1 expression as inclusion criteria	Combination/comparator	Primary EP
Nivolumab	II	Metastatic	TN	No	Monotherapy after induction with RT and CT	PFS
Pembrolizumab	II	Metastatic IBC	HER2-	No	monotherapy	Disease control rate
	Ib/II	Metastatic	TN	No	+ eribulin	DLT/ORR
	II	Metastatic	TN	Cohort B (positive) Cohort C (strong)	monotherapy	ORR/Safety
	Ib/II	Metastatic/ LABC	TN	Presence of PD-L1 expression	+ nabpaclitaxel	Safety/ORR
	II	Metastatic	HR+	No	+ Tamoxifen + Vorinostat	Safety/ORR
Atezolizumab	III	Metastatic	TN	No	+ nabpaclitaxel vs nabpaclitaxel	PFS
Durvalumab	II	Metastatic	HER2-	No	+ tremelimumab (AZ)	ORR

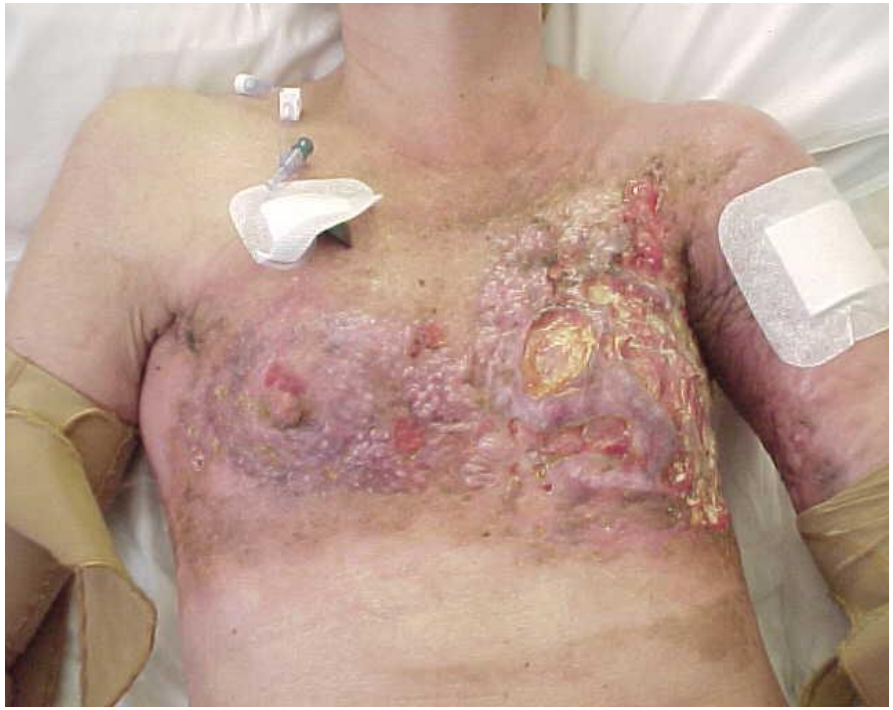
Adaptive Phase II Randomized Non-comparative Trial of Nivolumab After Induction Treatment in Triple-negative Breast Cancer (TNBC) Patients: TONIC-trial (The Netherlands Cancer Institute)

Treatment Arm	Assigned intervention
Active Comparator: Radiation therapy Radiotherapy on metastatic lesion	Nivolumab 3 mg/kg, every 2 weeks after induction treatment Radiation: Radiation therapy 20 Gy to metastatic lesion
Active Comparator: Low dose doxorubicin 15 mg flat dose, once weekly for 2 weeks	Nivolumab 3 mg/kg, every 2 weeks after induction treatment Low dose doxorubicn
Active Comparator: Cyclophosphamide metronomic schedule, 50 mg daily orally for 2 weeks	Nivolumab 3 mg/kg, every 2 weeks after induction treatment Metronomics CTX
Active Comparator: Cisplatin 40 mg/m2, weekly for 2 weeks	Nivolumab 3 mg/kg, every 2 weeks after induction treatment Weekly cisplatin
Active Comparator: No induction treatment	Nivolumab 3 mg/kg, every 2 weeks after induction treatment

Targeting stroma and inflammation



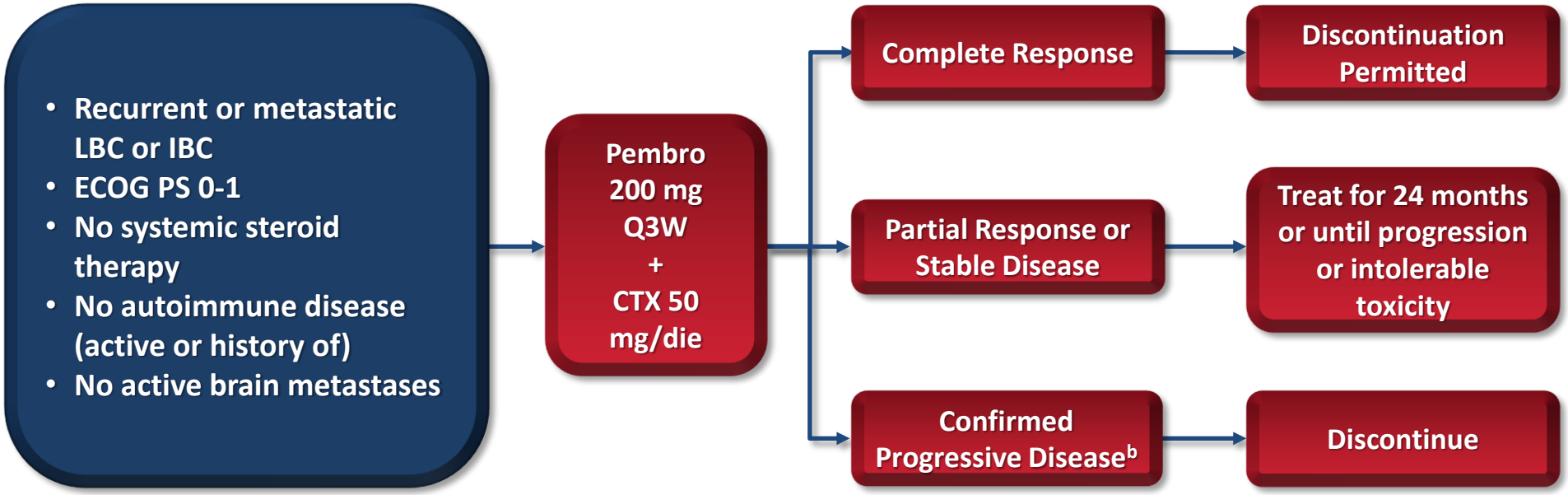
19.07.2007



18.10.2007

G. Curigliano et al. The Breast, 2015

Targeting stroma and inflammation



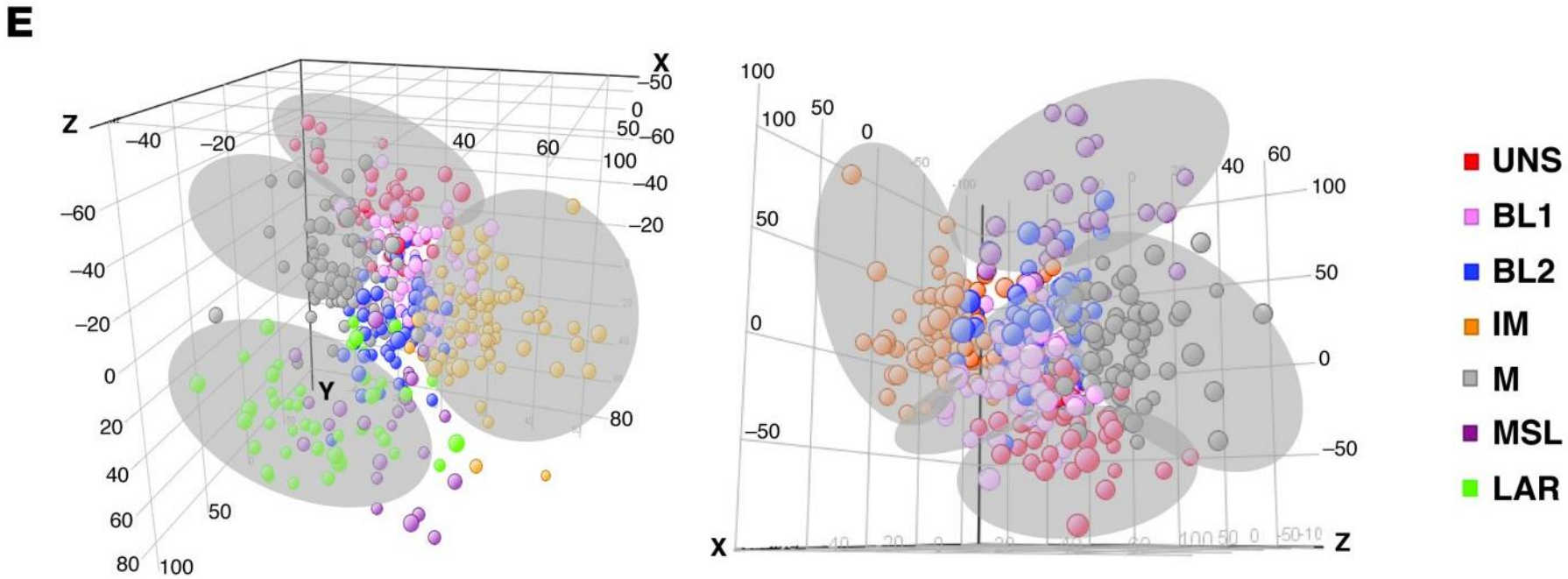
- **PD-L1 positivity:** Stratification factor
- **Treatment:** metronomic CT plus pembrolizumab
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

PI G. Curigliano et al.

Immunotherapy of TNBC?

- Is there a rational for immune-based therapy in TNBC? YES
- Evidences from clinical data? LIMITED
- Can you enhance immunogenicity? MAY BE
- Can we monitor and to predict response? NO, BUT…

Clinical Heterogeneity of TNBC

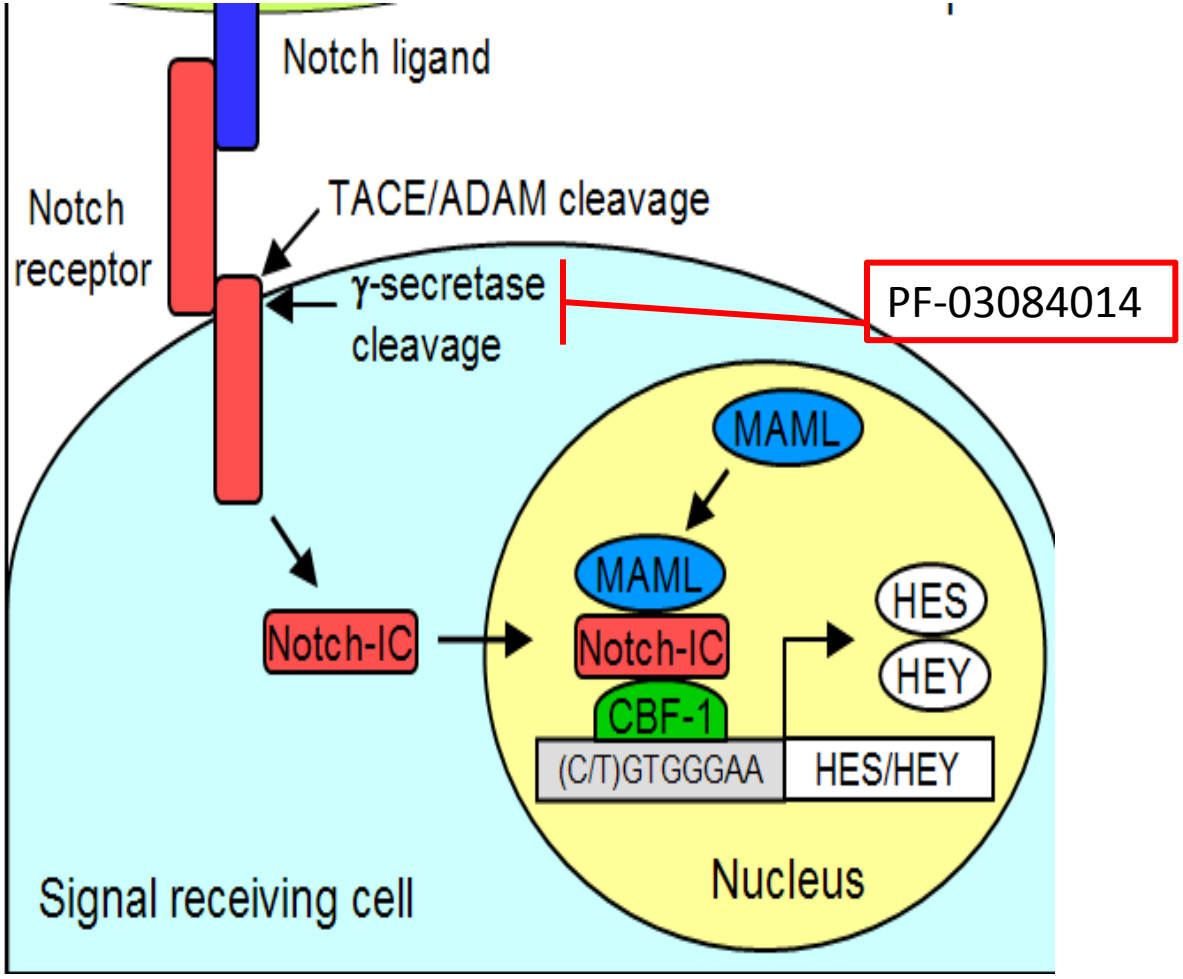


Subtype	Gene expression profile	Clinical
Basal-like 1	high Ki-67; DNA damage response	BRCA-associated
Basal-like 2	GF pathways	Higher pCR
Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

Notch pathway

Phase 1b Study of docetaxel + PF-03084014 in Triple-negative Breast Cancer

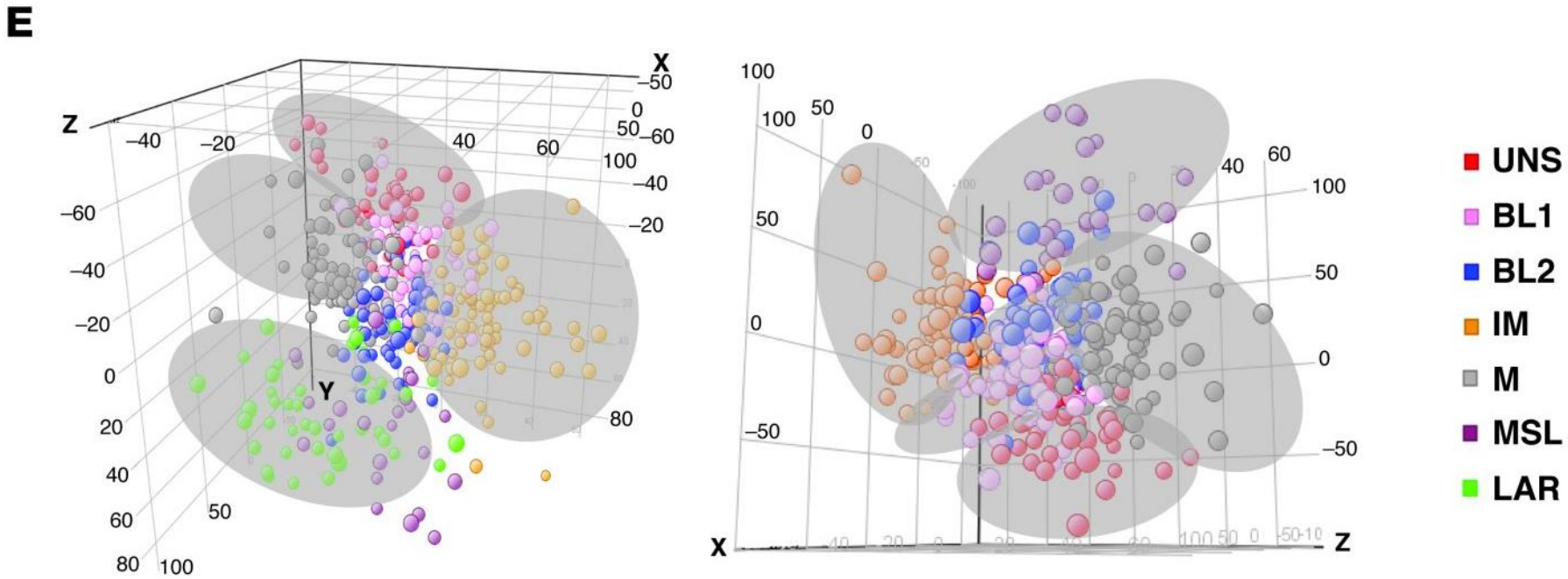


Notch pathway

Characteristic	PF-1000 mg BID/ D-75 mg/m^2 (N=8)	PF-1000 mg BID/ D-100 mg/m^2 (N=3)	PF-1500 mg BID/ D-75 mg/m^2 (N=11)	All Dose Levels (N=22)
Mean (range) age, years	57 (43-76)	43 (32-64)	46 (27-69)	50 (27-76)
ECOG PS, n (%) 0/1	4/4 (50/50)	1/2 (33/67)	8/3 (73/27)	13/9 (59/41)
Primary Diagnosis, n (%) locally recurrent/metastatic	1/7 (13/87)	0/3 (0/100)	3/8 (27/73)	4/18 (18/82)
Prior Systemic Therapies, n (%) 1st line/2nd line	4/4 (50/50)	3/0 (100/0)	7/4 (64/36)	14/8 (64/36)

G Curigliano, ASCO 2015

Clinical Heterogeneity of TNBC



Subtype	Gene expression profile	Clinical
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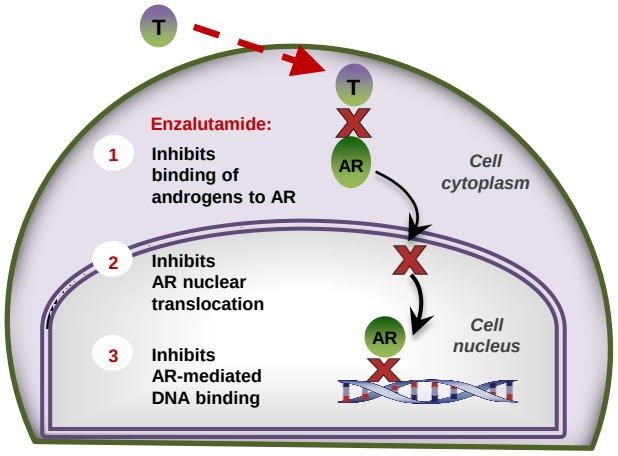
Basal-like 2	GF pathways	Higher pCR
Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

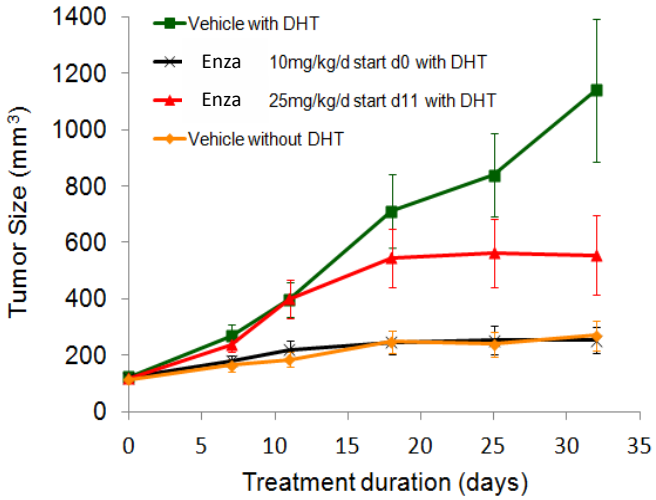
Luminal Androgen Receptor

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)



DHT = dihydrotestosterone; TNBC = triple-negative breast cancer.

Cochrane DR et al. *Breast Cancer Res*. 2014;16:R7;
Traina TA et al. *J Clin Oncol*. 2015;33(suppl 7):abstr 1003.

Luminal Androgen Receptor

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

Statistical Considerations

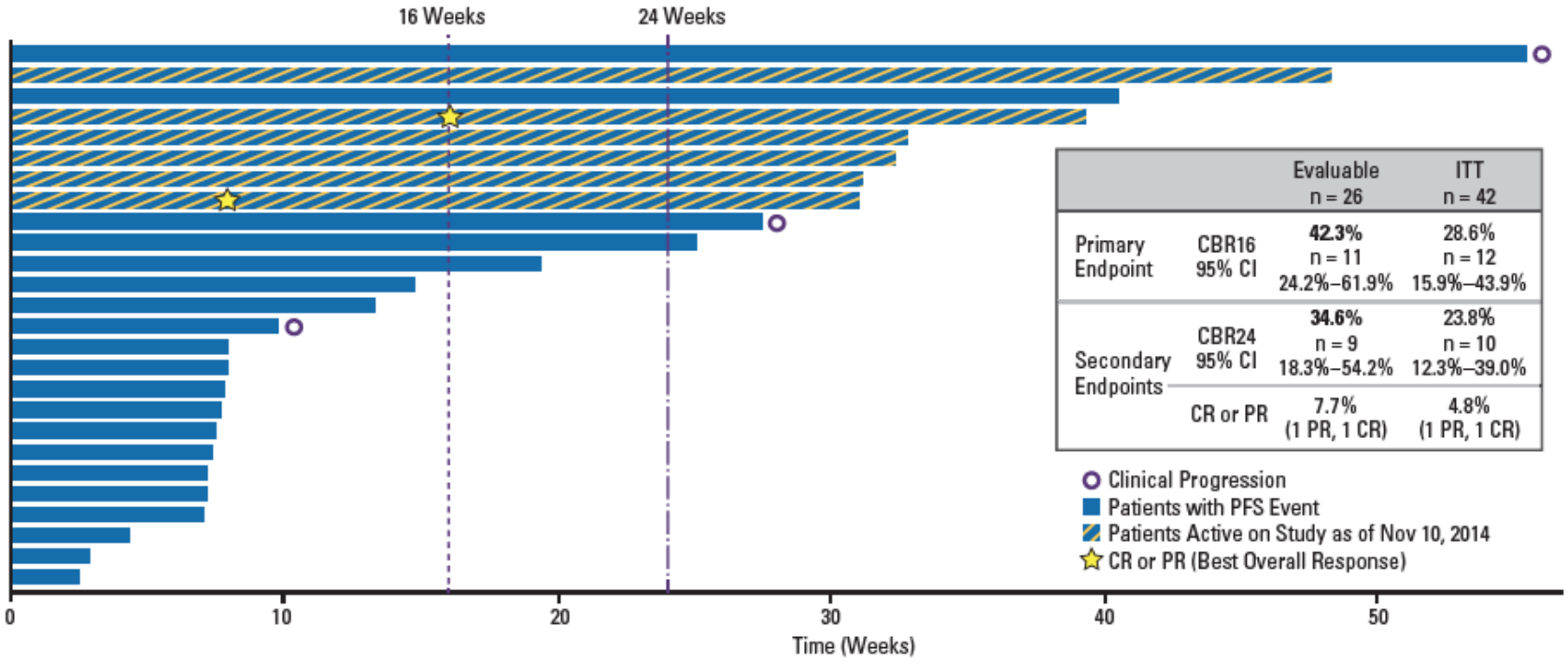
- 85% power to detect true CBR16 = 8% tested against 1-sided alternative (CBR16 ≥ 20%); alpha = 5%

*A separate consent allowed tissue submission for central AR IHC testing at any time. "AR positive" was defined as IHC staining in >0% of tumor nuclei. Physicians and patients were blinded to actual % AR staining. AR = androgen receptor; CBR = clinical benefit rate; CBR16 = 16-week CBR; CBR24 = 24-week CBR; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; H_0 = null hypothesis; IHC = immunohistochemistry; ITT = intent-to-treat.; TNBC = triple negative breast cancer www.clinicaltrials.gov, NCT01889238.

Courtesy of J. Cortes, ECCO 2015

Response to enzalutamide

Figure 4. Clinical Benefit Rate at 16 and 24 Weeks in Stage 1 Evaluable Patients

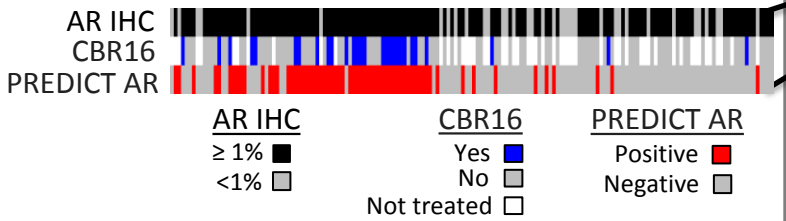


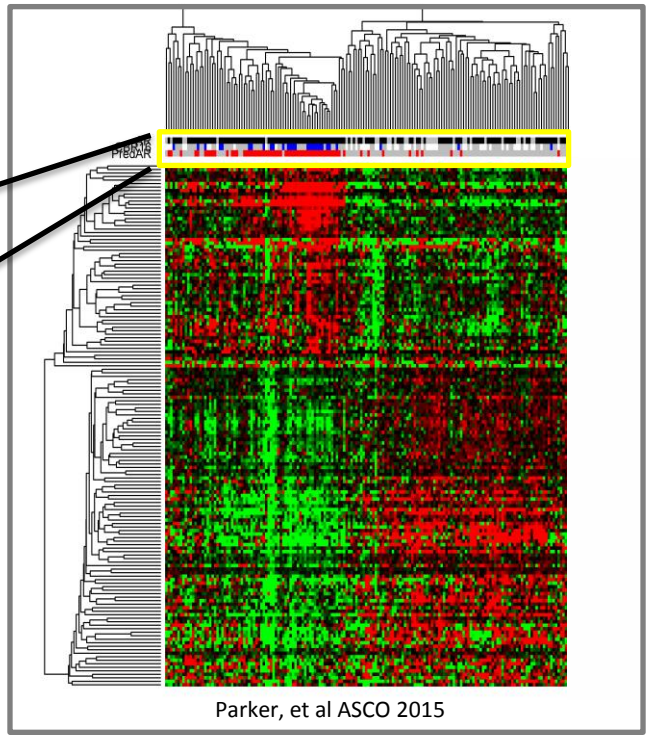
		Evaluable n = 26	ITT n = 42
Primary Endpoint	CBR16 95% CI	**42.3%** n = 11 24.2%–61.9%	28.6% n = 12 15.9%–43.9%
Secondary Endpoints	CBR24 95% CI	**34.6%** n = 9 18.3%–54.2%	23.8% n = 10 12.3%–39.0%
	CR or PR	7.7% (1 PR, 1 CR)	4.8% (1 PR, 1 CR)

Length of the horizontal bars indicate duration of PFS.

Luminal Androgen Receptor

- 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

Data Cut-off 01 July 2015

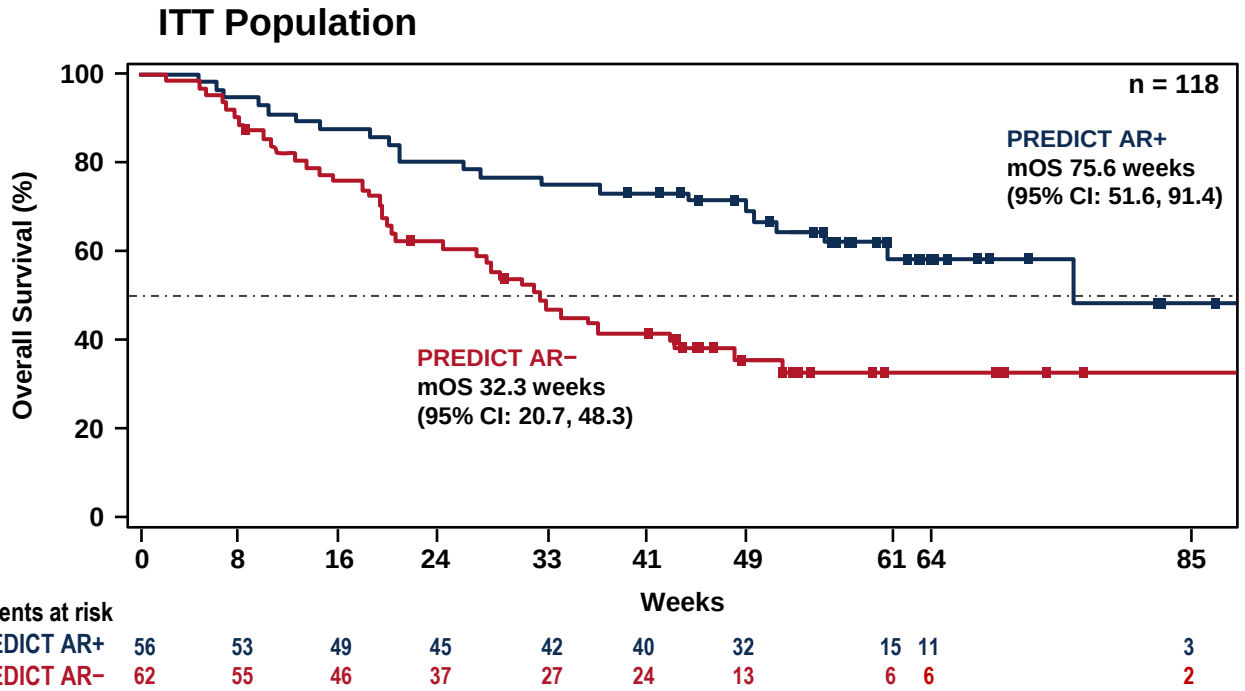
*Includes duplicates and samples from tissue collected for optional AR testing.; CBR16 = clinical benefit rate at week 16; AR = androgen receptor; IHC immunohistochemistry

1. Doane AS et al. *Oncogene*. 2006;25:3994-4008; 2. Farmer P et al. *Oncogene*. 2005;24:4660-4671; 3. Smid M et al. *Cancer Res.* 2008;68:3108-3114; 4. Charafe-Jauffret E et al. *Oncogene*. 2006;25:2273-2284.5. Parker , et al J Clin Oncol 2015

NCT01889238

Courtesy of J. Cortes, ECCO 2015

Luminal Androgen Receptor

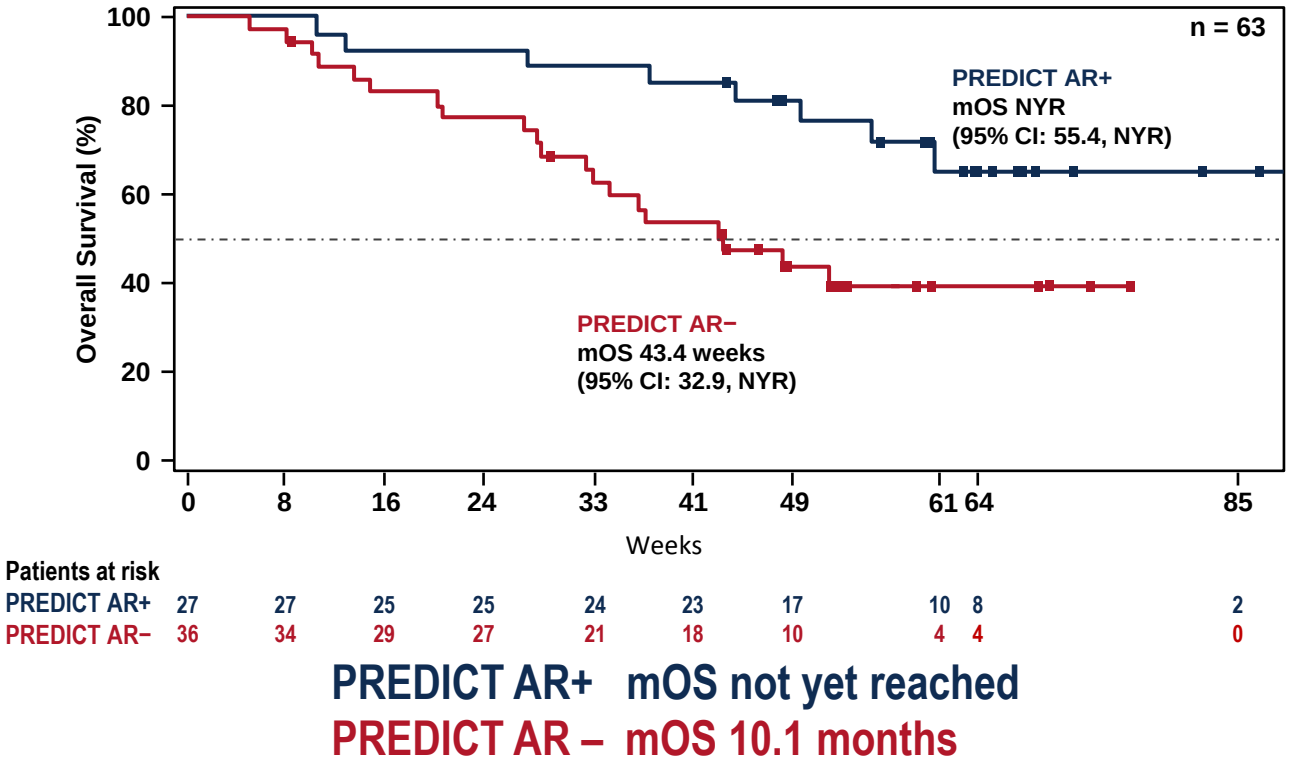


Data cutoff 1Jul2015
ITT = intent to treat; mOS = median survival; CI = confidence interval; .

NCT01889238

Courtesy of J. Cortes, ECCO 2015

Luminal Androgen Receptor



Data cutoff 1Jul2015.
CI= confidence interval; mOS = median survival; NYR = not yet reached

NCT01889238

Courtesy of J. Cortes, ECCO 2015

Challenges

- Small phase II maybe NOT be enough to interpret data
- Run large trials in low-incidence disease to generate knowledge about drug and disease
- Change statistical hypothesis since expectations are higher now

Conclusions

- Select the right partner and validate studies with the same backbone
- Demonstrate bioactivity and not MTD
- Metastatic breast cancer is not always the right setting:
- Neoadjuvant
- Post-neoadjuvant can be more informative

Thank you

Slides available contacting: giuseppe.curigliano@ieo.it