What is hot in breast cancer brain metastases?

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8th Annual Brain Metastases Research and Emerging Therapy Conference, Marseille 2018

Are brain metastases a problem in breast cancer?

- 15-20% of metastatic breast cancer patients
- incidence BM depends on breast cancer subtype

	incidence BM	median OS
hormone receptor positive and HER2 negative	14%	9-10 months
HER2 positive	30-50%	11-18 months
triple negative	46%	5 months

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What is hot in breast cancer brain metastases (BCBM)?

1. definitive role and use of systemic therapy

2. new treatment strategies in metastatic breast cancer
   - PARP inhibitors
   - CDK4/6 inhibitors
   - immune checkpoint inhibitors

3. translational research:
   a. BM differ from primary tumor
   b. liquid biopsies in BM (session yesterday)

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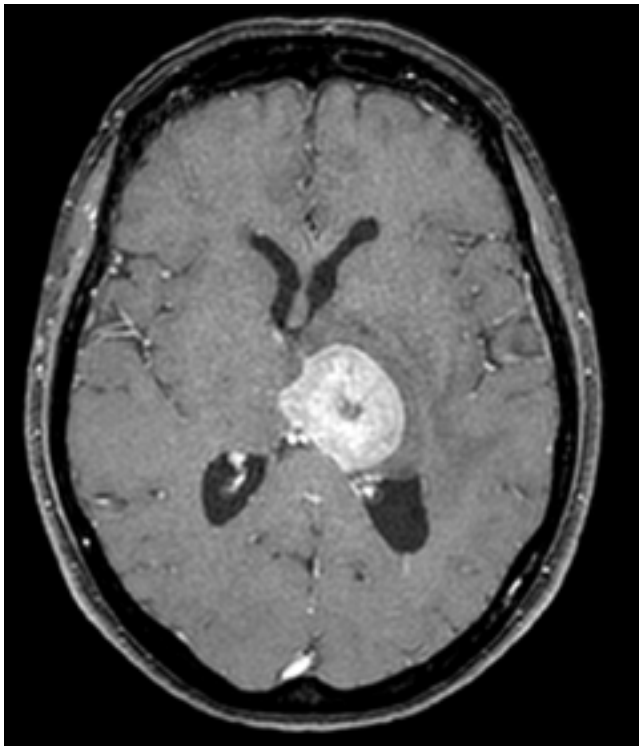
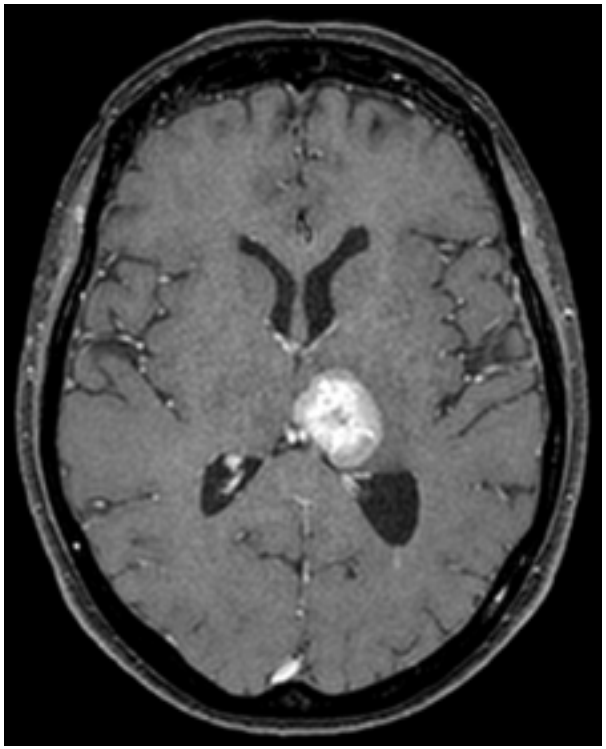
Case

woman, 60, metastatic HER2+ breast cancer
dysphasia and right-sided sensomotor symptoms



May 2018



August 2018

4 courses of capecitabin + trastuzumab

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capecitabin + lapatinib in HER2+ BM patients

LANDS**CAPE trial**:

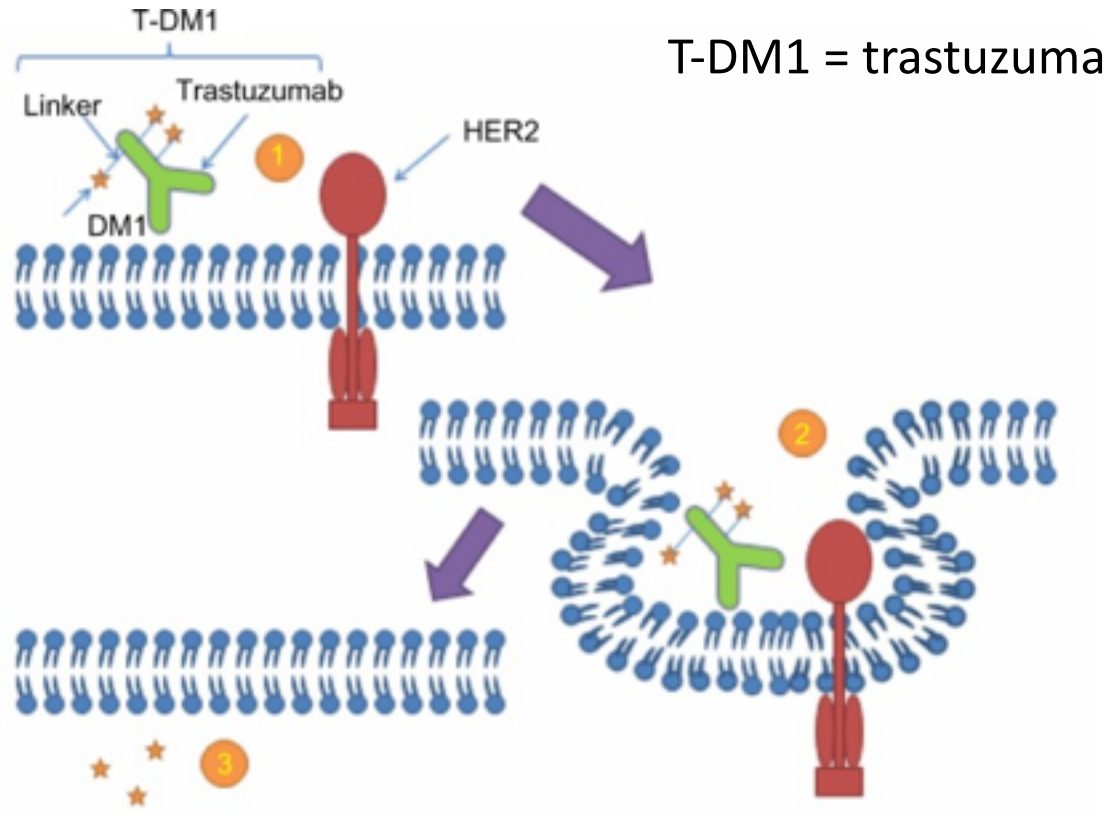
Phase 2 study on capecitabin + lapatinib in HER2+ metastatic breast cancer with previously untreated BM (n= 45, 60% symptomatic)

Results: objective response: 66%, all PR
median time to CNS progression = 6 months
median time to RT = 8 months

Discussion: authors propose RCT of upfront capecitabin+lapatinib vs WBRT

Bachelot et al., Landscape trial. **Lancet Oncol 2013** Jan; 14(1): 64-71

T-DM1



T-DM1 = trastuzumab linked to DM1

DM1 = emtansin, cytotoxic activity, microtubule-inhibitory agent

T-DM1 in metastatic HER2+ breast cancer

EMILIA trial, randomized clinical trial in 991 patients

	T-DM1	lapatinib + capecitabin	P value
objective response rate	44%	31%	P<0.001
PFS	10 months	6 months	P<0.001
OS	31 months	25 months	P<0.001

Conclusion: T-DM1 leads to a better response rate, PFS and OS

Verma et al. **N Engl J Med 2012** Nov 8;367(19): 1783-91

T-DM1 in HER2+ breast cancer with treated, asymptomatic CNS metastases

exploratory analysis EMILIA trial

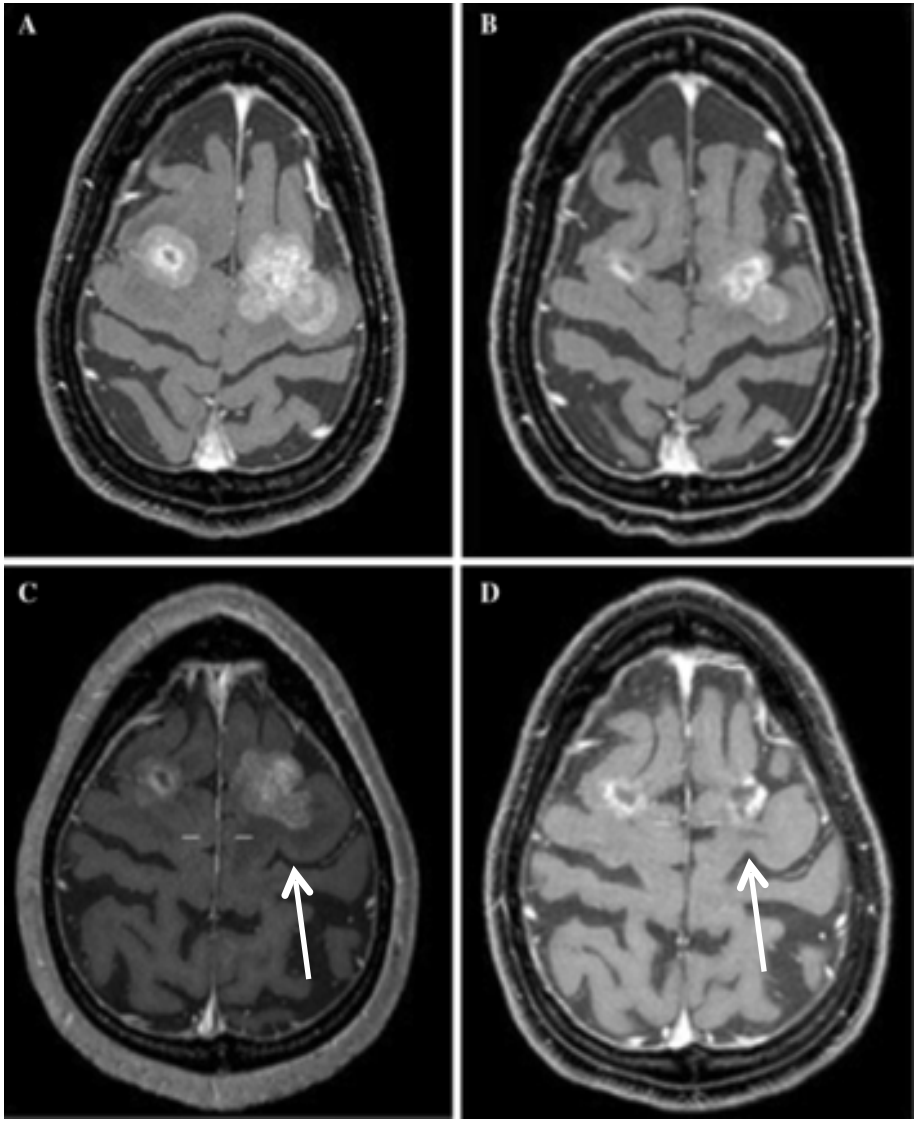
	T-DM1 (n=45)	lapatinib + capecitabin (n=50)	statistical significance
CNS progression	22%	16%	
PFS	6 months	6 months	P=1.000
OS	27 months	13 months	P= 0.008

Conclusion: significant better OS with T-DM1 probably due to better response of systemic metastases

Krop et al. **Ann Oncol 2015** Jan; 26 (1): 113-9

woman, 44, HER2+ breast cancer, symptomatic BM

at diagnosis



4 months after WBRT

6 months after WBRT

3 months T-DM1 treatment

J Neurooncol. 2016 Apr;127(2):401-3.

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retrospective analysis T-DM1 in HER2+ breast cancer with (and without) BM

	with BM (n=87)	without BM (n=216)	P-value
intracranial response (n=45) - complete - partial	**25%** **4%** **21%**	- - -	
extracranial response	**35%**	38%	NS
median cumulative PFS	**7 months**	8 months	P=0.06
median cumulative OS	**14 months**	32 months	P<0.001

Conclusion: T-DM1 is active in BM from HER2+ breast cancer and further studies are warranted

Fabi et al. **Breast 2018** Oct; 41:137-143. Epub ahead of print: 2018 Jul.

What is new on systemic therapy in triple negative BC in 2018?

Phase 3 trial on carboplatin vs docetaxel in advanced triple negative breast cancer: **the TNT Trial** (n=376)

Results:

- overall response rate carboplatin = 68% vs docetaxel = 33% in BRCA 1/2 mutated metastatic triple negative breast cancer (p=0.03)

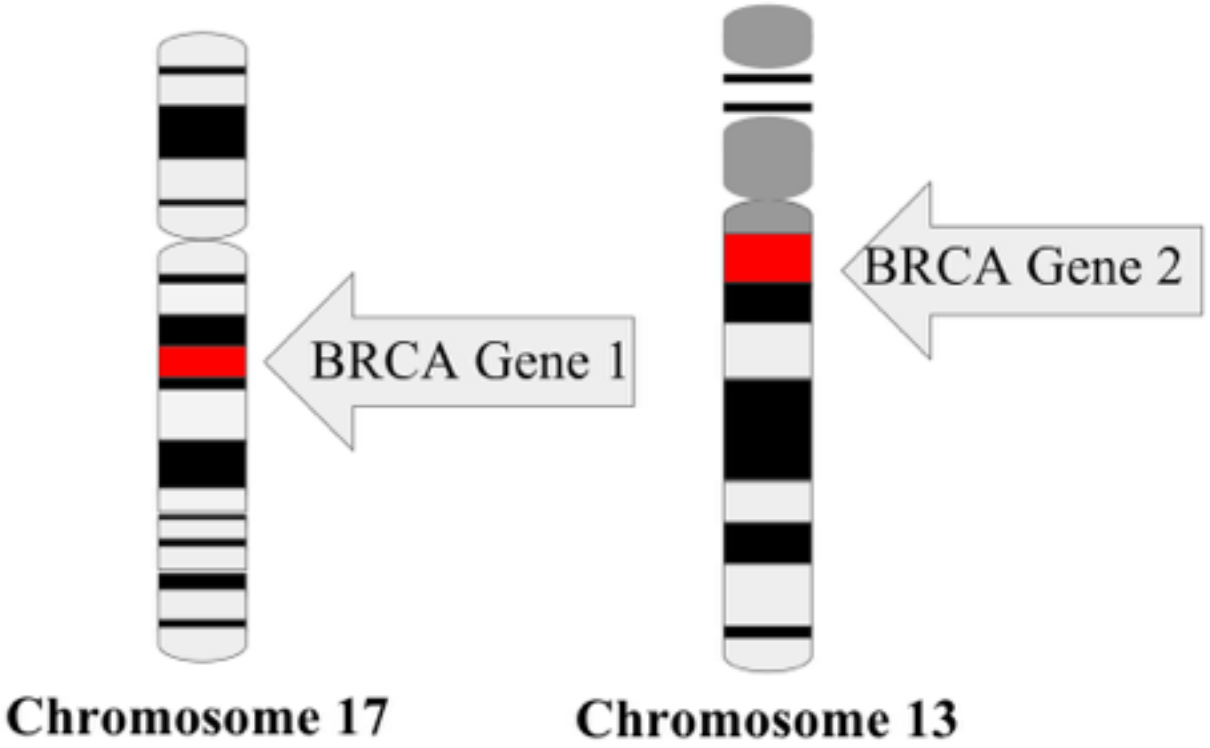
- ± 50% cross-over → no conclusion on OS

Tutt et al. **Nat Med 2018** May;24(5):628-637.

nature medicine

BReast CAncer-1 and -2 mutations

- BRCA proteins needed for homologous recombination to repair double DNA strand breaks
- 5% breast cancer patients: BRCA mutation



BReast CAncer (BRCA)-1 and -2 mutations

	life time risk breast cancer	life time risk ovarian cancer
BRCA 1	60-80%	35-45%
BRCA 2	60-80%	10-20%

BRCA1 : triple negative breast cancer

BRCA2 : estrogen positive breast cancer

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   - **Poly (ADP-Ribose) Polymerase = PARP inhibitors**
   - CDK4/6 inhibitors
   - immune checkpoint inhibitors

3. translational research:
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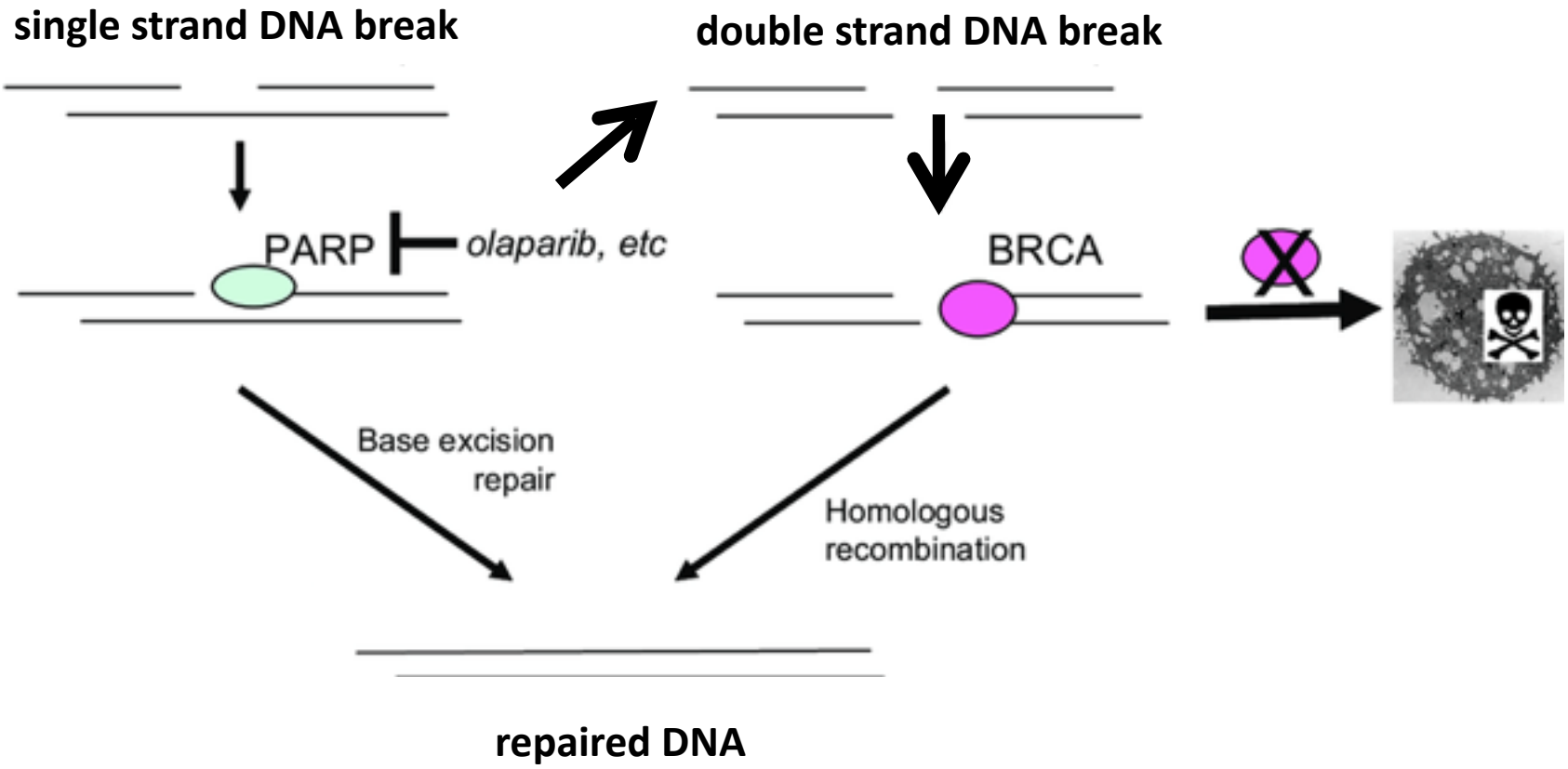
PARP inhibition in BRCA mutated cancer



BRCA mutated cancers are in particular sensitive to PARP inhibition

PARP inhibition in germline BRCA mutated HER2 negative metastatic breast cancer - Olympiad trial

	olaparib (n=205)	single-agent chemotherapy (n=97)	P-value
response rate	60%	29%	
median PFS	7 months	4 months	P<0.001
median OS	17 months (estimate)	17 months (estimate)	not significant HR 0.90; 95%CI 0.63-0.91

Conclusion: significant benefit olaparib monotherapy over non-platinum single-agent chemotherapy

Robson et al. **N Engl J Med 2017** Aug 10;377 (6): 523-533

PARP inhibition in germline BRCA mutated metastatic HER2 negative breast cancer - EMBRACA trial

	talozoparib (n=287)	single-agent chemotherapy (n=144)	P -value
response rate	63%	27%	P<0.001
median PFS	9 months	6 months	P<0.001
median OS	22 months	19 months	P=0.11 (HR 0.76 95% CI= 0.55 -1.06)

Conclusion: significant benefit talozoparib over non-platinum single-agent chemotherapy

Litton et al. **N Engl J Med 2018** Aug 23;379 (8): 753-763

PARP inhibition and breast cancer BM

- Phase I trial: veliparib + WBRT in BM from primary solid tumors

  * 30% fatigue, 20% nausea, no new toxicities
  * median OS breast cancer group, n=25: 8 months (2.8-15.0)
  * nomogram-model-predicted 4.9 months (4.2-5.5)

- no ongoing trials on PARP inhibitors in BM of breast cancer

Mehta et al. Veliparib in combination with WBRT in patients with brain metastases: results of a phase I study. **J Neurooncol 2015** Apr;122(2): 409-417.

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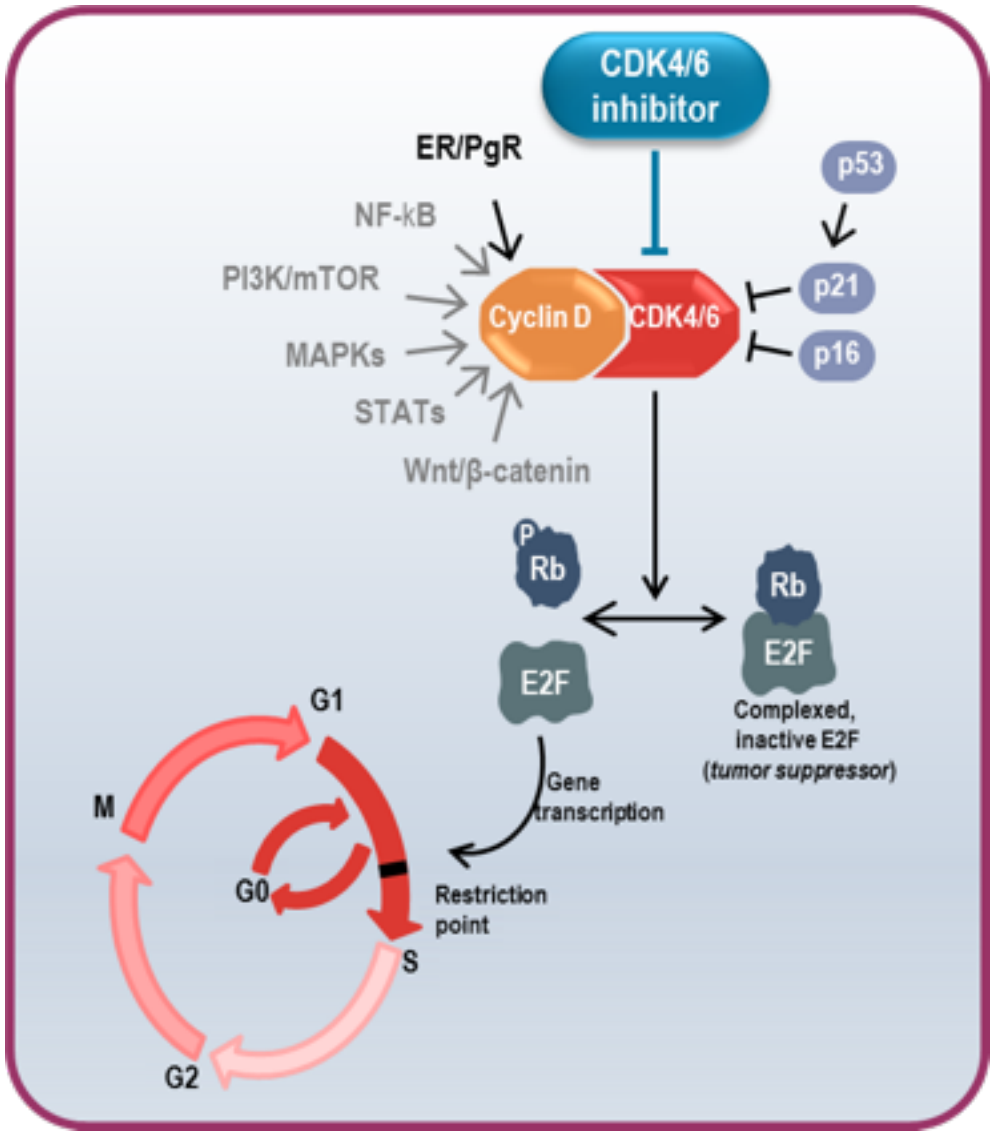
CDK4/6 inhibition in hormone receptor positive breast cancer leads to cell cycle arrest



efficacy of CDK4/6 inhibitors in hormone receptor positive metastatic breast cancer

6 randomized clinical trials (2015-2018):

PALOMA: palbociclib + fulvestrant vs fulvestrant

MONALEESA: ribociclib + letrozole vs letrozole

MONARCH: abemaciclib + fulvestrant vs fulvestrant

Conclusion: consistent doubling of PFS in 1st and 2nd line treatment, no effect on OS (yet)

→ CDK4/6 inhibitors used in clinical practice

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CDK4/6 inhibition and breast cancer BM

- phase I and phase II study: abemaciclib in CSF similar to plasma

- open-label phase II study in hormone receptor positive metastatic breast cancer with BM (n=23): 2 PR (9%)

- 3 ongoing trials with CDK4/6 inhibitors in breast cancer BM (NCT02896335, NCT02774681, NCT02308020)

Shebjam et al. **ASCO meeting abstract 2016**;34 (suppl): 526

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Immune checkpoint inhibitors in metastatic breast cancer

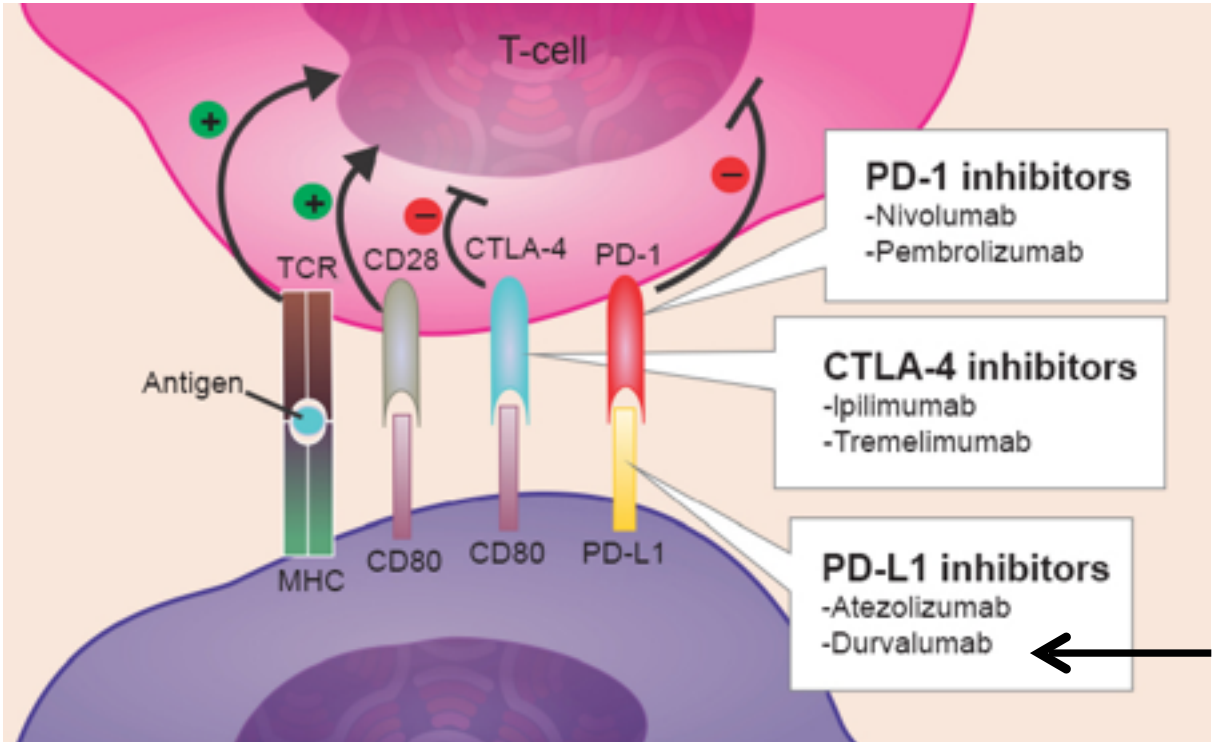
Announcement Roche dd. July 2018:

Phase III *Impassion 130* study on **atezolizumab** + paclitaxel vs placebo + paclitaxel in metastatic triple negative breast cancer:

- significant increase PFS in intention-to-treat and PD-L1 positive group
- encouraging overall survival (OS) benefit for PD-L1 positive group at interim analysis

Immune checkpoint inhibitors in breast cancer BM

Ongoing clinical trial of durvalumab in patients with BM from epithelial-derived tumors including breast cancer (NCT02669914)



translational research
BM differ from primary tumor

- genetic differences between BM and primary breast cancer
  * mutations in CDK- and PI3K/AKT/mTOR pathway
    (Brastianos et al., Cancer Discovery 2015)
  * gene expression profiles
    (Vareslija et al. J Natl Cancer Inst 2018)

- more homologous recombinant deficiency in BM compared to primary breast cancer (Diossy et al., Ann Oncol 2018)

- immune micro-environment:
  * fewer TILs in BM than in primary breast cancer
    (Ogiya et al. Oncotarget 2017)

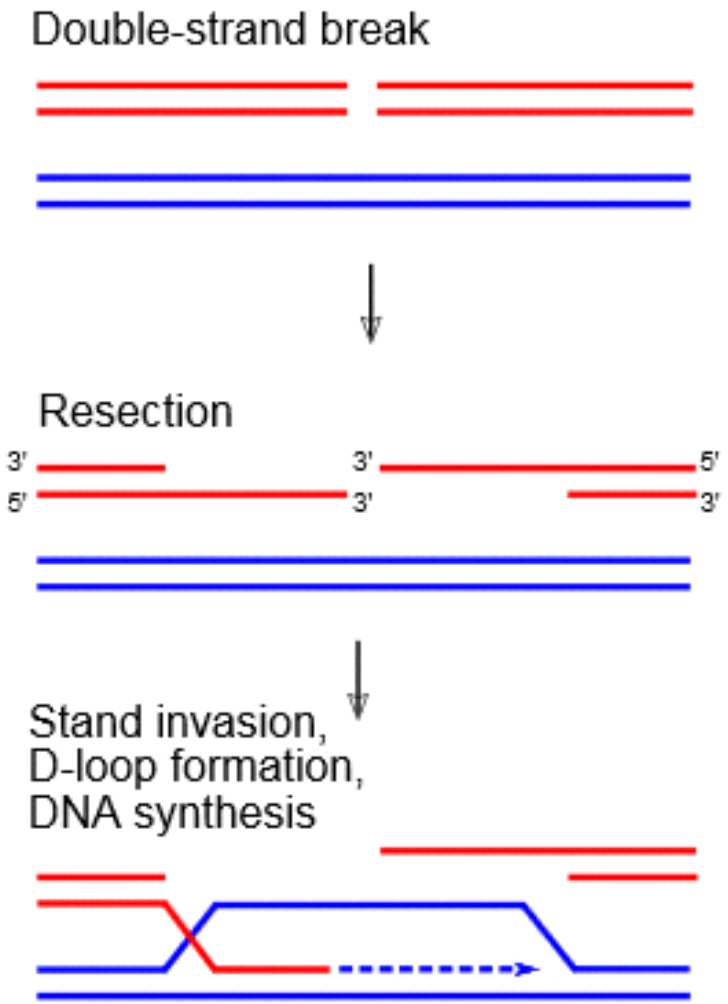
THE FUTURE - BREAST CANCER BRAIN METASTASES

- increased use of upfront systemic therapy
- further data on effect of PARP-, CDK4/6- and immune-checkpoint inhibitors in BM
- differences BM and primary tumor may tailor future treatment

Thank you for your attention!

8th Annual Brain Metastases Research and Emerging Therapy Conference, Marseille 2018

homologous recombination during mitosis: repair of double strand DNA breaks



DNA repair via exchange of nucleotides between homologous chromosomes

more homologous recombination deficiency in non-BRCA mutated BCBM

Translational study in non-BRCA mutated breast cancer (n=37)

- significant increase of HRD in BM relative to primary tumor
- increased HRD level 87.5% of BM vs primary tumor
- 56% of BM = HRD deficient

Question: should HRD measurement be used for stratification of patients for PARP inhibition?

Diossy et al., Breast cancer brain metastases show increased levels of genomic aberration based homologous recombination deficiency scores relative to correponding primary tumors.
Ann Oncol Jun 2018, Epub ahead of print.