Metastasi cerebrali nelle pazienti con carcinoma mammario e mutazione di BRCA

Roma 4 ottobre 2019

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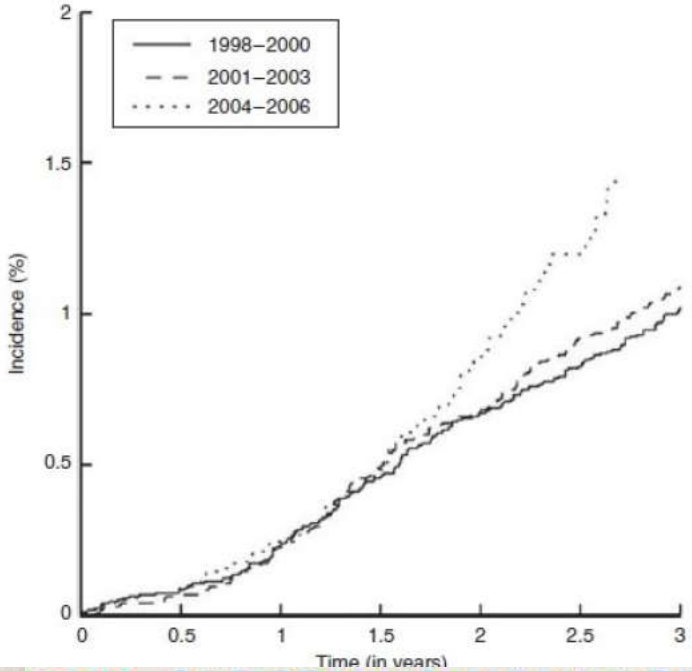
Outline

- Different incidence of brain metastases according to breast cancer subtype
- Incidence of brain metastases in BRCA-mutated patients
- Systemic treatments
  - Platinum
  - PARP-i

How many women with brain metastases during their breast cancer?

Early stage breast cancer: 3%-6%
Stage IV disease: 10-16%
Incidence increased in recent years and varies according to tumor biology

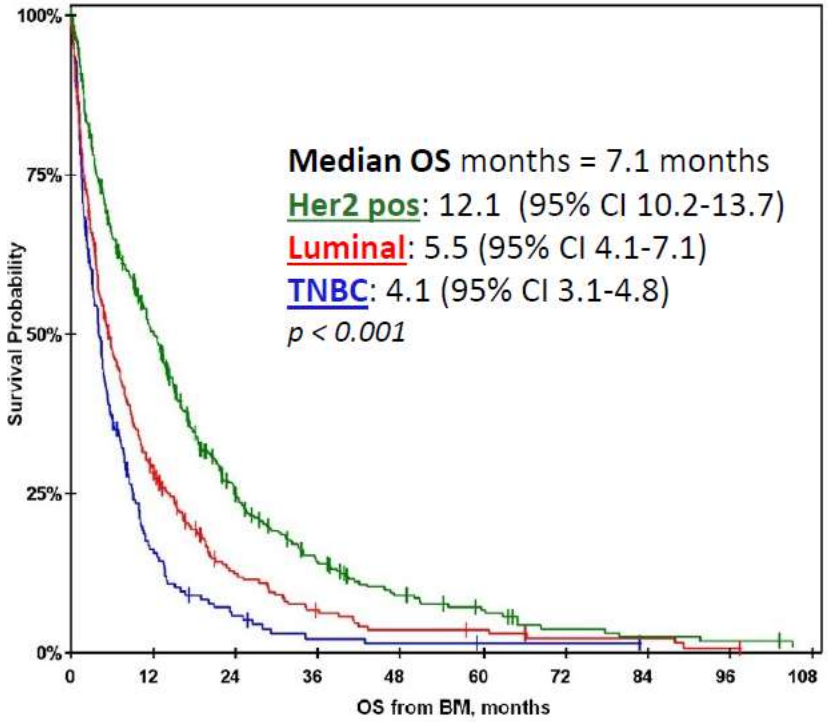


FREQUENCY OF BRAIN METASTASIS AMONG PATIENTS WHO DEVELOPED DISTANT DISEASE

Subtype	No. of Patients	Brain	
		No.	%
Luminal A	458	35	7.6
Luminal B	378	41	10.8
HER2 positive, ER/PR positive	117	18	15.4
HER2 positive, ER/PR negative	136	39	28.7
Basal-like	159	40	25.2
TN nonbasal	109	24	22.0
P			< .001

Kennecke H et al.JCO2010

Overall survival with brain metastases according to breast cancer subtypes



Mueller V et al, ASCO 2016

SUBTYPES AND SURVIVAL IN TWO DIFFERENT TIME PERIOD

Parameter	Year of diagnosis		p-value
	2000–2009	2010–2015	
	N (%)	N (%)	
	N = 507	N = 893	
Subtype			
TNBC	105 (20.7)	198 (22.2)	
Luminal like	144 (28.4)	303 (33.9)	
HER2 positive	258 (50.9)	392 (43.9)	0.0331
	N = 623	N = 967	
Median overall survival	Months (95% CI) 7.6 (6.5–9.2)	Months (95% CI) 5.8 (5.0–6.5)	<0.0001

Witzel I. et al, Eur J Cancer 2018

Different behavior according to subtypes

Clinical features	HER2-positive	TNBC	Luminal
Timing of CNS relapse	Continuous over time	Tends to be early	Tends to be late
Control of extracranial disease at time of CNS relapse	Frequent	Uncommon	Varies
Median OS from time of CNS relapse	≈12 months	≈4-5 months	≈5-6 months
Leptomeningeal involvement	Less frequent	More frequent and tends to be early	More frequent and tends to be late

Mueller V. ASCO 2016, Witzel I. Eur J Cancer 2018, Darlix A. J Neurooncol 2018, Lin NU Clin Cancer Res 2013

Different phenotype of BRCA1 and BRCA2 breast cancer

Phenotype	*BRCA1*	*BRCA2*	Notes
ER expression	Negative in 80–90%	Positive in 60–65%	One of the major mysteries to be solved
PR expression	Predominantly negative	Positive in the majority of cases	Less complete data relative to ER expression
ERBB2 amplification	Usually absent	~15% have amplification	*ERBB2* amplification can occur in BRCA mutation carriers
Early onset	Highly prevalent between 30 and 50 years of age	Less prevalent between 40 and 70 years of age	
Lobular cancers	Less likely	As frequent as in sporadic breast cancer (~15%)	
High grade	Likely	Common	More common than sporadic cancers
Basal markers	Frequent	Less common	Tumours have cytokeratin profile of basal or myoepithelial markers
HR function	Defective	Defective	Some debate over the frequency of LOH for the wild-type allele

Roy R et al. Nature Rev Cancer 2012

Brain metastases and BRCA status

In BRCA1 mutated-patients higher incidence of brain metastases[1,2]

Predilection for CNS spread because of:

- **downstream effects of BRCA1 mutation**

or

- **association of BRCA1 with basal-like triple negative disease (worse prognosis)?**

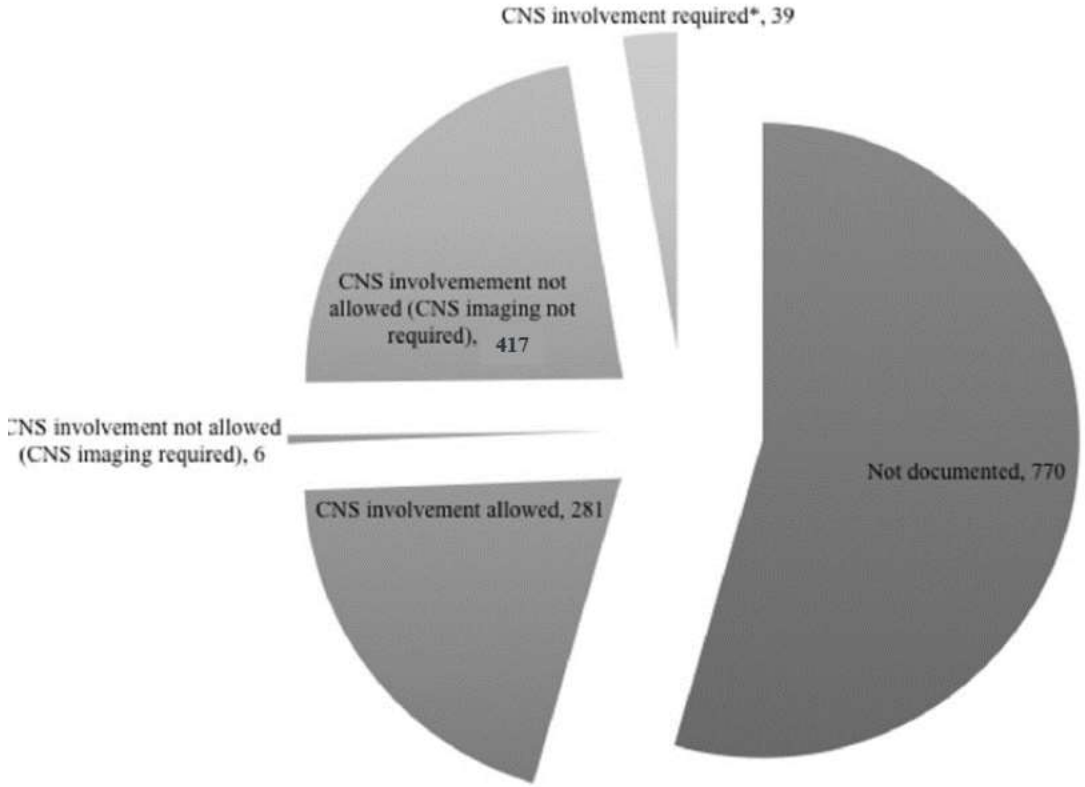
1 Lee L, et al. Cancer 2011;117:3093-3100
2 Albiges L et al. Ann Oncol 2005;16:1846-1847

Brain metastases and BRCA status

- Limited data
- Biological predilection of basal-like TN breast cancer fon CNS spread may explain high rate of brain metastases
- Retrospective data suggest shorter interval to brain progression compared with BRCA-negative patients.

Zavitsanos PJ et al. Am J Clinical Oncol 2018

Patients with brain metastases systemically excluded from most clinical trials



Total: 1474 trial

Among **109** early phase studies limited to **HR+/HER2- MBC**

- **17** (15.6%) allowed history of CNS involvement

Need to include brain metastasis patients in clinical trial

- Most published early phase clinical trials either did not clearly document or did not allow for accrual of patients with CNS disease.
- Early phase trials with targeted agents or enrolling HER2+ MBC had higher odds of permitting CNS metastases.

Costa R et al. Cancer Treat Rev2017

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Edward S. Kim, Suanna S. Gore, ...

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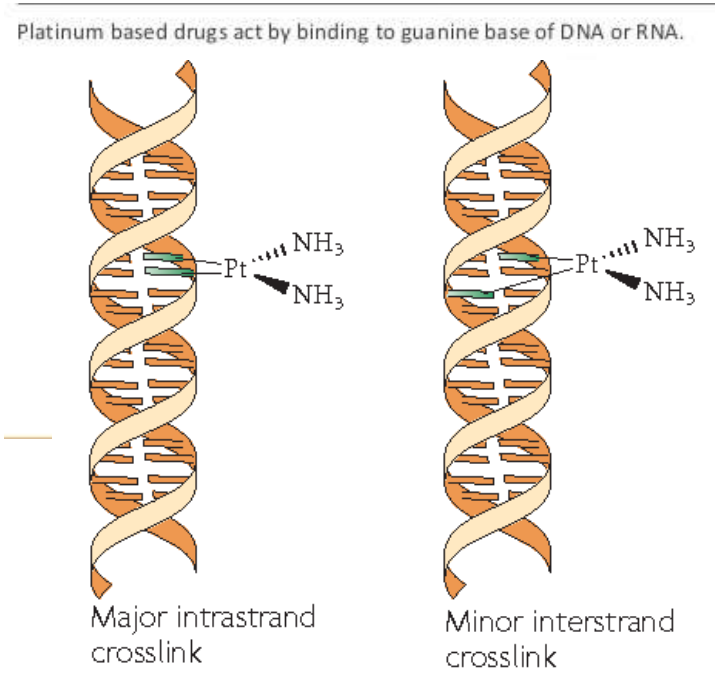
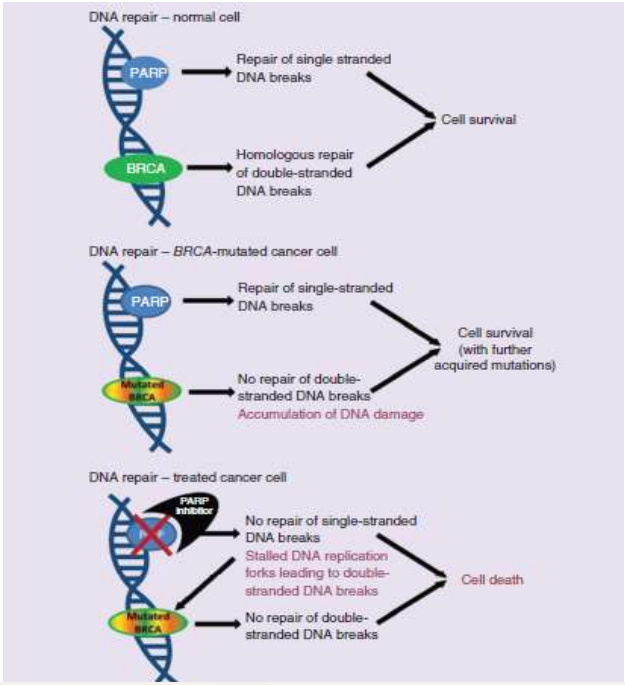
Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group

Nancy U. Lin, Tatiana Prowell, Antoinette R. Tan, Marina Kozak, Oliver Rosen, Laleh Amiri-Kordestani, ...

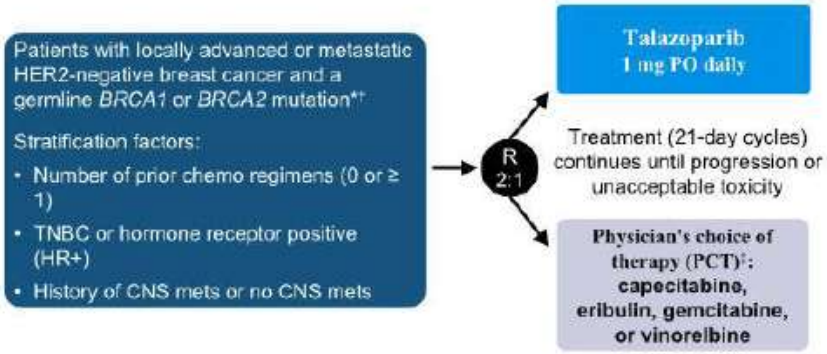
Systemic treatment of brain metastases in BRCA-mutated patients

- Conderations include status of extra-CNS disease, history of brain metastases (initial vs subsequent, timing), local therapy options
- No systemic agents with a specific indication
- Consider platinum and PARP-inhibitors





Study Design: EMBRACA



Primary endpoint
- Progression-free survival by RECIST by blinded central review

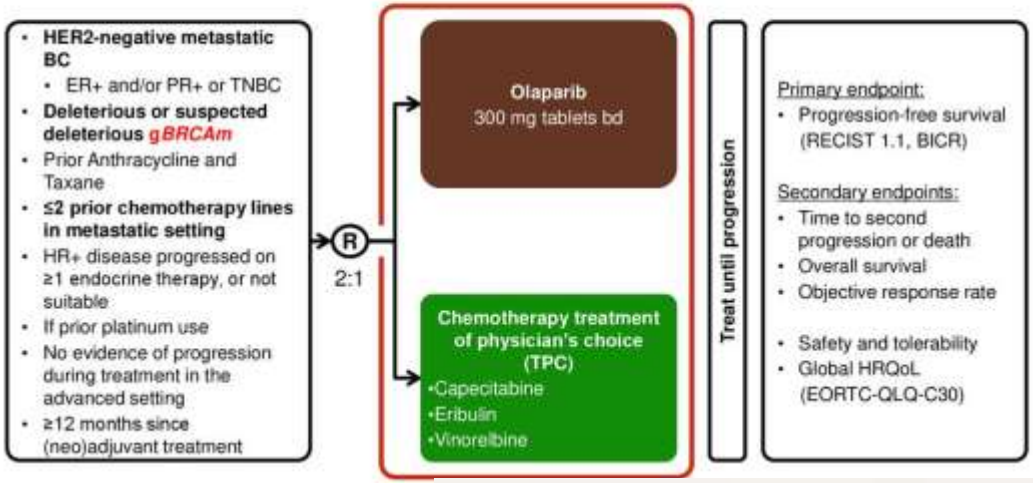
Key secondary efficacy endpoints
- Overall survival (OS)
- ORR by investigator
- Safety

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

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

Litton JK et al, NEJM 2018

OlympiAD – Phase III trial of Olaparib monotherapy versus chemotherapy for patients with HER2- mBC and a germline *BRCA mutation*



Robson M et al, NEJM 2017

OlympiAD trial: patients population

	Olaparib n=205	TPC n=97
Age (median)	44	45
BRCA1 BRCA2	117 (57) 84 (41)	51 (53) 46 (47)
HR+ TN	103 (50) 102 (50)	49 (51) 48 (49)
New MBC	26 (13)	12 (12)
Previous CT for MBC	146 (71)	69 (71)
Previous platinum	60 (29)	26 (27)
≥2 met sites	159 (78)	72 (74)
Bone only	16 (8)	6 (6)

A/T PRETREATED

MOST pts RECEIVED CT FOR MBC

HR+: ENDOCRINE RESISTANT

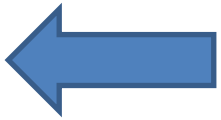
TN: NON-PLATINUM RESISTANT

Robson M et al, NEJM 2017

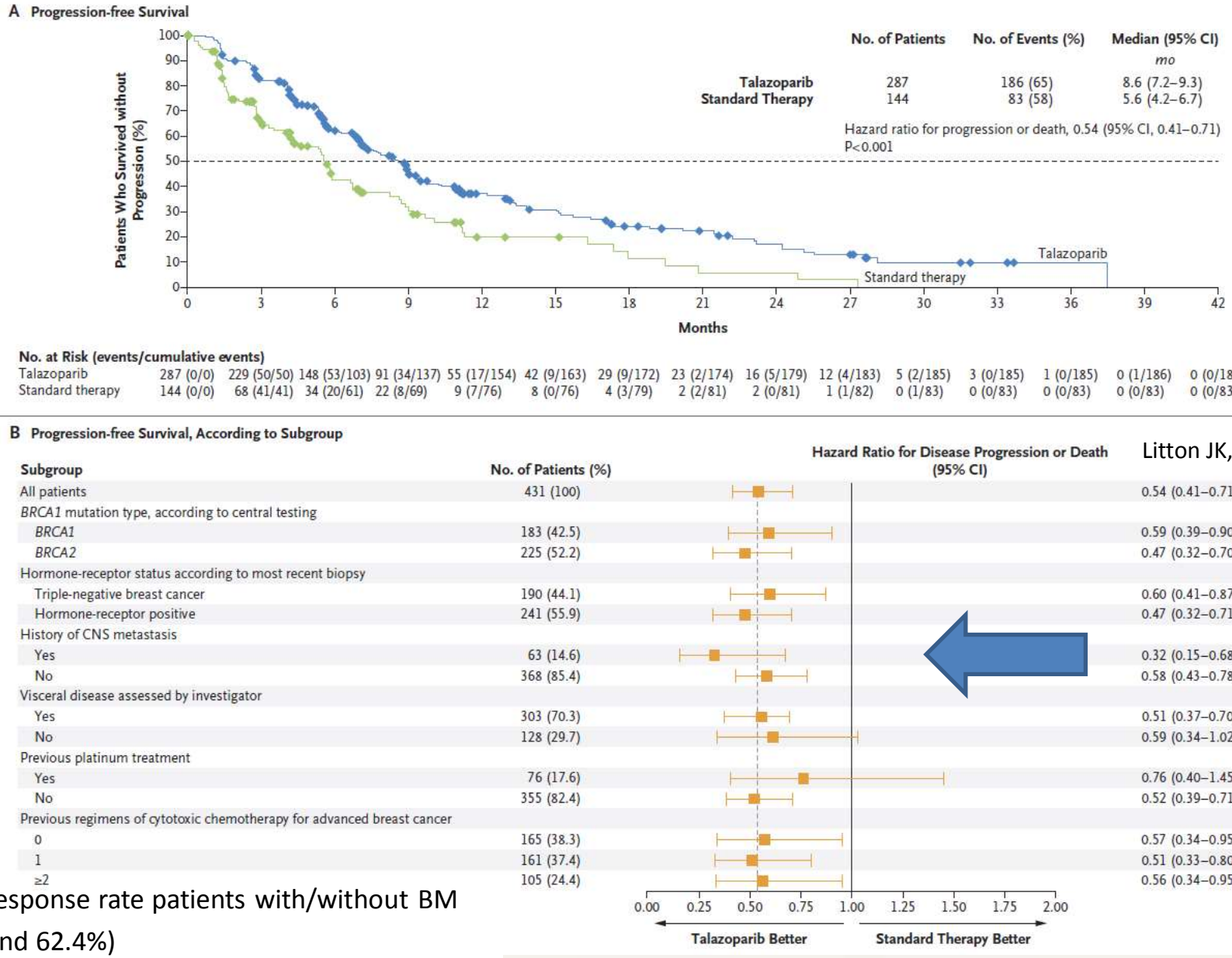
What about brain metastases?

EMBRACA trial: patients population

	Talazoparib	TPC
Age	45	50
BRCA1	46.3	46.8
BRCA2	53.7	56.2
HR+	54.7	58.3
TN	45.3	41.7
Visceral disease	69.7	71.5
History CNS metastases	15	13.9
Previous platinum	16	20.8



Litton JK, NEJM 2018



Litton JK, NEJM 2018

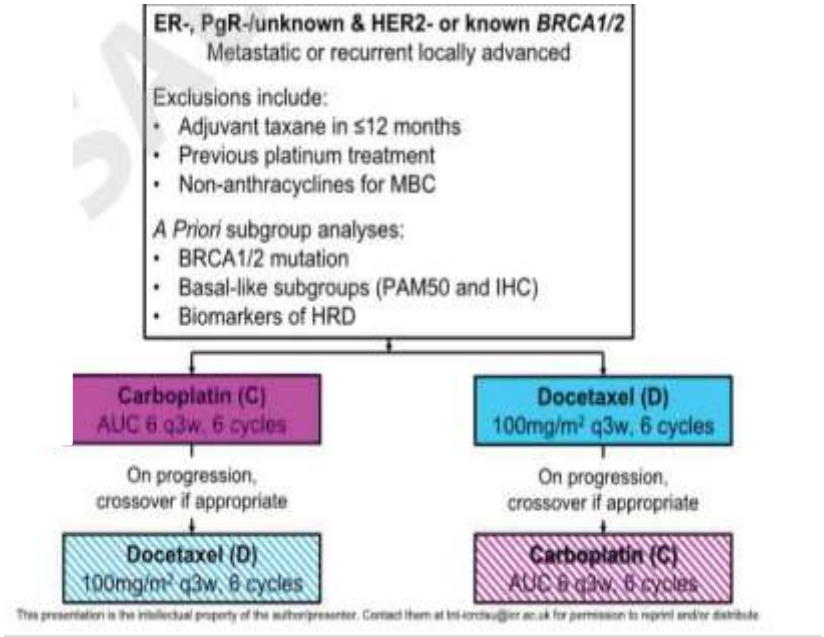
Similar response rate patients with/without BM (63.2% and 62.4%)

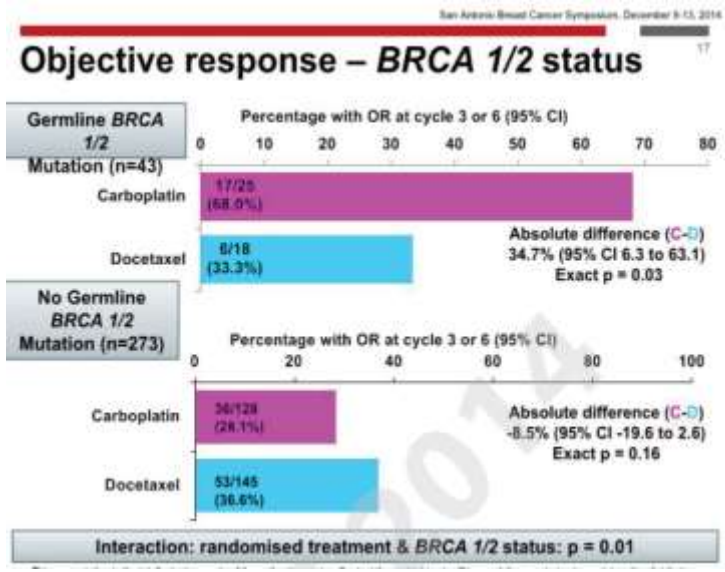
Platinum for BRCA-mutated breast cancer

Study	N pts/BRCAm	Tumor type	Prior CT	CT regimen	ORR,%	
					BRCA carriers	BRCA wt
Byrski	20	TN (15) Other (5)	Any	Cis	80%	--
Isakoff	86/11	TN	≤1	Cis/Carbo	54.5%	25.6%
Tutt	376/67	TN	No	Carbo vs Doce	68% 33.3%	28% 34.5%
Somlo	28 Phase I 44 Phase II	Any	Any	Vel+carbo Vel>carbo	53% 50%	--
Han	284	Any	≤2	Pcarbo vs Vel+Pcarbo	61.3% 77.8%	--

Byrski T et al. Breast Cancer Res 2012; Isakoff SJ, et al. JCO 2015; Tutt A et al. Nature Med 2018; Baselga J et al. JCO 2013; Somlo et al. Clin Cancer Res 2017;Han HS et al. Ann Oncol 2018

TNT trial: a randomized phase III of carboplatin compared with docetaxel in triple negative or BRCA1/2 breast cancer

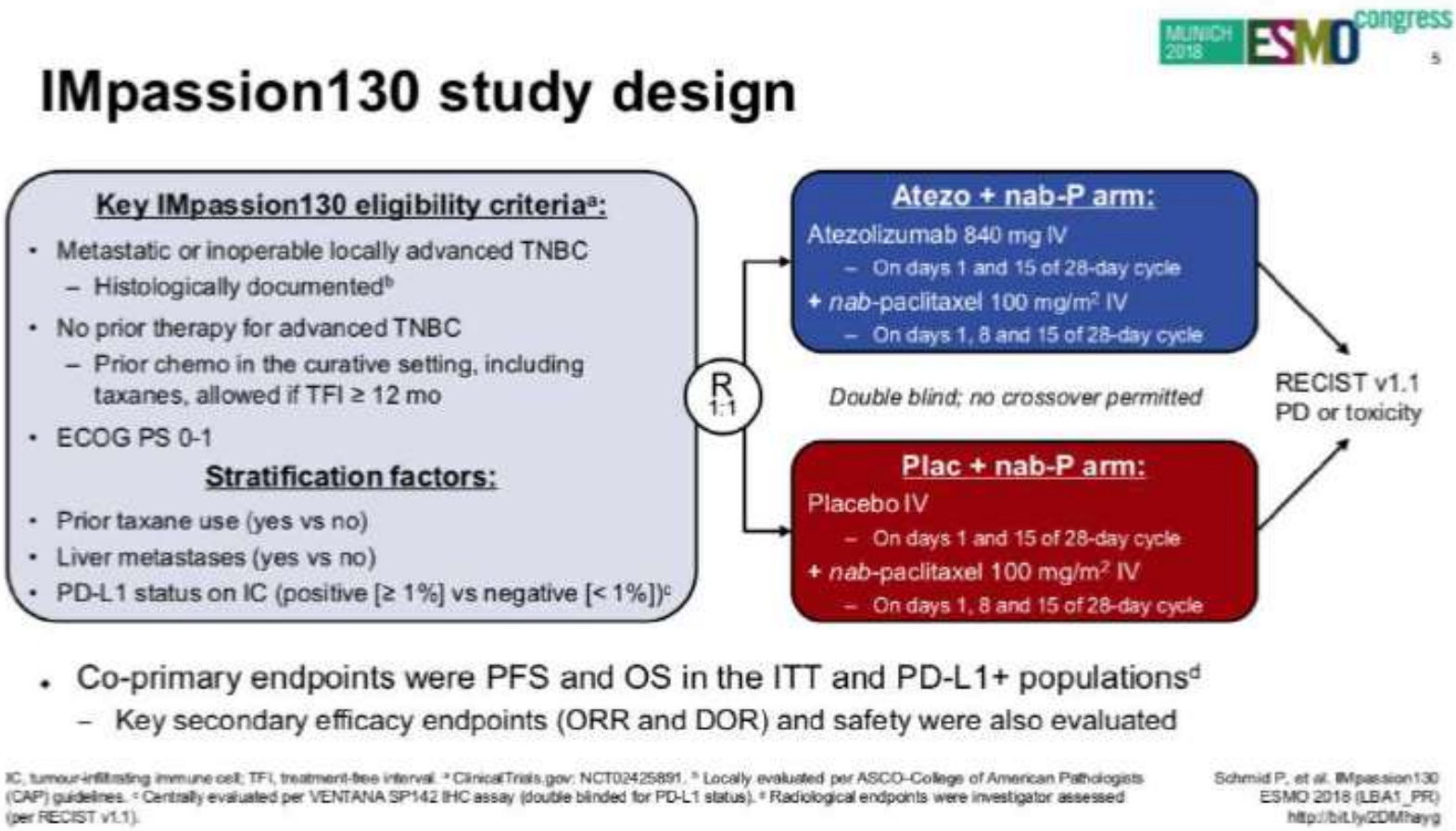




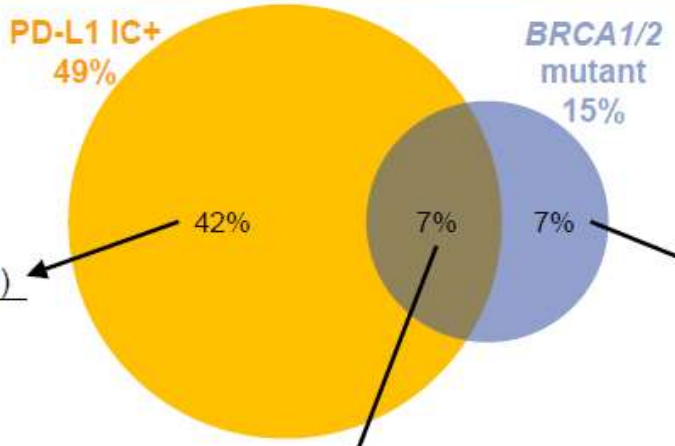
Tutt A et al.SABCS2014
Tutt A et al. Nature med 2018

«Patients with stable, treated brain metastases will be eligibile with other sites of measurable disease»

Immunotherapy: clinical benefit in BRCA mutated pts?



The clinical benefit derived by PD-L1 IC+ patients was independent of their *BRCA1/2* mutation status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)[a]
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+[b]***

BEP (BRCA1/2): n = 612. Per FoundationOne *BRCA1/2* testing, *BRCA1/2* mutant: known and likely mutations. All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests. [b] Data interpretation limited by small number of *BRCA1/2*-mutant patients.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

<7% pts (n=61) with brain metastases

Brain metastases				
Yes	61	4.9	4.4	0.86 (0.50–1.49)
No	841	7.2	5.5	0.80 (0.69–0.93)

Challanges: combining PARP-i with..

- **Platinum**

Phase II trial with cisplatin +/- veliparib in metastastic triple-negative and/or BRCA mutation BC with/without brain metastases (NCT02595905)

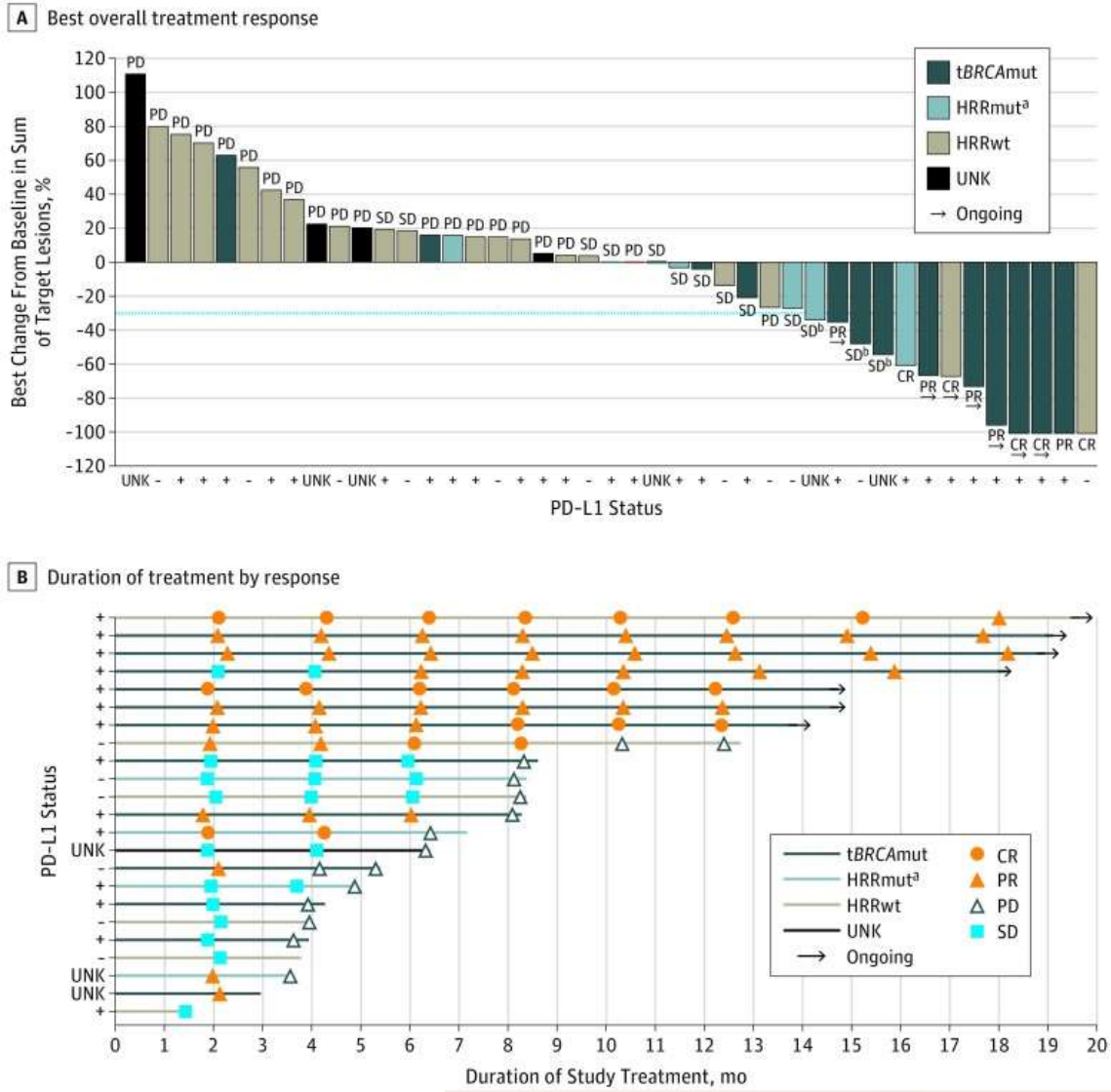
- **Targeted agents**

Synthetic lethal interactions by targeting several levels of the DNA repair machinery (i.e. combinations with ATR or HDAC inhibitors), take advantage of the relation between angiogenesis, hypoxia and DNA damage or exploit the cross-talk between DDR and hormone receptor–driven pathways

- **Checkpoint inhibitors**

PARPinhibition may trigger neoantigen and non-neoantigen based mechanisms of tumour cell recognition by the immune system

Topacio trial phase II single-arm, open label pembrolizumab +niraparib in metastatic triple negative



Vinayak S et al. JAMA Oncol 2019

Take-home messages

- Incidence of brain metastases in BRCA1+ patients is higher than BRCA2+ and BRCA wt patients
- No specific systemic agents approved.
  Consider Platinum-regimen and PARP-i
- Promising studies including PARP-i, immunecheck point and platinum are ongoing
- Need to include brain metastases patients in clinical trials and multidisciplinary approach