

Metastasi cerebrali nelle pazienti con carcinoma mammario e mutazione di BRCA

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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

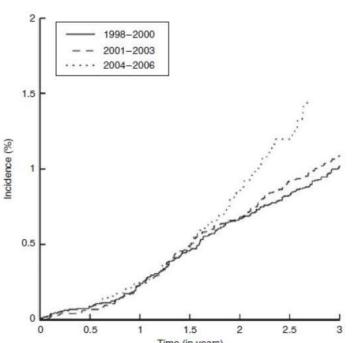


How many women with brain metastases during their breast cancer?

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

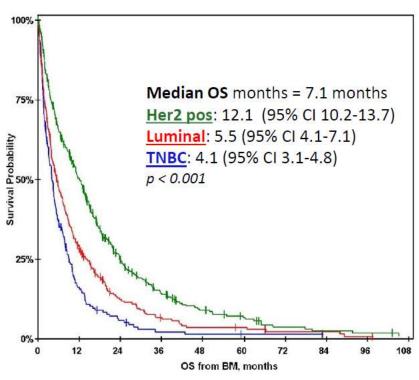
	No. of	Brain		
Subtype	Patients	No.	%	
Luminal A	458	35	7.6	
Luminal B	378	41	10.8	
HER2 positive, ER/PR positive	117	18	15.4	
HER2 positive, ER/PR negative	136	39	28.7	
Basal-like	159	40	25.2	
TN nonbasal	109	24	22.0	
P		< .001		

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 (%)	
<u> </u>	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	Months (95% CI)	Months (95% CI)	
survival	7.6 (6.5-9.2)	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

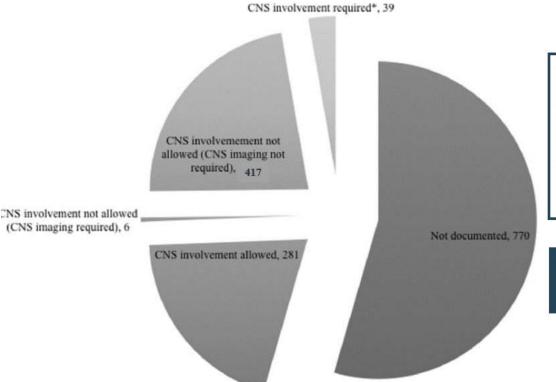
 Retrospective data suggest shorter interval to brain progression compared with BRCA-negative patients.

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





Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement

Edward S. Kim S, Suanna S. Journal of Clinical Oncology® An American Society of Clinical Oncology Journal

- ASCO, in colla launched a cc determining (
- The project le that common brain metasta organ dysfunc

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2017 SPECIAL SERIES ASCO SPECIAL ARTICLES

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

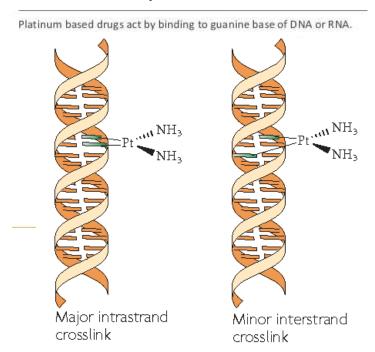
Nancy U. Lin Attiana Prowell, Antoinette R. Tan, Marina Kozak, Oliver Rosen, Laleh Amiri-Kordestani, ...

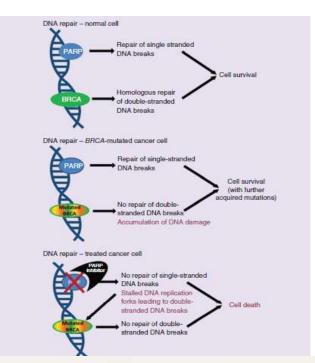




Systemic treatment of brain metastases in BRCA-mutated patients

- 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

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline BRCA1 or BRCA2 mutation*†

Stratification factors:

Number of prior chemo regimens (0 or ≥

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

Talazoparib
1 mg FO daily

Treatment (21-day cycles)
continues until progression or
unacceptable toxicity

Physician's choice of
therapy (PCT):
capecitabine,

eribulin, gemcitabine,

or vinorelbine

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

- HER2-negative metastatic
 BC
- · ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior Anthracycline and Taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
- No evidence of progression during treatment in the advanced setting
- ≥12 months since (neo)adjuvant treatment

Chemotherapy treatment of physician's choice (TPC)

•Capecitabine
•Eribuan
•Vinorelibine

Primary endpoint:

 Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:

- Time to second progression or death
- Overall survival

Treat until progression

- Objective response rate
- · Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

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

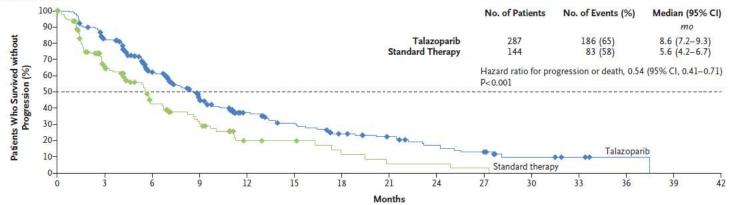


Litton JK, NEJM 2018





A Progression-free Survival



No. at Risk (events/cumulative events)

Talazoparib 229 (50/50) 148 (53/103) 91 (34/137) 55 (17/154) 42 (9/163) 29 (9/172) 23 (2/174) 16 (5/179) 12 (4/183) 5 (2/185) 3 (0/185) 1 (0/185) 0 (1/186) 0 (0/186) Standard therapy 144 (0/0) 68 (41/41) 34 (20/61) 22 (8/69) 9 (7/76) 8 (0/76) 4 (3/79) 2 (2/81) 2 (0/81) 1 (1/82) 0 (1/83) 0 (0/83) 0 (0/83) 0 (0/83) 0 (0/83)

B Progression-free Survival, According to Subgroup Litton JK, NEJM 2018 Hazard Ratio for Disease Progression or Death Subgroup No. of Patients (%) (95% CI) All patients 431 (100) 0.54 (0.41-0.71) BRCA1 mutation type, according to central testing BRCA1 183 (42.5) 0.59 (0.39-0.90) BRCA2 225 (52.2) 0.47 (0.32-0.70) Hormone-receptor status according to most recent biopsy 0.60 (0.41-0.87) Triple-negative breast cancer 190 (44.1) Hormone-receptor positive 241 (55.9) 0.47 (0.32-0.71) History of CNS metastasis 63 (14.6) 0.32 (0.15-0.68) Yes No 368 (85.4) 0.58 (0.43-0.78) Visceral disease assessed by investigator Yes 303 (70.3) 0.51 (0.37-0.70) No 128 (29.7) 0.59 (0.34-1.02) Previous platinum treatment Yes 76 (17.6) 0.76 (0.40-1.45) No 355 (82.4) 0.52 (0.39-0.71) Previous regimens of cytotoxic chemotherapy for advanced breast cancer 0 165 (38.3) 0.57 (0.34-0.95) 1 161 (37.4) 0.51 (0.33-0.80) 105 (24.4) 0.56 (0.34-0.95) 0.00 0.25 0.50 0.75 1.25 1.50 1.75 2.00 1.00 Talazoparib Better Standard Therapy Better

Similar response rate patients with/without BM





Platinum for BRCA-mutated breast cancer

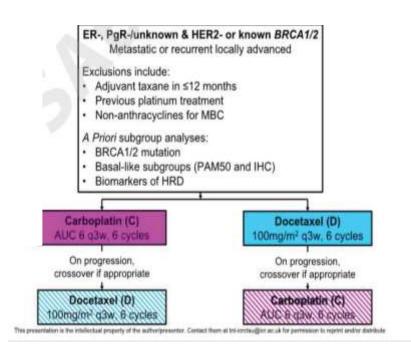
Study	N pts/BRCA	Tumor type	Prior CT	CT regimen	OR	RR,%
	m				BRCA carriers	BRCA wt
Byrski	20	TN (15) Other (5)	Any	Cis	80%	
Isakoff	86/11	TN	≤1	Cis/Carbo	54.5%	25.6%
Tutt	376/67	TN	No	Carbo vs Doce	68% 33.3%	28% 34.5%
Somlo	28 Phase I 44 Phase II	Any	Any	Vel+carbo Vel>carbo	53% 50%	
Han	284	Any	≤2	Pcarbo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

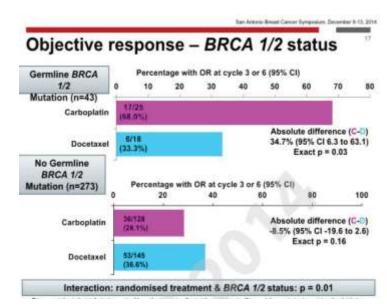
Byrski T et al. Breast Cancer Res 2012; Isakoff SJ, et al. JCO 2015; Tutt A et al. Nature Med 2018; Baselga J et al. JCO 2013; Somlo et al. Clin Cancer Res 2017; Han HS et al. Ann Oncol 2018





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?



IMpassion130 study design

Atezo + nab-P arm: Key IMpassion130 eligibility criteria: Atezolizumab 840 mg IV Metastatic or inoperable locally advanced TNBC - On days 1 and 15 of 28-day cycle Histologically documented^b + nab-paclitaxel 100 mg/m2 IV · No prior therapy for advanced TNBC On days 1, 8 and 15 of 28-day cycle - Prior chemo in the curative setting, including RECIST v1.1 taxanes, allowed if TFI ≥ 12 mo Double blind; no crossover permitted PD or toxicity ECOG PS 0-1 Plac + nab-P arm: Stratification factors: Placebo IV · Prior taxane use (yes vs no) On days 1 and 15 of 28-day cycle Liver metastases (yes vs no) + nab-paclitaxel 100 mg/m2 IV PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%]) On days 1, 8 and 15 of 28-day cycle

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations^d
 - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC. turnour-infiltrating immune cell: TFI, treatment-free interval. * ClinicalTrisis.gov: NCT02425891. * Locally evaluated per ASCO-College of American Pathologists (CAP) guidelines. Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). Radiological endpoints were investigator assessed. (per RECIST v1.1).

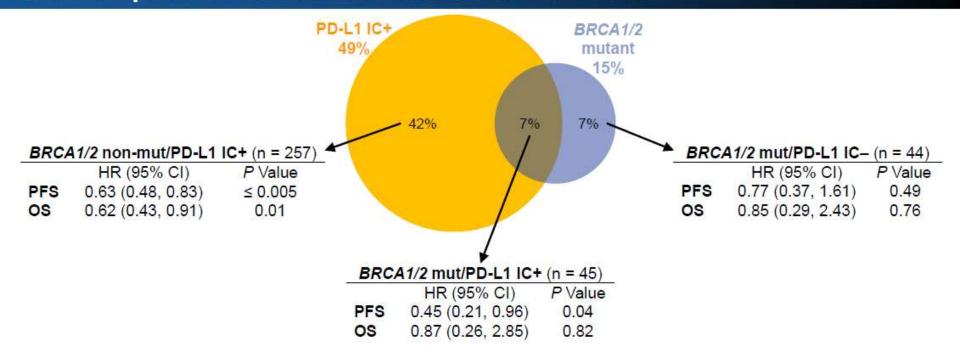
Schmid P, et al. Mpassion 130 ESMO 2018 (LBA1 PR) http://bit.ly/2DMhavg

Investigative Clinical Oncology





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



- 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. a 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	1770 Pt	.5 (11–01) V		tastases	
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

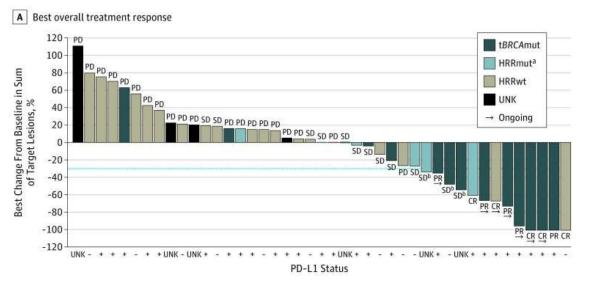
Checkpoint inhibitors

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

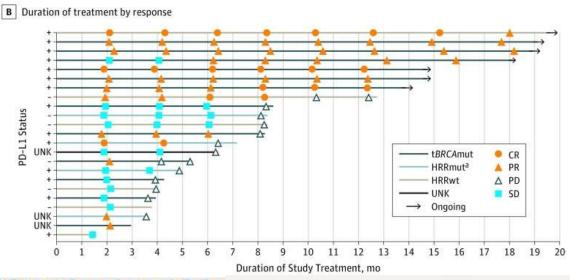




Topacio trial phase II single-arm, open label pembrolizumab +niraparib in metastatic triple negative



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



