Which of the following is the best approach for a patient with TNBC who suffers recurrent, metastatic breast cancer 8 months after completion of adjuvant chemotherapy with an anthracycline + cyclophosphamide + taxane?

1. **Platinum-containing combination chemotherapy**

2. **Bevacizumab-containing combination therapy**

3. **Clinical trial with other agents targeting VEGF/VEGFR, EGFR, mTOR, PARP**

Which of the following is the best approach for a patient with TNBC who suffers recurrent, metastatic breast cancer 8 months after completion of adjuvant chemotherapy with an anthracycline + cyclophosphamide + taxane?

1. **Platinum-containing combination chemotherapy**

28.1%

2. **Bevacizumab-containing combination therapy**

34.4%

3. **Clinical trial with other agents targeting VEGF/VEGFR, EGFR, mTOR, PARP**

37.5%

Optimizing Outcomes in Metastatic Triple-Negative Breast Cancer (TNBC): The Search for Targets

David Miles, MD, FRCP
Mount Vernon Cancer Centre
United Kingdom

Optimizing Outcomes in Metastatic Triple-Negative Breast Cancer (TNBC): The Search for Targets

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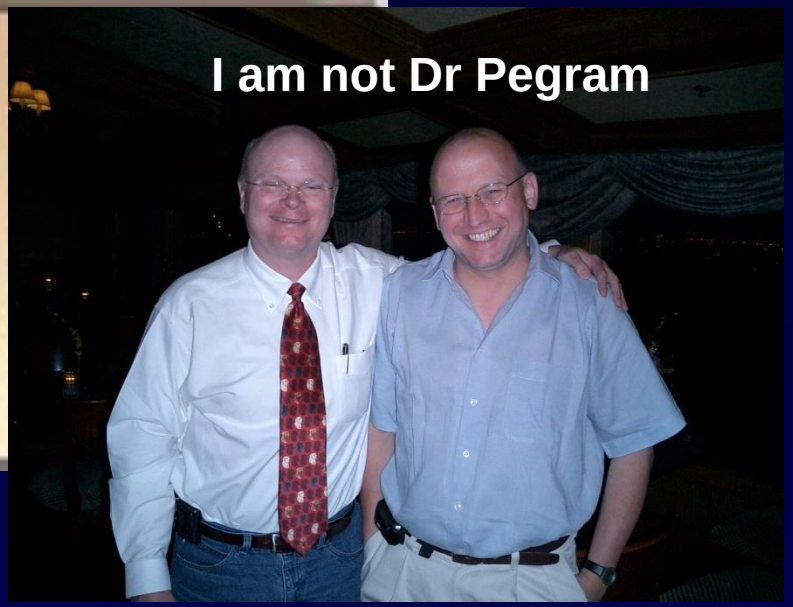
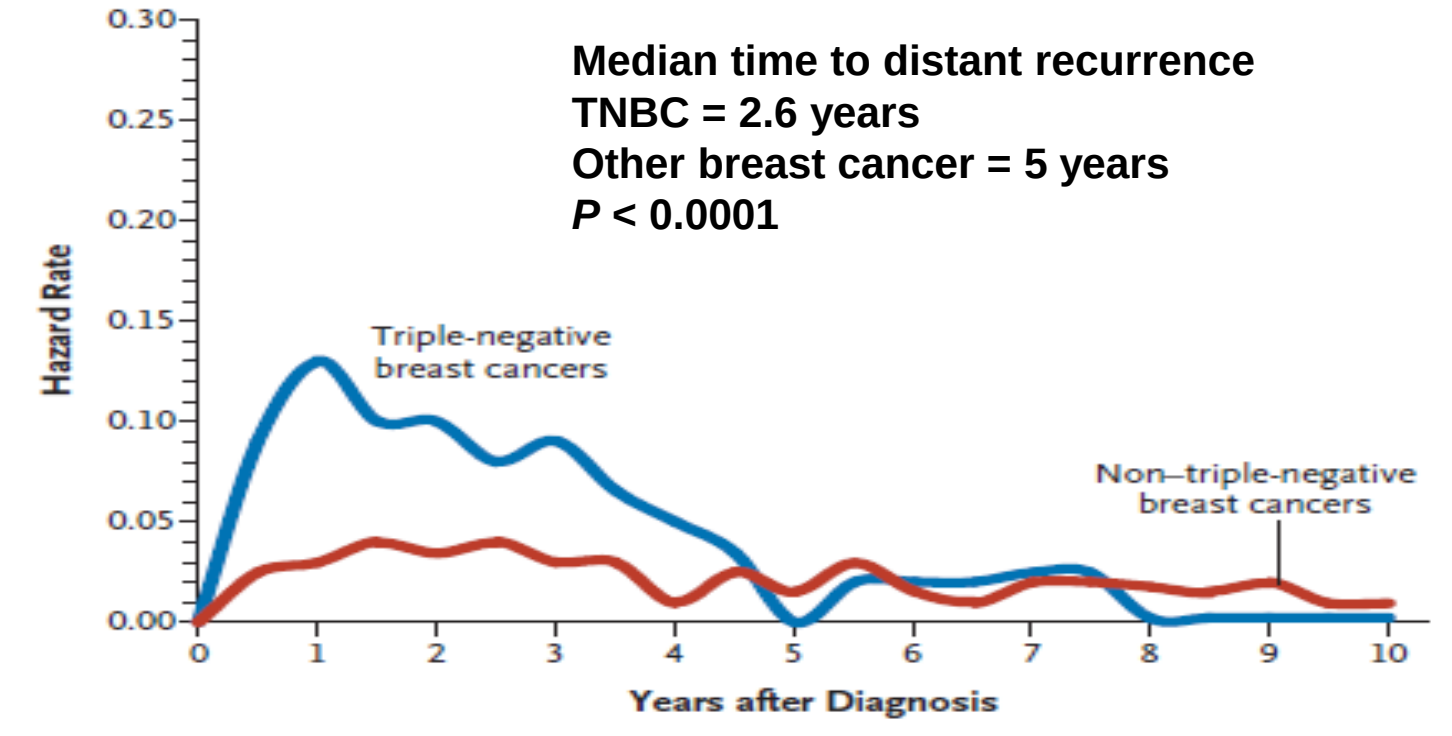
Optimizing Outcomes in Metastatic Triple-Negative Breast Cancer (TNBC): The Search for Targets



Optimizing Outcomes in Metastatic Triple-Negative Breast Cancer (TNBC): The Search for Targets

Triple-Negative Breast Cancer: Hazard Rates for Distant Recurrence



Dent R, et al. *Clin Cancer Res*. 2007;13(15 Pt 1):4429-4434.

Chemotherapy in TNBC

Reference	Regimen	n	Prior treatment	Response rate (RR)	PFS	OS
046/048 (2008)	Capecitabine (Cap) + Ixabepilone	230 213	A + T A + T	15% 31%	1.7 m 4.2 m	9 m 10.3 m
Solti-0701	Cap 1g/m2 bd	33	0-1	NR	2.5 m	16.1 m
AC01B07	Gemcitabine (Gem) 1g/m2 OR Cap 1g/m2 bd	27	0-1	NR	2.6 m	NR
EGF30001 (2009)	Paclitaxel (Pac) 175	60	0	NR	4.8 m	NR
E2100	Pac 90mg/m^2, D1, 8, 15	110	0	NR	5.3 m	NR
AVADO	Docetaxel 100/m^2, D1	52	0	NR	5.4 m	NR
Ribbon-1	Taxane or anthracycline	50	0	NR	4.2 m	NR

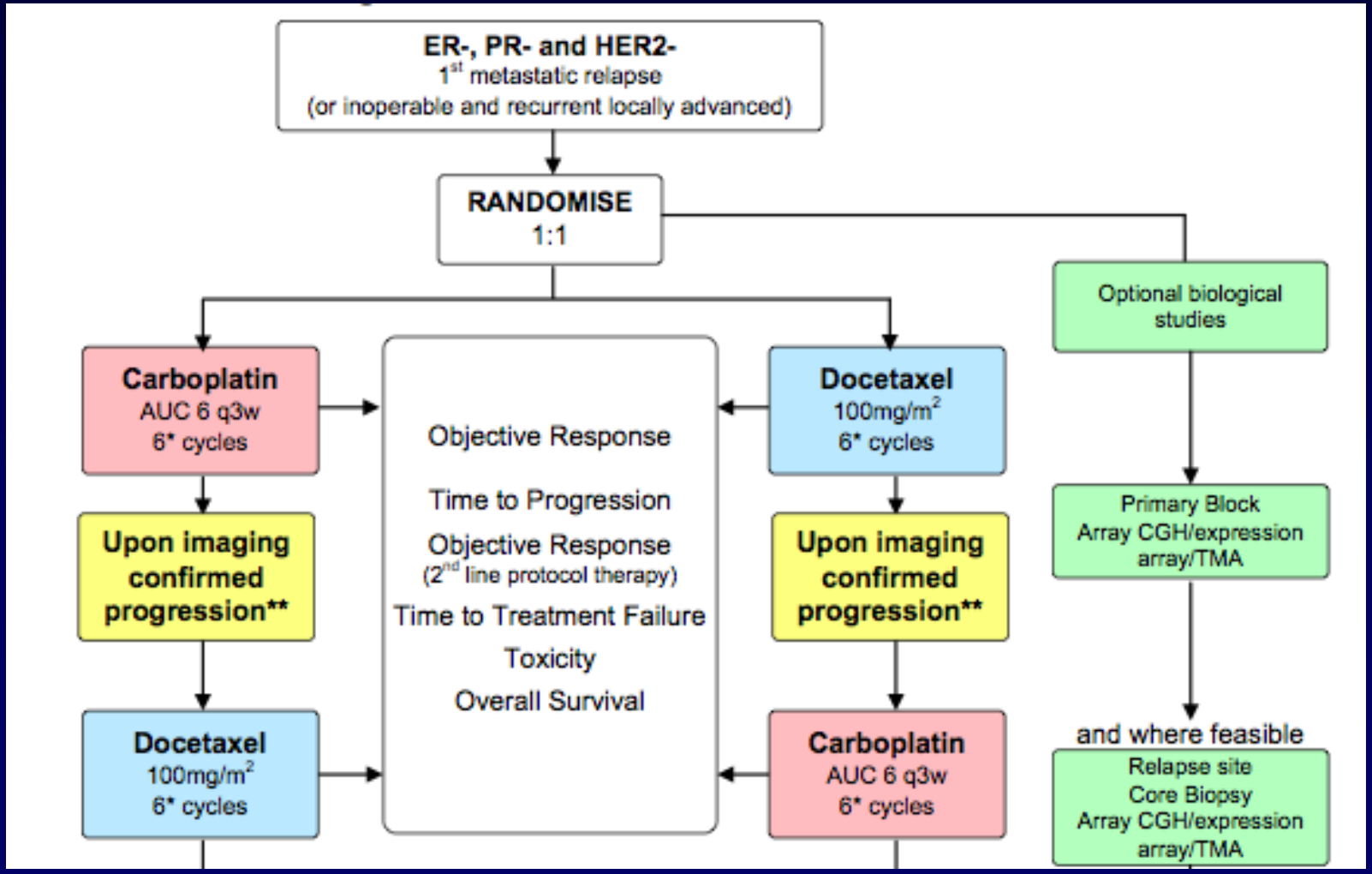
m, months

Platinum-Containing Regimens in TNBC

Reference	Regimen	n	Prior treatment	RR	PFS/DFS	OS
Sirohi, et al	Mitomycin C, vinblastine cisplatin (Cis)	34	0-5	41%	6 m	11 m
Bhattacharyya, et al	CtxMtx (metronomic) Cis	66	1	62%	13 m	16 m
Isakoff, et al	Carboplatin (Carbo) or cis	86	0-1	30%	3.2 m	NR
			BRCA1/2+ve 55%: BRCA1/2-ve26%			
Staudacher, et al	Cis + ifosfamide	93	0-2 (A+T)	33%	6 m	22 m
			BRCA1/2+ve 5/11 responses			
O'Shaughnessy, et al	Gem 1 g/m^2 D1,8, Carbo AUC2, d1,8 q3w	62	0-3	32%	3.6 m	7.7 m
O'Shaughnessy, et al	Gem 1 g/m^2 D1,8, Carbo AUC2, D1,8 q3w	258	0-2	30%	4.1 m	11.1 m
Baselga, et al	Cis 75 mg/m2 D1 q3w	58	0-1	10%	1.5 m	9.4 m

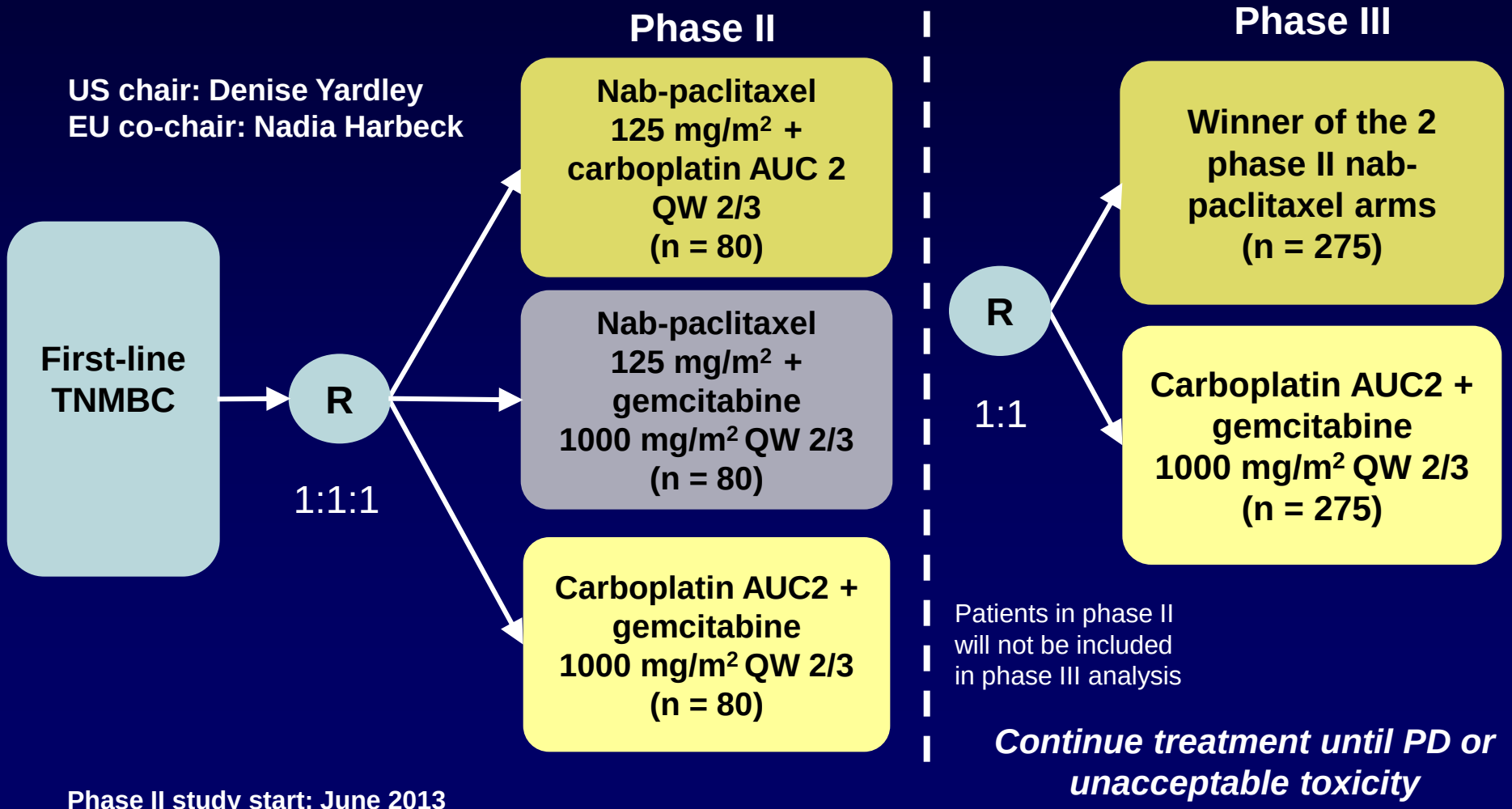
Sirohi B, et al. *Ann Oncol.* 2008;19(11):1847-1852. Bhattacharyya G, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 41LBA. Isakoff S, et al. *J Clin Oncol*. 2011;29(15S): Abstract 1025. Staudacher L, et al. *Ann Oncol*. 2011;22(4):848-856. O'Shaughnessy J, et al. *N Engl J Med*. 2011;364(3):205-214. O'Shaughnessy J, et al. *J Clin Oncol*. 2011;29(suppl): Abstract 1007. Baselga J, et al. *J Clin Oncol*. 2013;31(20):2586-2592.

Carboplatin vs Docetaxel Triple-Negative Trial (TNT)



PI Andrew Tutt

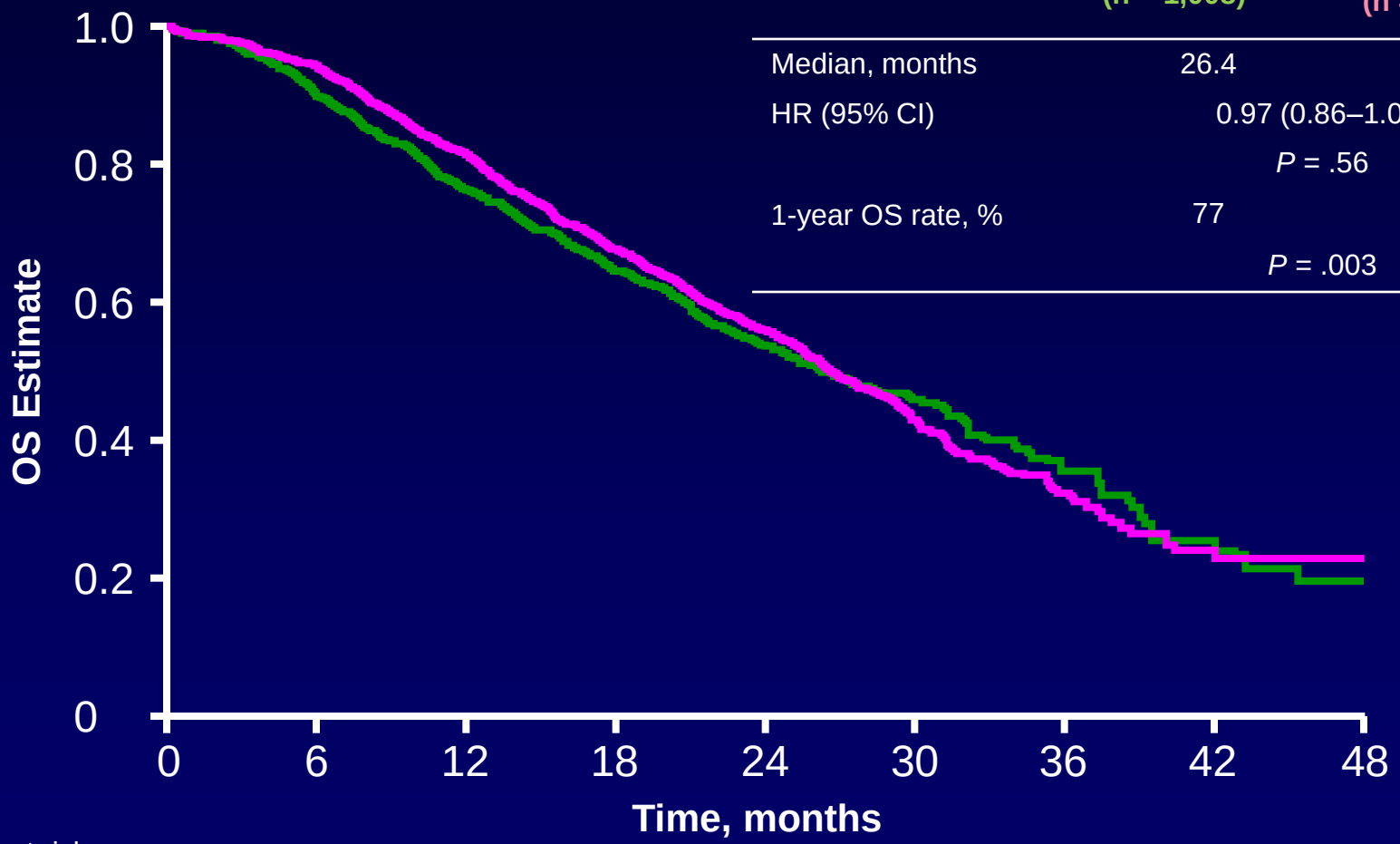
tnAcity: Study Design



Phase II study start: June 2013
Phase II estimated completion (primary analysis): June 2015
Phase III 'go/no go' decision : Sep 2015

What About Bevacizumab?

	Non-bevacizumab (n = 1,008)	Bevacizumab (n = 1,439)
Median, months	26.4	26.7
HR (95% CI)	0.97 (0.86–1.08)	
	P = .56	
1-year OS rate, %	77	82
	P = .003	



Number at risk:

Non-bevacizumab	1008	892	746	621	426	178	51	19	8
Bevacizumab	1439	1333	1127	916	591	204	55	23	5

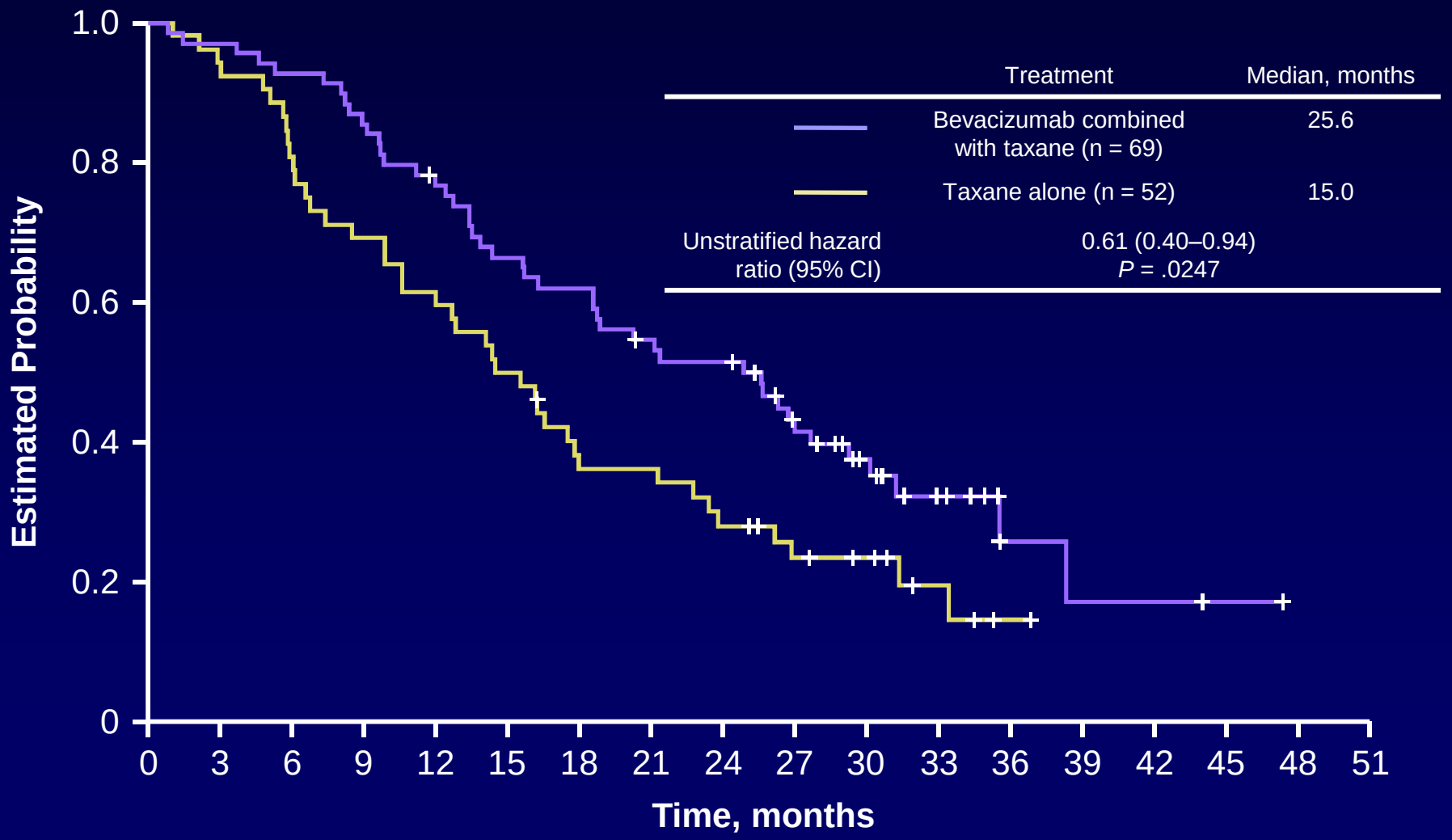
Miles DW, et al. *Ann Oncol*. 2013;24(11):2773-2780.

First-Line Bevacizumab (E2100, AVADO, Ribbon-1, n = 2447): Subset Analyses

		Median PFS, months		Median OS, months			
	PFS HR (95% CI)	BEV	Non-BEV	BEV	Non-BEV	1-year OS diff	OS HR
TNBC (n = 621)	0.63 (0.52-0.76)	8.1	5.4	18.9	17.5	6.1% (1.5-13.6)	0.96 (0.79-1.16)
Prior (neo) adjuvant taxane (n = 558)	0.54 (0.44-0.67)	9.2	6.0	26.7	20.5	7.3% (3.0-11.6)	0.72 (0.57-0.90)
TNBC and prior taxane	NR	NR	NR	25.6	15.0	16%	0.61 (0.40-0.94)

Miles DW, et al. *Ann Oncol*. 2013;24(11):2773-2780.

First-Line Chemotherapy ± Bevacizumab Overall Survival (TNBC, Taxane Pretreated)



Miles D, et al. *Ann Oncol*. 2010;21(Suppl 8): Abstract 279PD.

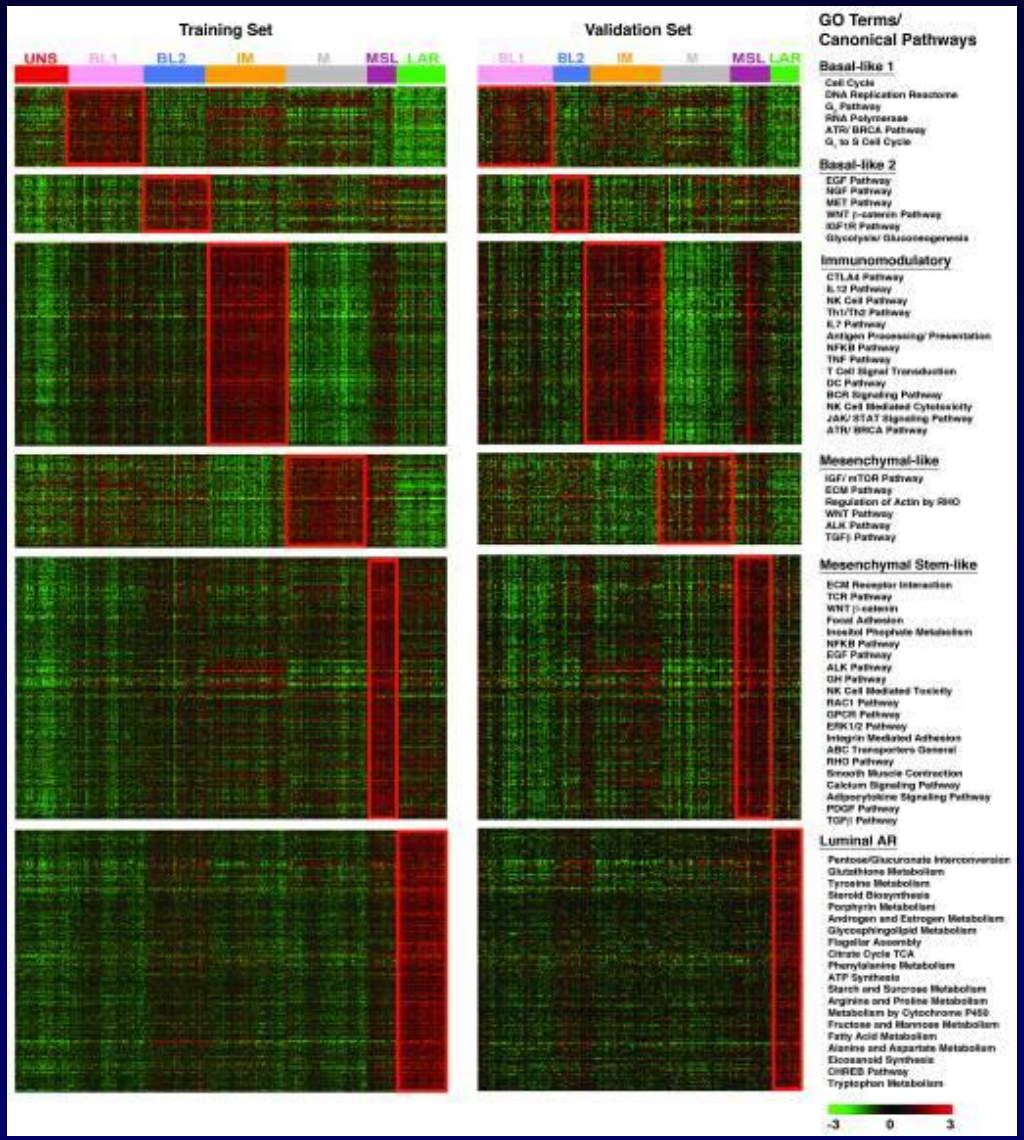
Efficacy Data From First-Line Studies With Bevacizumab in TNBC

Trial	ORR	PFS, months	HR –PFS/ 95%CI	OS
TURANDOT (n = 130)				
Paclitaxel + BEV	49%	9.0	1.37 (0.93-2.0)	78 (1 year)
Capecitabine + BEV	19%	5.6		63 (1 year)
ATHENA (n = 585)	49%	7.2	(6.6-7.8) months	18.3 months (16.4-19.7)
CALGB 40502 (n = 218)				
Nab-paclitaxel + BEV		≈ 7	0.93 (*P* = .74)	NR
Paclitaxel + BEV		≈ 7		NR
Ixabepilone + BEV		≈ 5	1.46 (*P* = .06)	NR
AVAREG (n = 106)				
Paclitaxel + BEV		8.3	(7.8-8.8) months	NR

Brodowicz T, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract P6-06-40. Thomssen C, et al. *Oncology*. 2012;82(4):218-27. Rugo H, et al. *J Clin Oncol*. 2012;30(15S): Abstract CRA1002. Dank M, et al. *Anticancer Res*. 2014;34(3):1275-1280.

Some of these agents may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

Identification of Human TNBC Subtypes



Basal-like 1: Cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: Immune cell processes (medullary breast cancer)

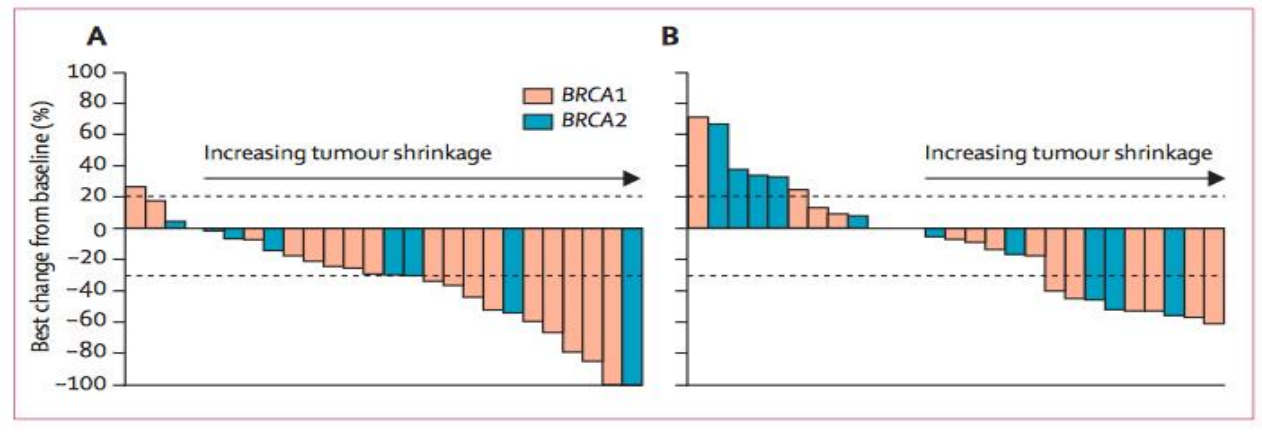
M: Cell motility and differentiation, EMT processes

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

Lehmann BD, et al. *J Clin Invest*. 2011;121(7):2750-2767.

Olaparib in MBC: Patients With BRCA1/2 Mutations

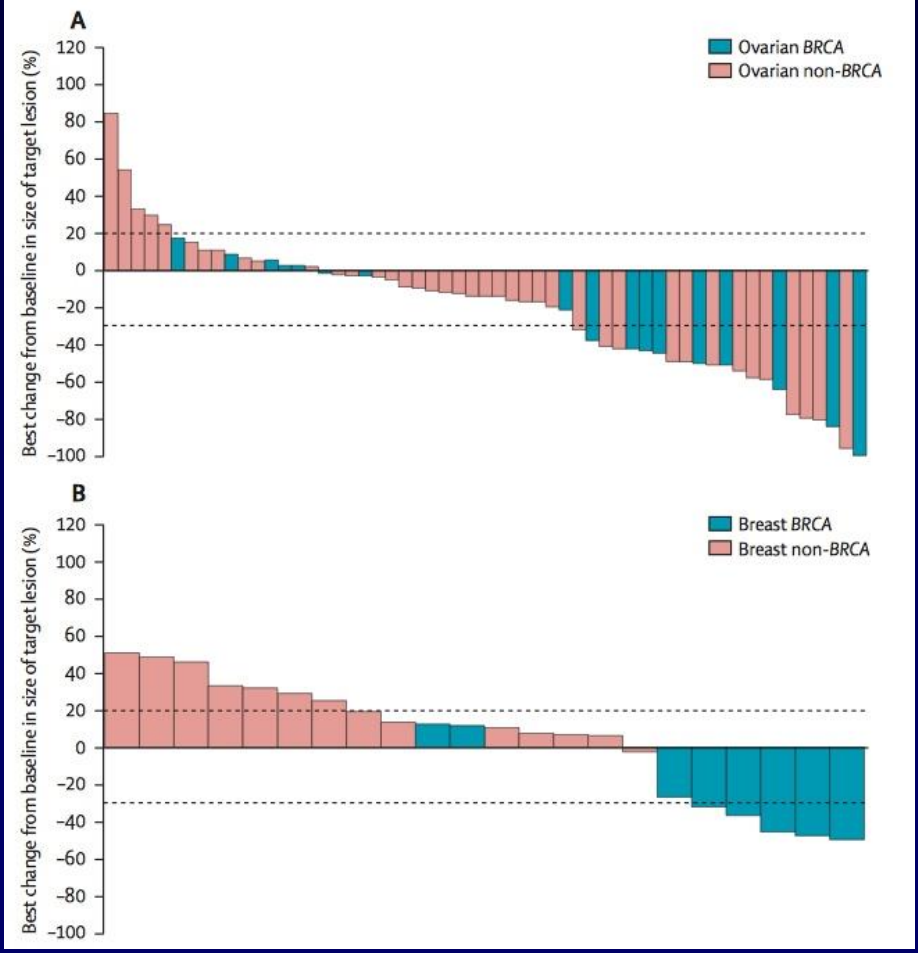


Efficacy	Olaparib 400 mg bid (n = 27)	Olaparib 100 mg bid (n = 27)
ORR	11 (41%)*	6 (22%)
CR	1 (4%)	0
PR	10 (37%)	6 (22%)
PFS	5.7 months	3.8 months

Tutt A, et al. *Lancet.* 2010;376(9737):235-244

This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

Olaparib in Ovarian and TNBC



	Status	Responses	
Ovarian cancer	BRCA1/2	7/17	41%
Ovarian cancer	Non-BRCA	11/46	24%
Breast cancer	BRCA1/2	0/8	0
Breast cancer	Non-BRCA	0/15	0

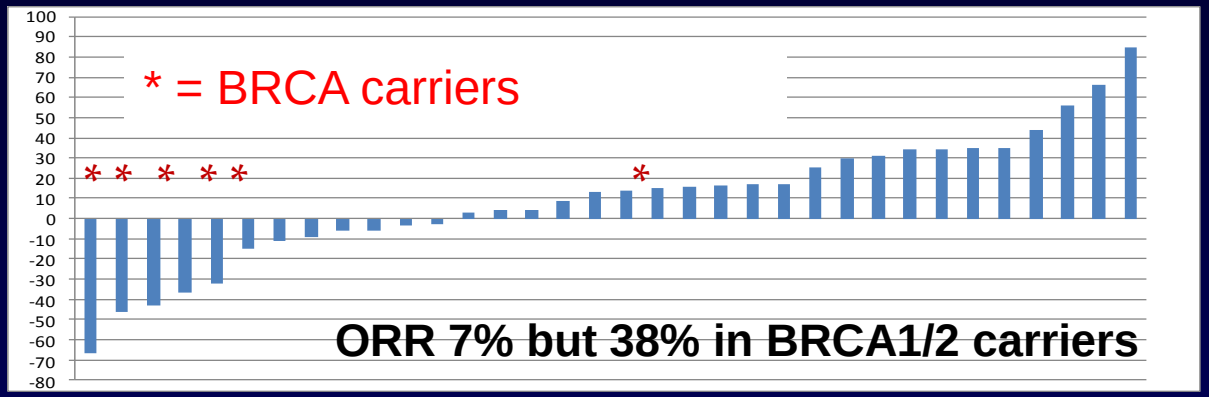
Gelmon KA, et al. *Lancet Oncol*. 2011;12(9):852-861.

This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

PARPi in Combination?

Phase II study veliparib (ABT-888) + temozolomide

Isakoff S, et al, *J Clin Oncol.* 2010;28(15S): Abstract 1019.



Phase I study olaparib + paclitaxel

Dent R, et al. *Breast Cancer Res.* 2013;15(5):R88.

Paclitaxel 90 (D1,8,15) + olaparib	Cohort 1 n = 9 (no G-CSF)	Cohort 2 n = 10 (G-CSF)
CR	0	0
PR	3	3
Unconfirmed PR	1	2

Phase I study olaparib + cisplatin

Balmaña J, et al. *Ann Oncol.* 2014;25(8):1656-1663.

*"**Olaparib** in combination with **cisplatin 75** mg/m(2) was not considered tolerable"*

"Promising antitumor activity in patients with germline BRCA1/2 mutations was observed"

These agents may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

What Is the Prevalence of BRCA1 Mutation in Patients With TNBC?

Approximately 10%-30%

Table 1 Studies with over 50 cases that have evaluated *BRCA1* mutation prevalence in TN cancers

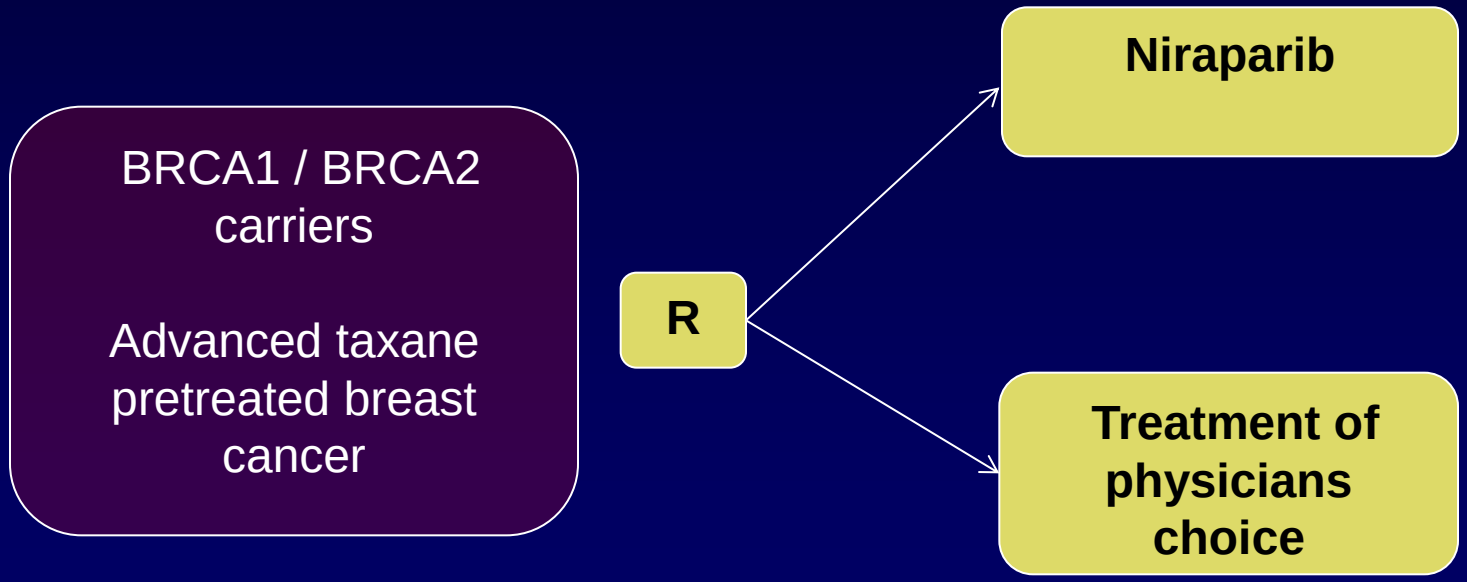
Number of cases	BRCA1 mutations (%)	Unselected/selected	Selection criteria	Reference
144	20 (14)	Unselected		Collins *et al* (2009)
96	9 (9)	Selected	Bilateral and/or family history of breast cancer.	Zhang *et al* (2011)
93	32 (34)	Selected	Seen in Genetic clinics and underwent BRCA testing.	Atchley *et al* (2008)
77	12 (16)	Unselected		Gonzalez-Angulo *et al* (2011)
64	19 (30)	Selected	Ashkenazi Jewish heritage. Tested for founder mutations.	Comen *et al* (2011)
63	8 (13)	Selected and unselected	TN <41 years	Evans *et al* (2011)
54	5 (9)	Selected	TN <40 years *and* did not qualify for testing according to ASCO guidelines	Young *et al* (2009)

Abbreviation: TN = Triple-negative.

"For now, perhaps the simplest recommendation is to test women ***under age 50 years with triple-negative breast cancer*** *and women with a* ***family history of early-onset breast cancer or ovarian cancer" Steven Narod JCO***

Robertson L, et al. *Br J Cancer.* 2012;106(6):1234-1238.

Tesaro Trial in *BRCA1 / BRCA2* Carriers With Advanced Breast Cancer



TNBC Subtypes: (Some) Research Strategies

Basal-like 1: Cell cycle, DNA repair and proliferation genes → **PARPi, ± DNA damaging agents homologous recombination deficiency assay (BRCA-1 ness)**

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R) → **EGFR (cetuximab, lapatinib)**
Self-renewal pathways (stem cell)
Wnt
Notch (PF03084014, AACR 2012

IM: Immune cell processes (medullary breast cancer) → **Immune check point**
PD1/PDL1, CTLA4
Vaccines: MUC1, NYO-ESO1

M: Cell motility and differentiation, EMT processes

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

Plus
PI3Ki, RAS/MEK/Erk, MET, PTEN
etc, etc

LAR: Androgen receptor and downstream genes, luminal features → **Agents targeting androgen receptor (enzalutamide, bicalutamide, etc)**

Conclusions: Treatment of TNBC

- No standard therapy for metastatic TNBC
  - No evidence that one chemotherapy is superior to another
  - Are triple negative breast cancers truly more susceptible to platinum-based vs other chemotherapy (hence TNT)?
  - Which sub-groups benefit most?
  - Is there a difference between cisplatin and carboplatin?
- Most active agents currently licensed for use appear to be:
  - Cisplatin based chemotherapy
  - Chemotherapy + bevacizumab
- Find out BRCA1/2 status and put your patients into clinical trials
  - Entry criteria MUST reflect the natural history of the disease

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions