Introduction: Recent failures in drug development for triple negative breast cancer

Fabrice ANDRE

Institut Gustave Roussy

Villejuif, France

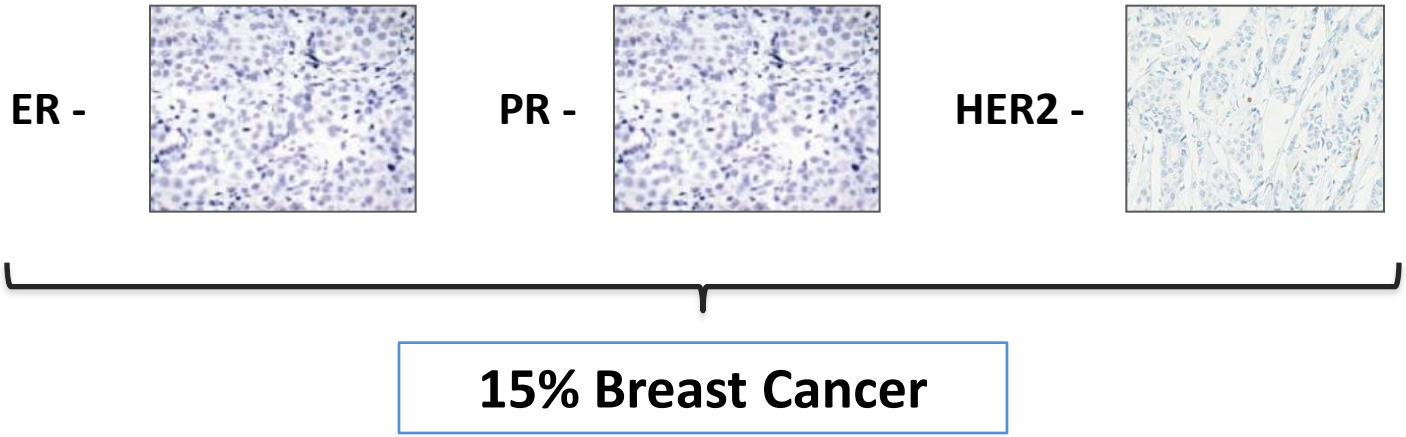
Conflicts of interest

- Astra Zeneca
- Sanofi
- Novartis
- Roche

« The criticism is easy, the Art difficult »

Le Glorieux, II, 5

Triple negative breast cancer



Enriched in basal-like breast cancer

- Enriched in BRCA1-germline mutations
- High chemosensitivity and high chemoresistance
- High frequency of p53 mutations

Outline

- **Medical need is TOO important**

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  - Need for biomarker to homogeneize the population

- Chemotherapy is the backbone treatment

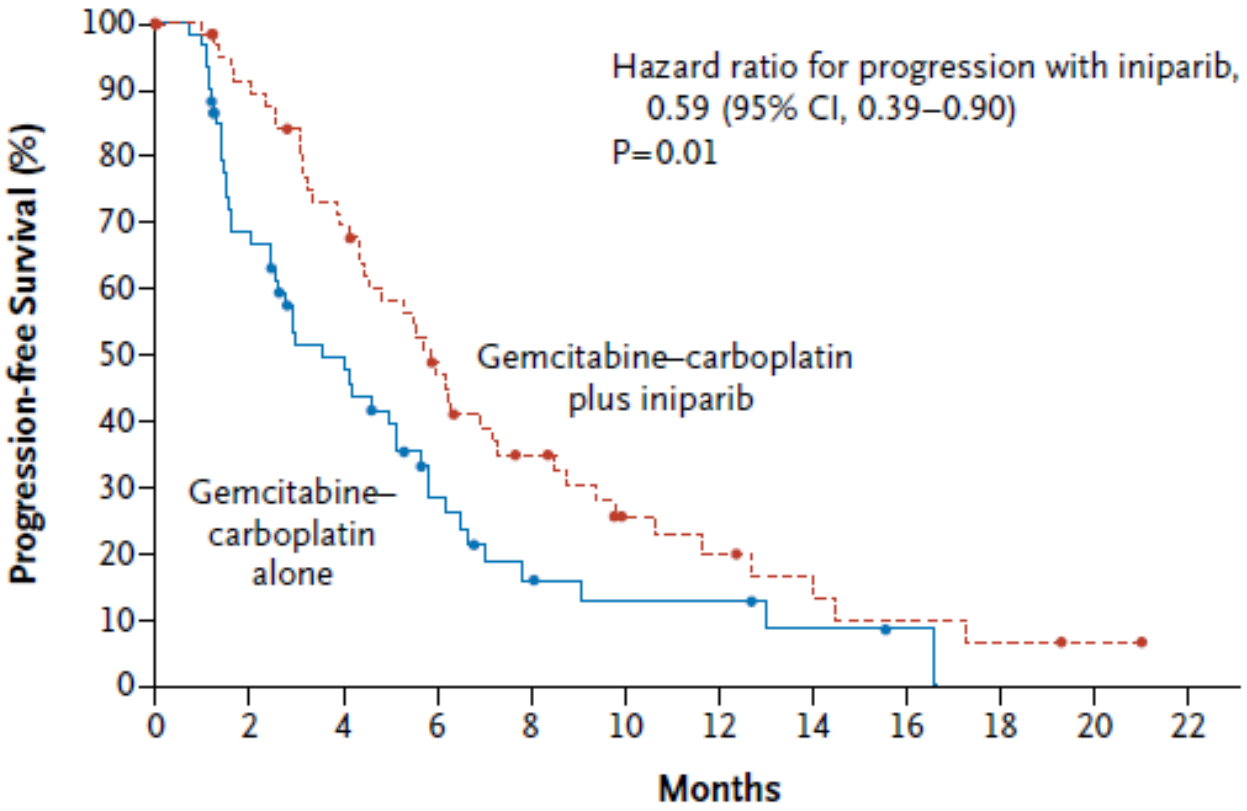
- Partner matters

- Survival is short and OS should be the endpoint

- Disease is complex, instable and heterogenous
  - Combined targeted agents ?

- An effective drug in breast cancer MUST give signal in patients who are resistant to chemotherapy

Phase II randomized trial evaluating Iniparib



Major difference between experimental arm and control arm

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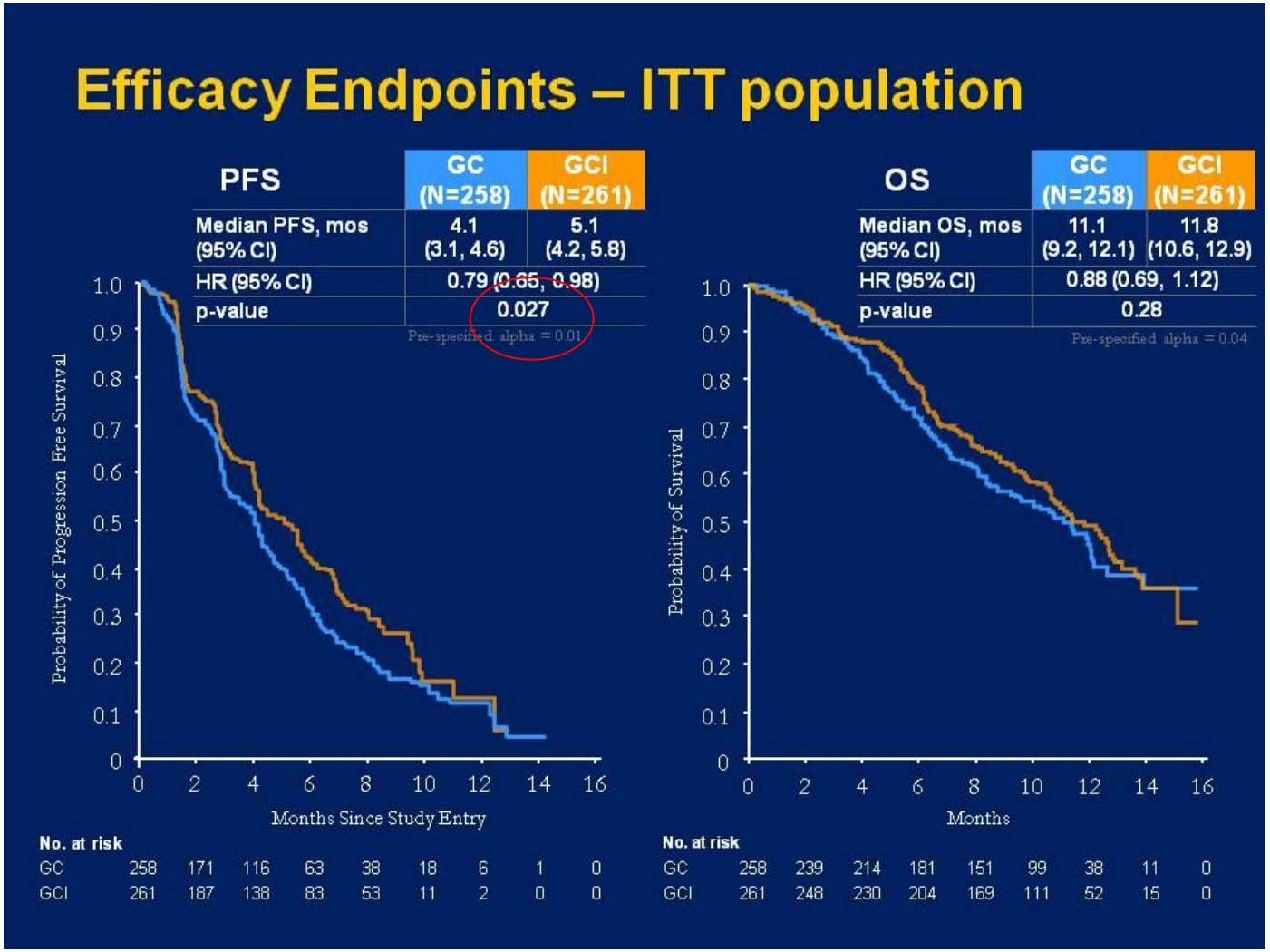
Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.

Iniparib: registration trial

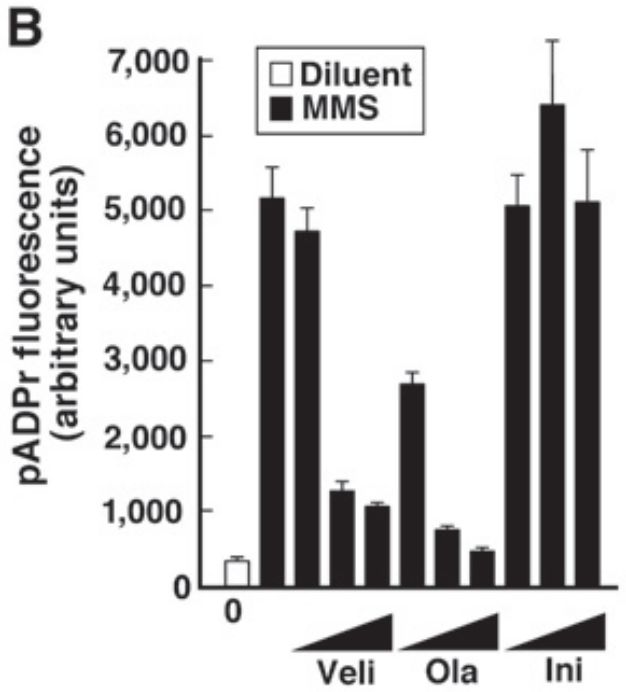


Study did not meet pre-specified p value

But was statistically significant using « old » threshold

O'Shaughnessy, ASCO, 2010

Post-hoc research work on bioactivity



Iniparib does not present biological properties initially thought

Iniparib: phase I/II data

?

Take home messages

- Development was too quick and not based on science

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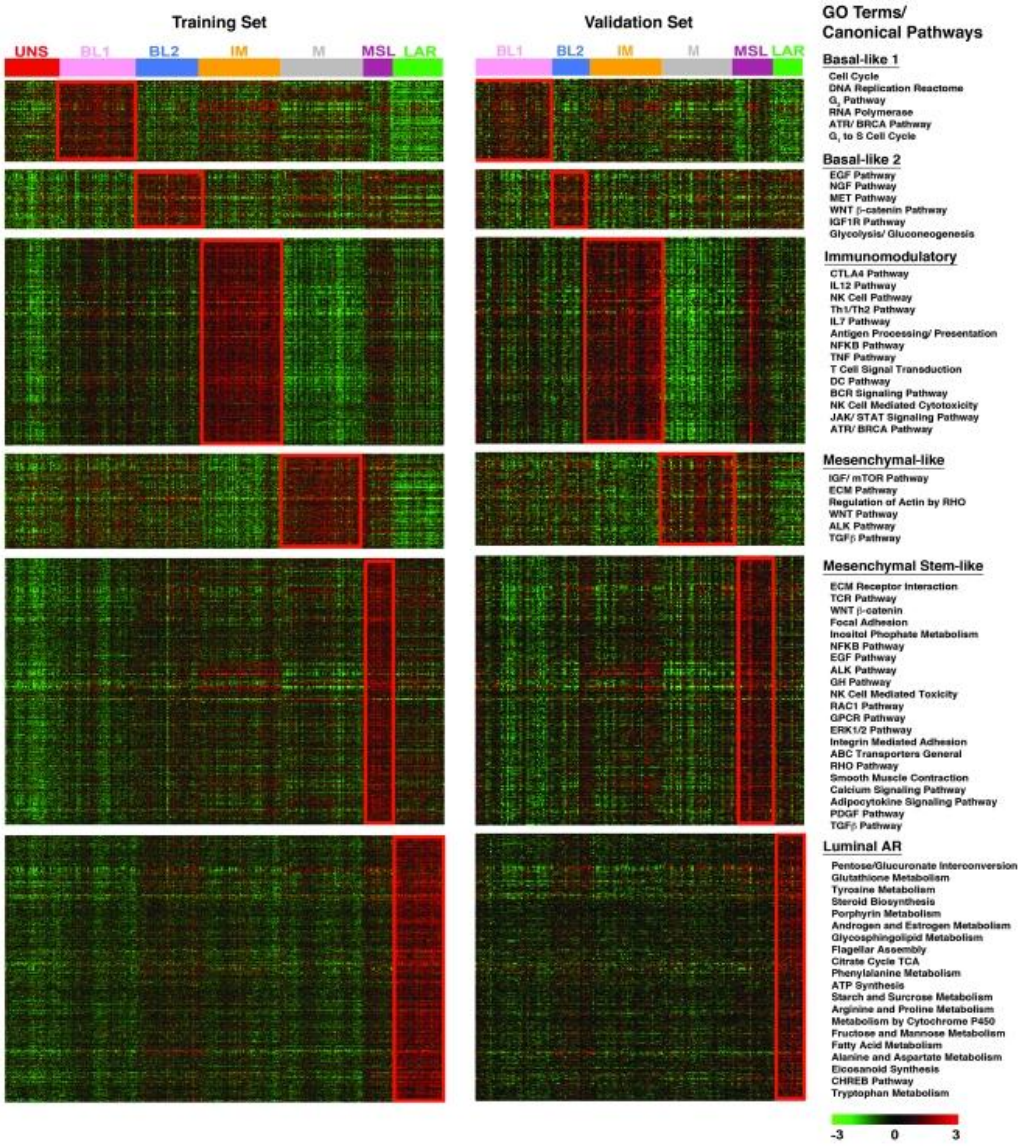
TN Breast Cancer: a heterogeneous entity



DNA repair

TK/ WNT pathways

Immune stimulation

mTOR
ALK
Erk

AR

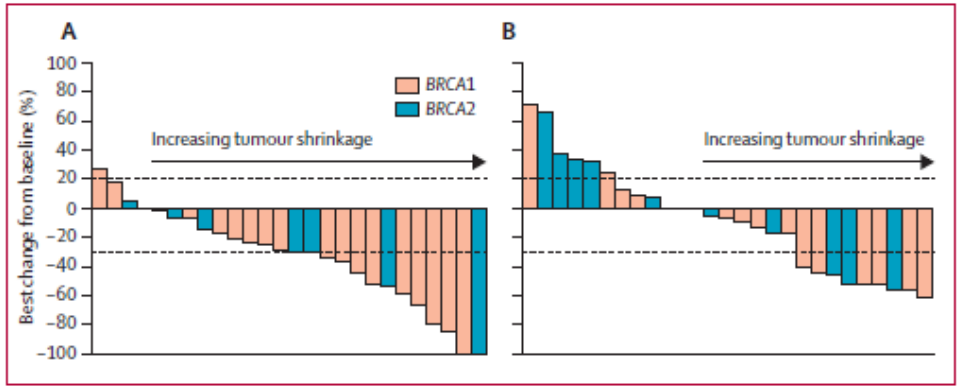
Lehmann, J Clin Invest, 2011

Phase II Trial Testing Olaparib (a PARP 1 Inhibitor) in BRCA-Deficient Advanced Breast Cancer

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

Table 2: **Best overall confirmed tumour response status (intention-to-treat population)**



Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

… but non consistent response rates across trials

	Ovarian cancer						Breast cancer					
	BRCA (n=17)				Non-*BRCA* (n=46)	Total (n=63)	*BRCA* (n=8)				Non-*BRCA* (n=15)	Total (n=23)
	BRCA1	*BRCA2*	Both	Total			*BRCA1*	*BRCA2*	Both	Total		
Confirmed objective response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)	0	0	0	0	0	0
Complete response	0	0	0	0	0	0	0	0	0	0	0	0
Partial response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)	0	0	0	0	0	0
Stable disease ≥8 weeks	5 (29%)	1 (6%)	0	6 (35%)	18 (39%)	24 (38%)	2 (25%)	3 (38%)	0	5 (63%)	2 (13%)	7 (30%)
Progressive disease	1 (6%)	1 (6%)	1 (6%)	3 (18%)	13 (28%)	16 (25%)	1 (13%)	2 (25%)	0	3 (38%)	12 (80%)	15 (65%)
Not evaluable	1 (6%)	0	0	1 (6%)	4 (9%)	5 (8%)	0	0	0	0	1 (7%)	1 (4%)

Data are only for those patients assessable for objective Response Evaluation Criteria in Solid Tumors response (measurable lesions at baseline). One patient with non-*BRCA* ovarian cancer (best response was progressive disease) and one patient with *BRCA1*, one with *BRCA2*, and one with non-*BRCA* breast cancer (all best responses were stable disease) were excluded from the table.

***Table 2*: Best objective response rates (Response Evaluation Criteria in Solid Tumors) for patients with ovarian cancer and breast cancer**

Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study

Karen A Gelmon, Marc Tischkowitz, Helen Mackay, Kenneth Swenerton, André Robidoux, Katia Tonkin, Hal Hirte, David Huntsman, Mark Clemons, Blake Gilks, Rinat Yerushalmi, Evan Macpherson, James Carmichael, Amit Oza

Phase II trials in biomarker-defined populations

Sample size of phase II trials needs to be increased to generate more data

- Need for large consortium
- Reference centers

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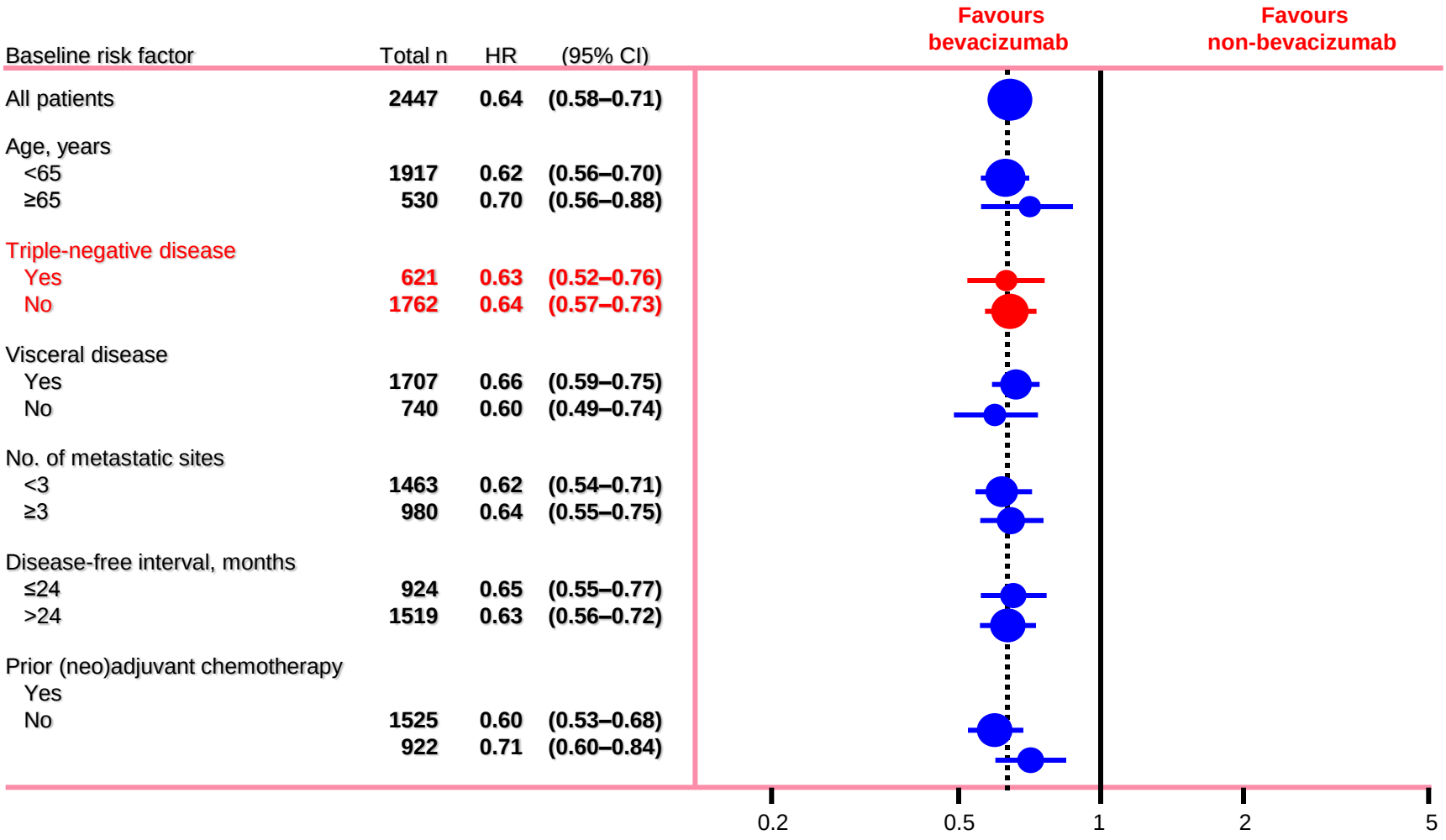
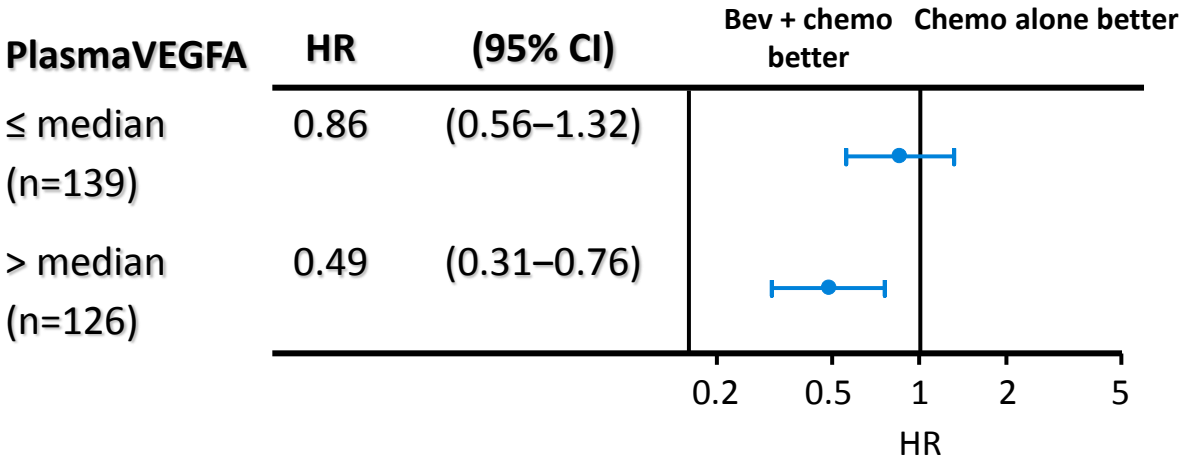
Efficacy of bevacizumab according to TNBC subype: 1st line treatment



Baseline risk factor	Total n	HR	(95% CI)
All patients	2447	0.64	(0.58–0.71)
Age, years			
<65	1917	0.62	(0.56–0.70)
≥65	530	0.70	(0.56–0.88)
Triple-negative disease			
Yes	621	0.63	(0.52–0.76)
No	1762	0.64	(0.57–0.73)
Visceral disease			
Yes	1707	0.66	(0.59–0.75)
No	740	0.60	(0.49–0.74)
No. of metastatic sites			
<3	1463	0.62	(0.54–0.71)
≥3	980	0.64	(0.55–0.75)
Disease-free interval, months			
≤24	924	0.65	(0.55–0.77)
>24	1519	0.63	(0.56–0.72)
Prior (neo)adjuvant chemotherapy			
Yes	1525	0.60	(0.53–0.68)
No	922	0.71	(0.60–0.84)

O'Shaughnessy et al. ASCO 2010

Biomarker for bevacizumab efficacy



Interaction p-value = 0.08

Interpatient heterogeneity regarding bevacizumab sensitivity

Miles, SABCS, 2010

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Phase II Trial of Sunitinib Single-Agent in Advanced Breast Cancer Patients Previously Treated with Anthracyclines and Taxanes

Phase II single

ORR = 11% (7 PRs) (15% in triple negative breast cancer)

1816.

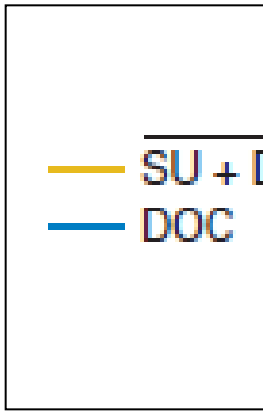

Table 2. Study Drug Exposure

Measure	Sunitinib + Docetaxel (n = 295)		Docetaxel (n = 293)
	Sunitinib	Docetaxel	
Average dose per cycle, mg/m^2			
Median	37.5*	73	96
Range	26-41	39-87	65-112
Relative dose-intensity, %			
Median	94	92	93
Range	14-142†	52-108	57-112
Duration of treatment, weeks			
Median	26	18	18
Range	23-29	17-21	16-19
Cycles started			
Median	8	7	6
Range	1-32	1-23	1-26

NOTE. As-treated data are presented.
*Median average daily dose in milligrams.
†Two patients inadvertently received sunitinib at a starting dose of 12.5 mg/d, and one patient received sunitinib at 75 mg/d during cycles 2 and 3.

Negative phase III trial

Low dose intensity for docetaxel in the experimental arm

Bergh J, J Clin Oncol, 2011

Lesson

- A targeted therapy cannot make it if it requires to reduce chemotherapy dose

- If MTD requires dose reduction of chemo: develop in maintenance phase ???

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- **Partner matters: paclitaxel versus docetaxel Bevacizumab**
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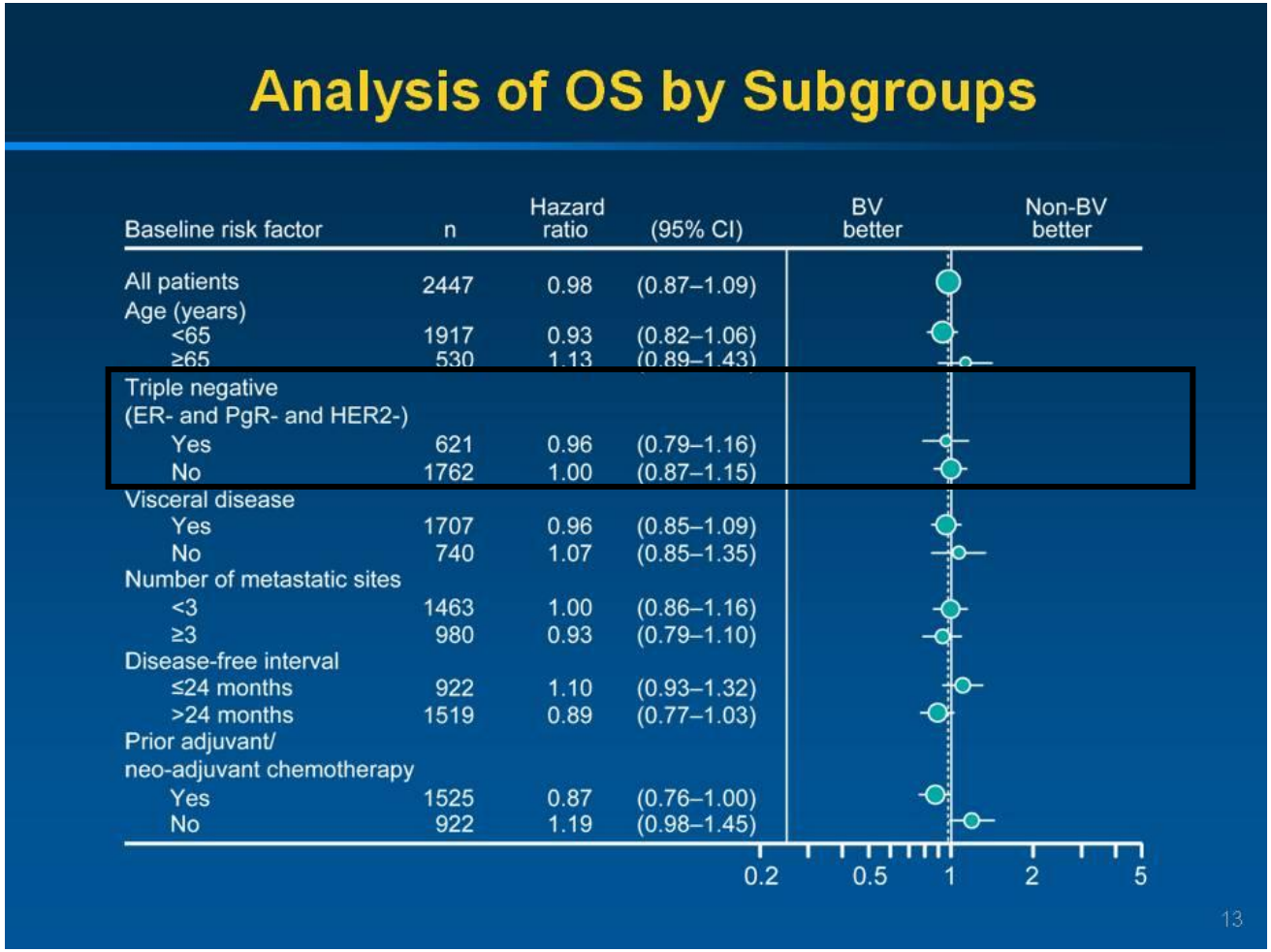
Bevacizumab efficacy: Metaanalysis



O'Shaughnessy, ASCO, 2010

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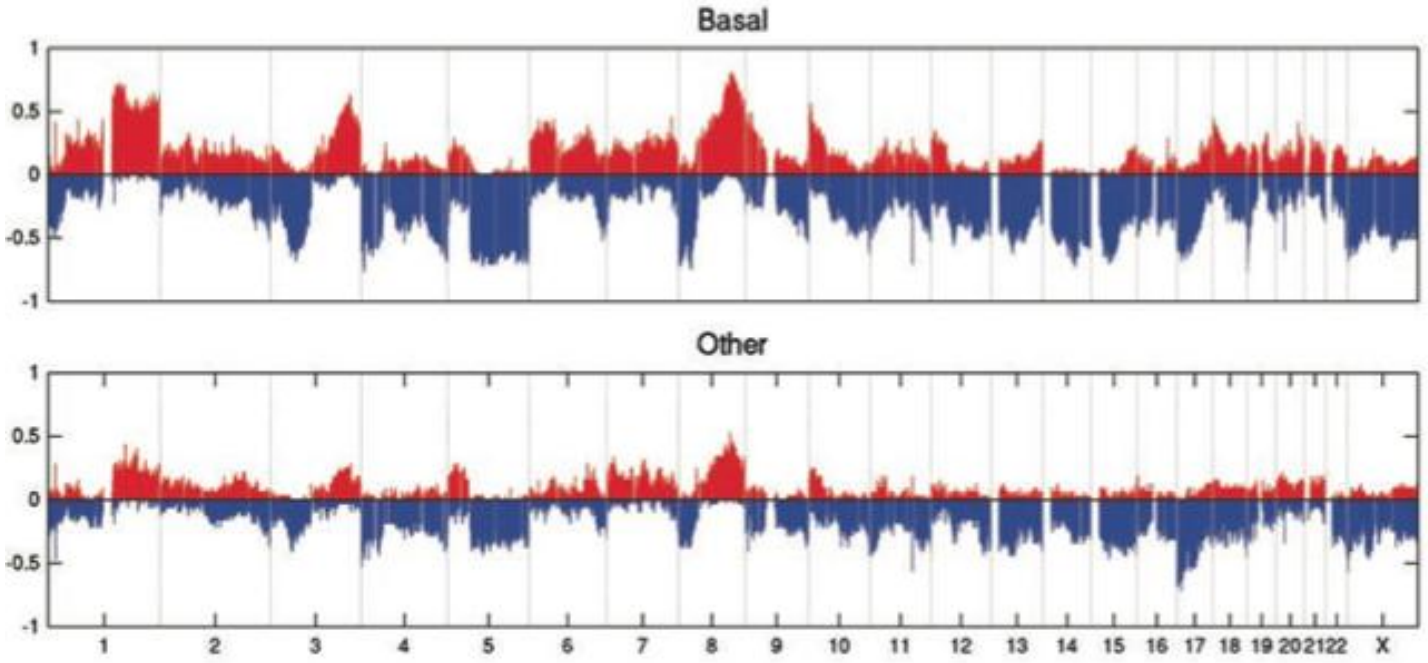
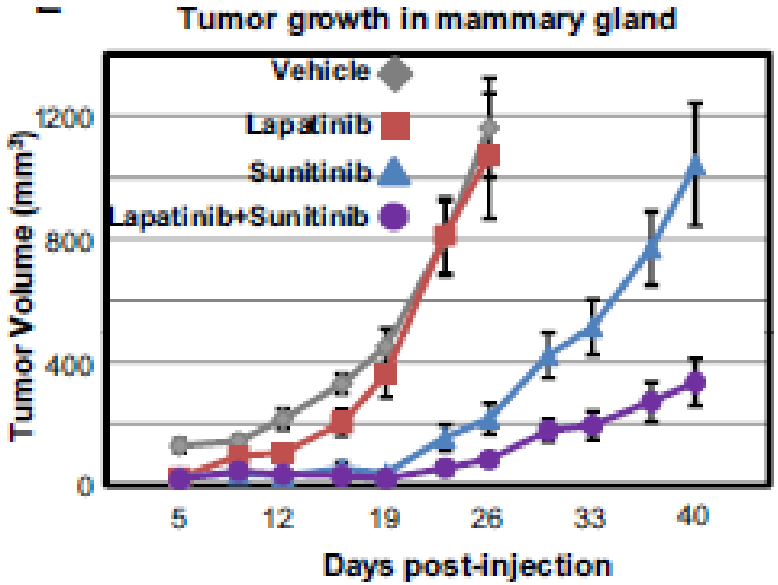
Genomic landscape TNBC



Shah et al, Nature, 2012

High level of genomic instability: Can a single agent improve outcome ?

Mechanisms of resistance: Moving toward combinations



Sun, Cell, 2011

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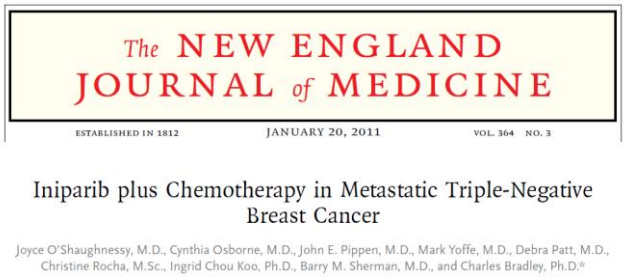
Cross-over data iniparib

- 83% discontinued treatment after 1 or 2 cycles
- 1 unconfirmed response out of 30 patients
- 13% stable disease

Iniparib did NOT reverse resistance to carboplatin…



Drug development TNBC: checklist

No rush: need for lot of science before moving phase III

Develop biomarker early in the development

Find signal in patients who are resistant to conventional treatment

Large phase II trials to generate science and robust clinical data

Combination with chemotherapy only if chemotherapy could
Be delivered full dose

Combine with the most synergistics chemotherapy

OS as primary endpoint

Combined several approaches: kinases / cytotoxic / host

Acknowledgements

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A. Tutt

M. Arnedos

S. Scherer