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Therapeutic approaches of Metastatic Breast Cancer: TNBC

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Disclosures

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TNBC: a clinical case

A 43 year old patient => surgery + LND

AP: IDC (3cm), 3 LN+, Grade 3, ER 0/8 PgR 0/8 and HER2-, Ki67 40%

Adjuvant therapy: EC dose dense (q2w) + 12 weekly paclitaxel

No germline BRCA mutation performed

16 months later, a CT showed one lung lesion (2cm) and 2 lesions in the liver. CA 15-3: 228. CTC: 123

Biopsy of one liver metastasis performed: TNBC

What do you propose?

1. To perform brain MRI
2. Gene profiling of the liver biopsy
3. NGS of the liver biopsy
4. PDL-1 expression
5. Germline BRCA mutation
6. All
7. 3 + 4 + 5
8. 4 + 5

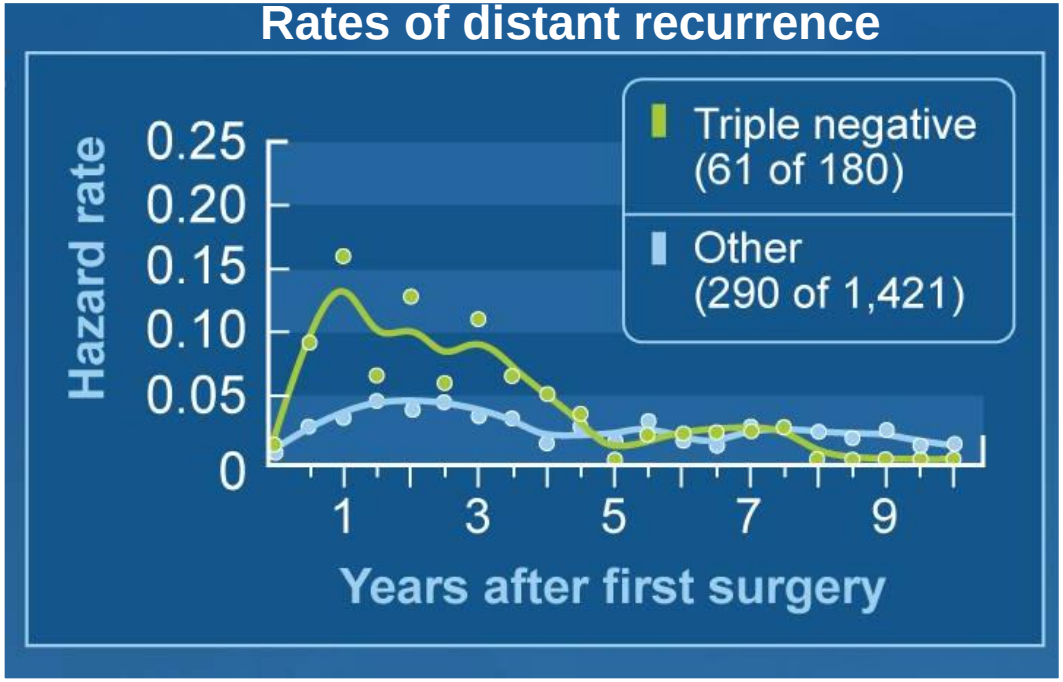
TNBC

Should therapeutic algorithm be based on Clinical or molecular subtyping ?

TNBC: Clinical Characteristics

* **Risk Factors**:
  - Young
  - BRCA1 carriers (80%)

* **Relapse pattern**:
  - Higher risk
  - Early timing
  - Sites differ from luminal:
    - e.g., CNS 46% over time



	N	Bone	Soft Tissue	Viscera
TNBC	79	13%	13%	74%
ER+	123	39%	7%	54%
HER2+	78	7%	12%	81%

1. Lin NU. *Cancer.* 2008;113(10):2638-2645. 2. Dent R. *Clin Cancer Res. 2*007;13(15 Pt1):4429-4434. *3.* Liedtke C. *J Clin Oncol.* 2008;26(8):1275-1281.

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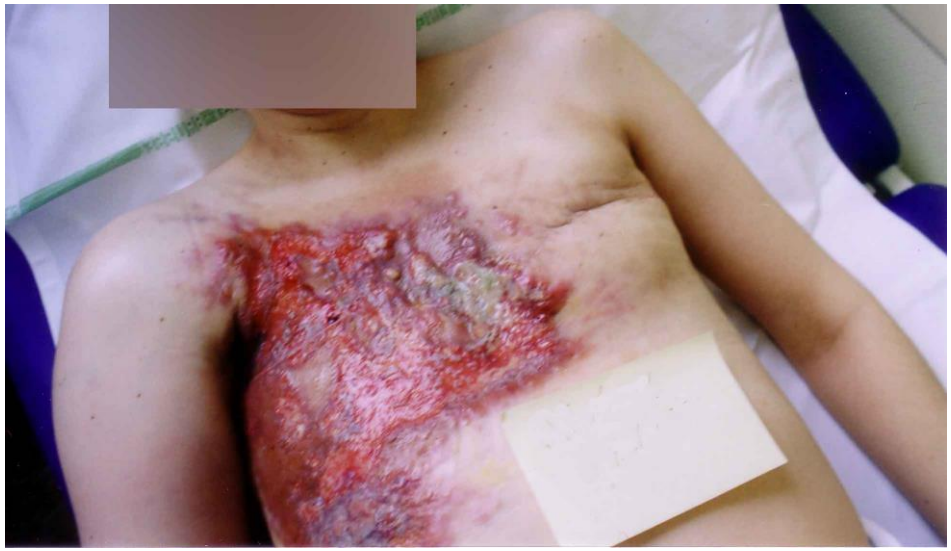
Poor outcome of a “triple negative” breast cancer clinical case



ER –
PgR –
HER-2 –
Ki67 80%

} "Triple Negative"

Progressive disease in spite of:

- FEC x 6
- Weekly paclitaxel
- Kinesin inhibitor
- Capecitabine
- Radiotherapy

Angiogenic and inflammatory pattern of the local recurrence !!!

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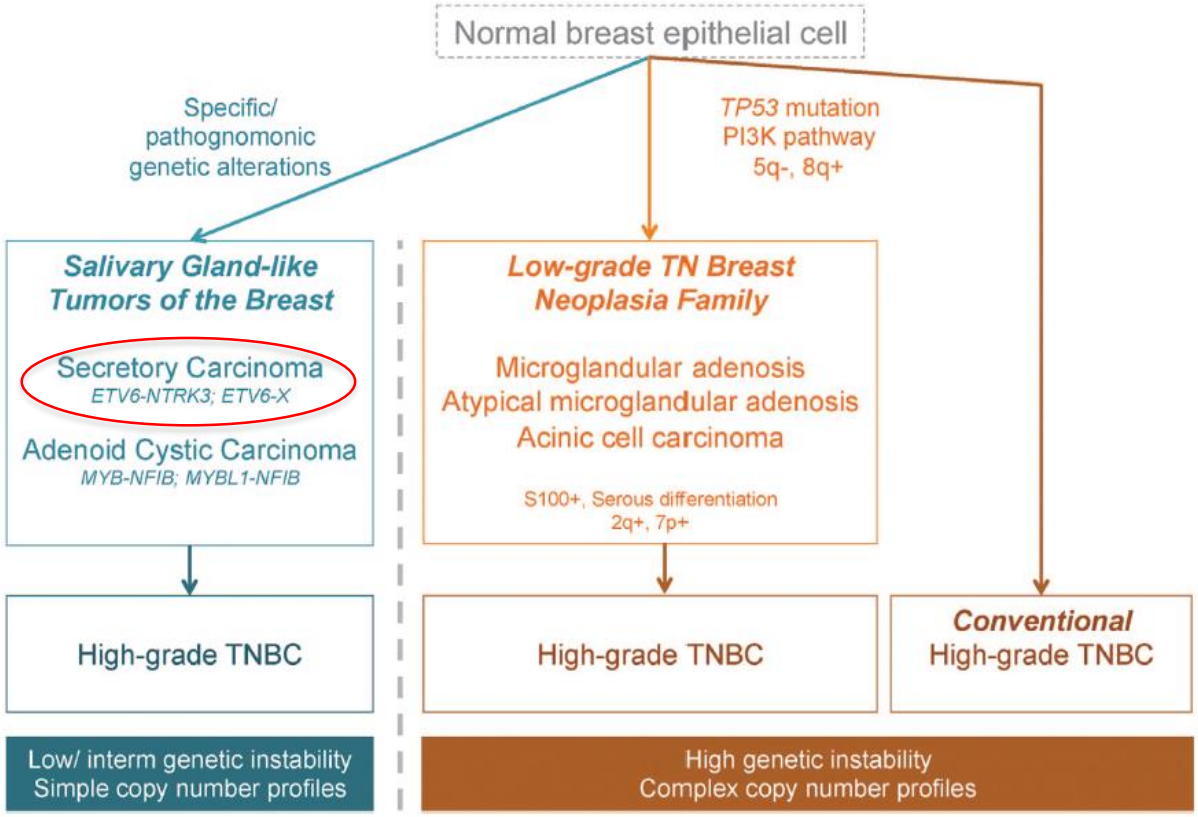
Hypothetical model of potential evolutionary paths of TNBCs



F. Pareja et al, *Triple-negative breast cancer: the importance of molecular and histologic subtyping, and recognition of low-grade variants,* NPJ Breast Cancer (2016)

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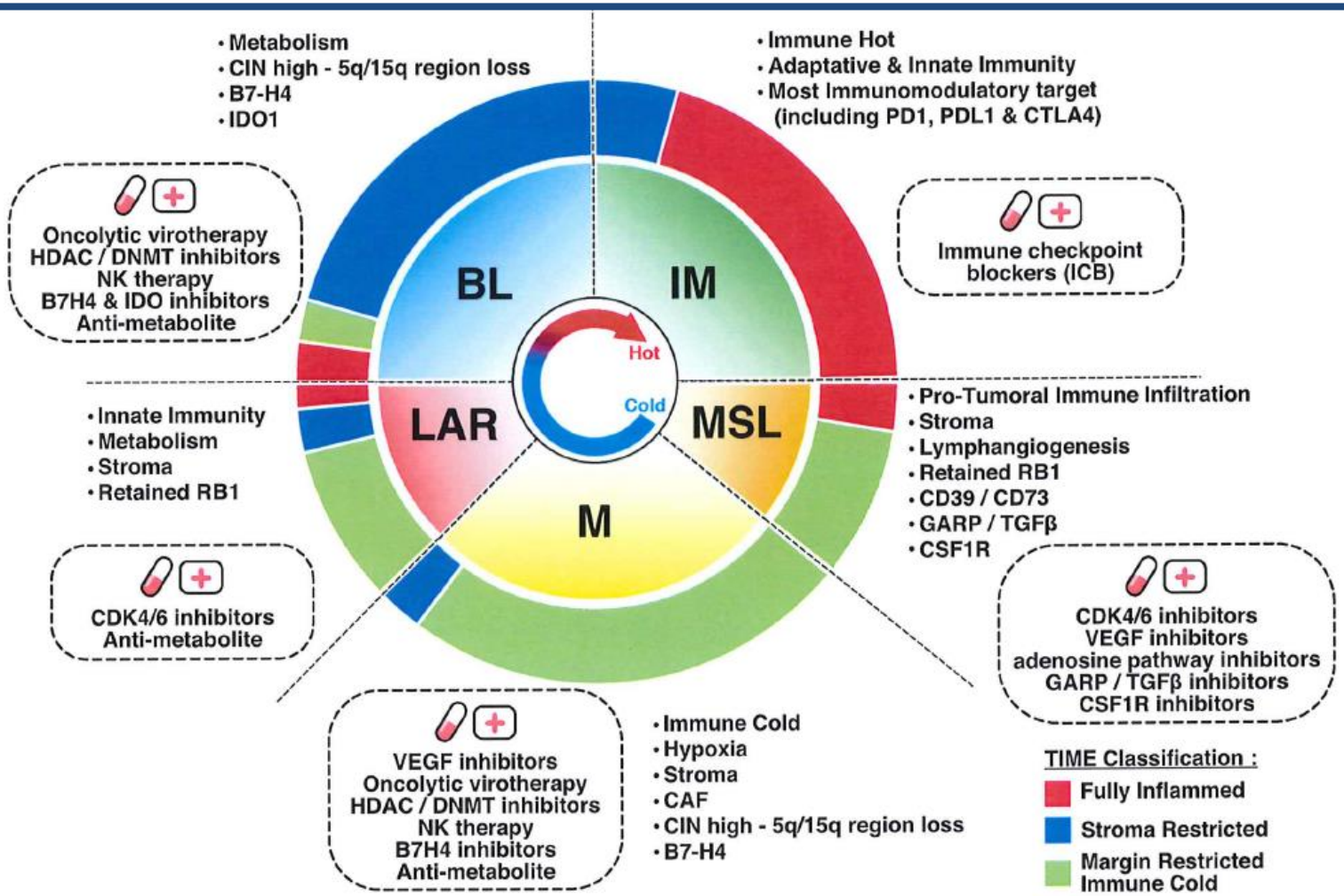
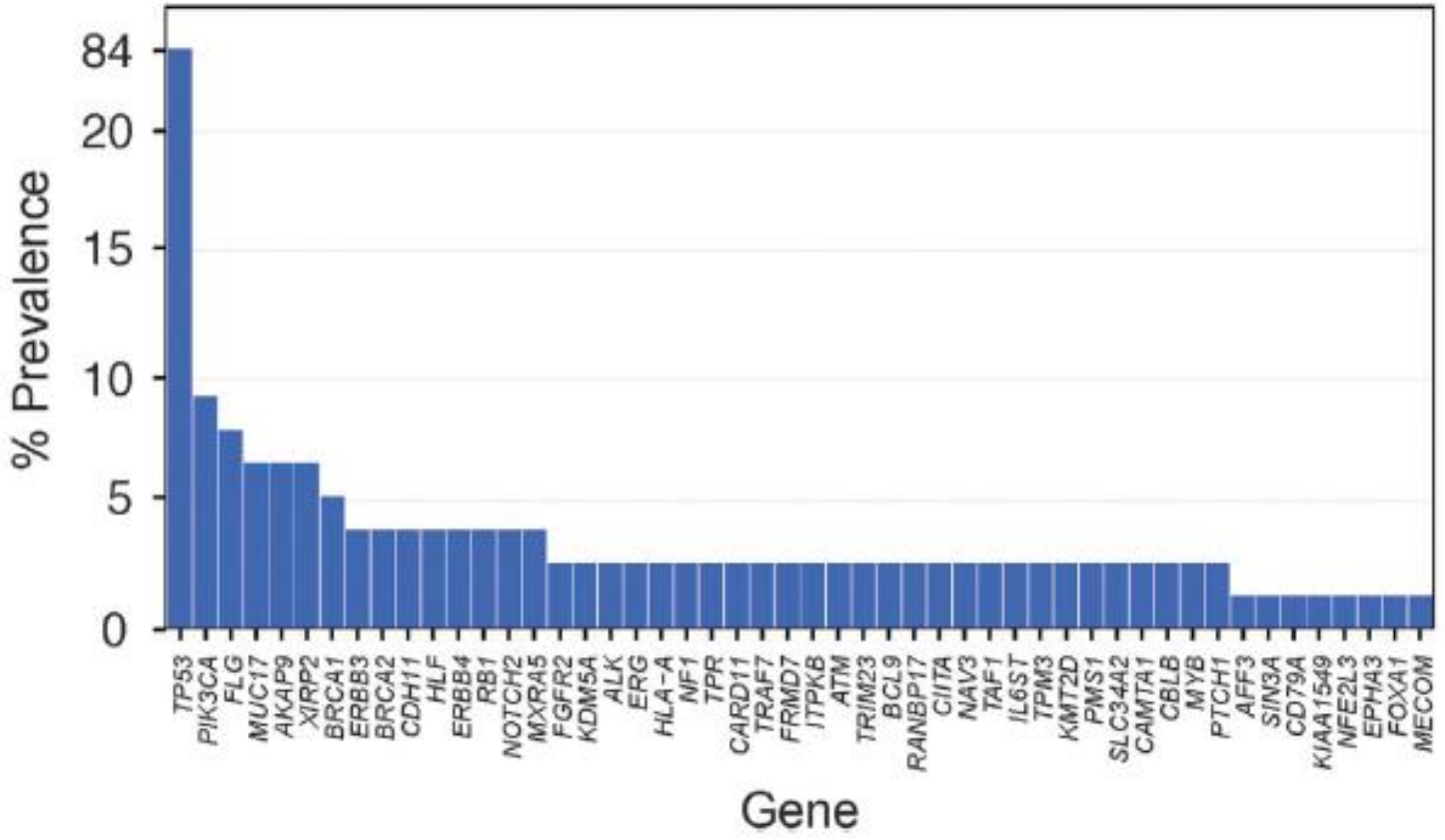
TNBC : Gene profiling, targets, pathways and potential modulators



Somatic mutations affecting cancer genes in TNBCs



The Cancer Genome Atlas (TCGA)

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If germline BRCA mutation and PD-L1 were both negative, what do you propose as therapy?

1. Taxane + bevacizumab
2. Chemo + CPIs
3. Capecitabine
4. Platinum-based therapy
5. Eribuline

Selected anticancer agents (cytotoxics, biologicals) studied clinically in TNBC

- Anthracyclines and taxanes
- Platinum compounds
- Antimetabolites (e.g., capecitabine, …)
- Eribulin
- Antibody drugs conjugates (Emerging active therapy)

- PARP inhibitors
- Bevacizumab
- Checkpoints inhibitors (e.g., atezolizumab,pembrolizumab…)
- Androgen receptor modulators
- Anti-AKT/PI3K?

T/FAC Neoadjuvant Response by PAM50 subtype

(12 weeks of paclitaxel followed by 4 cycles of FAC)

the overall pCR rate was 22%

T/FAC pathological complete response rates for PAM50 subtypes and the triple-negative classification

Classification	RD	pCR
Basal-like	11 (41%)	16 (59%)
HER2-enriched	17 (59%)	12 (41%)
LumA	36 (100%)	0 (0%)
LumB	22 (82%)	5 (18%)
Normal-like	13 (93%)	1 (7%)
Triple Negative	13 (50%)	13 (50%)
Any Positive	82 (80%)	20 (20%)
Triple Negative/Basal	6 (35%)	11 (65%)
Triple Negative/Non-Basal	7 (78%)	2 (22%)
Non-Triple Negative/Basal	4 (50%)	4 (50%)
Non-Triple Negative/Non-Basal	78 (83%)	16 (17%)

Parker et al. J Clin Oncol; 27:1160-1167 2009

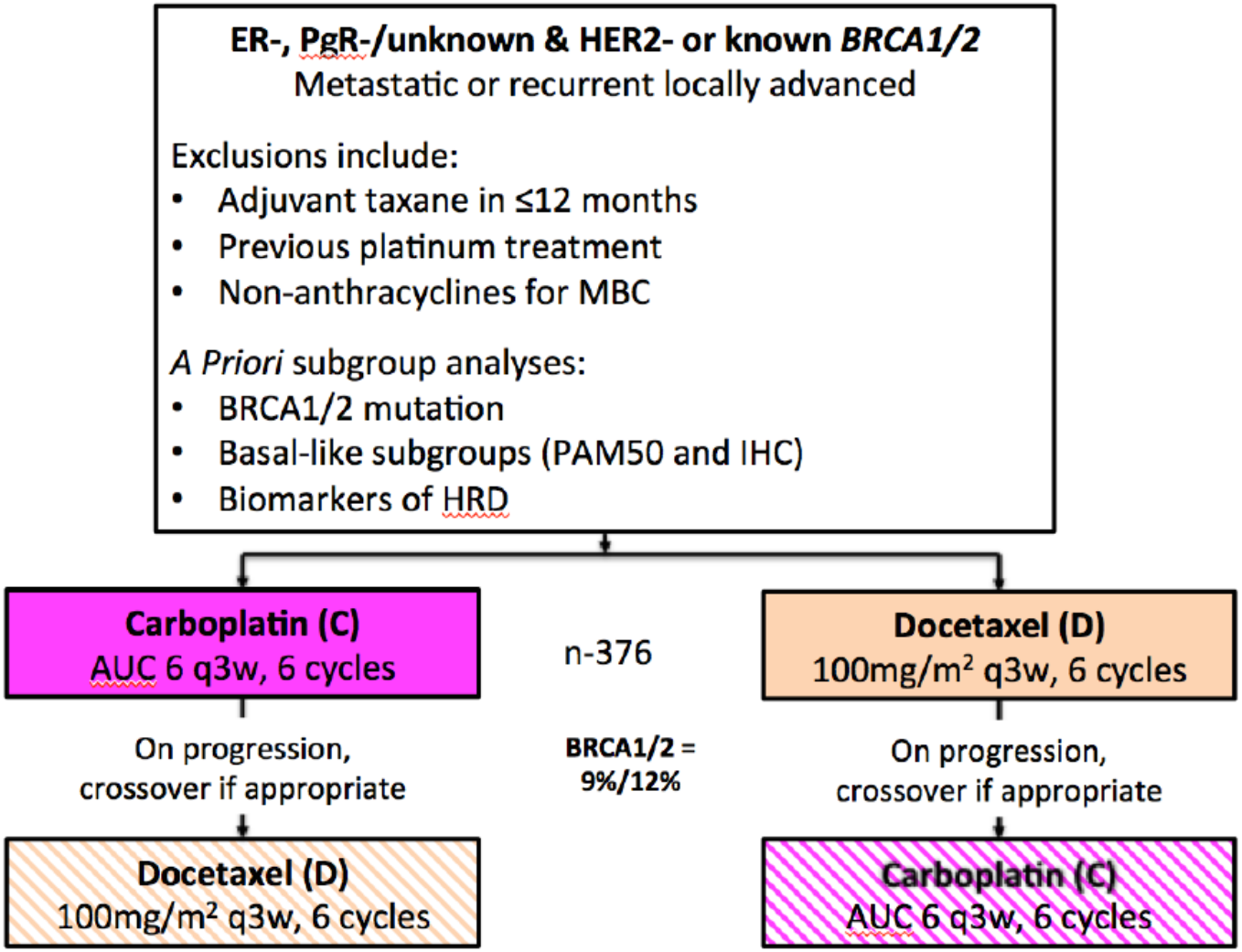
Neoadjuvant setting : Platinum Sensitivity in BRCA1+/TNBC

Trial	Pop'n	Regimen	N	pCR
Ryan	Sporadic TNBC	CDDP 75mg/m2 x4 + bevacizumab 15 mg/kg q3wk x3	51	8 (16%)
Silver	Sporadic TNBC	CDDP 75mg/m^2 x4	26	4 (15%)
Byrski	BRCA1+	Non-platinum	90	14 (16%)
Byrski	BRCA1+	CDDP 75mg/m^2 x4	12	10 (83%)
Gronwald	BRCA1+	CDDP 75mg/m^2 x4	25	18 (72%)

Byrski, JCO 2009; Gronwald, ASCO 2009, Silver JCO 2009: Baselga ESMO 2010; Isakoff SABCS 2010

First-Line Platinum-based Chemotherapy

TNT Trial: CRUK/07/012



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Tutt A et al, Nat Med 2018; [in press]

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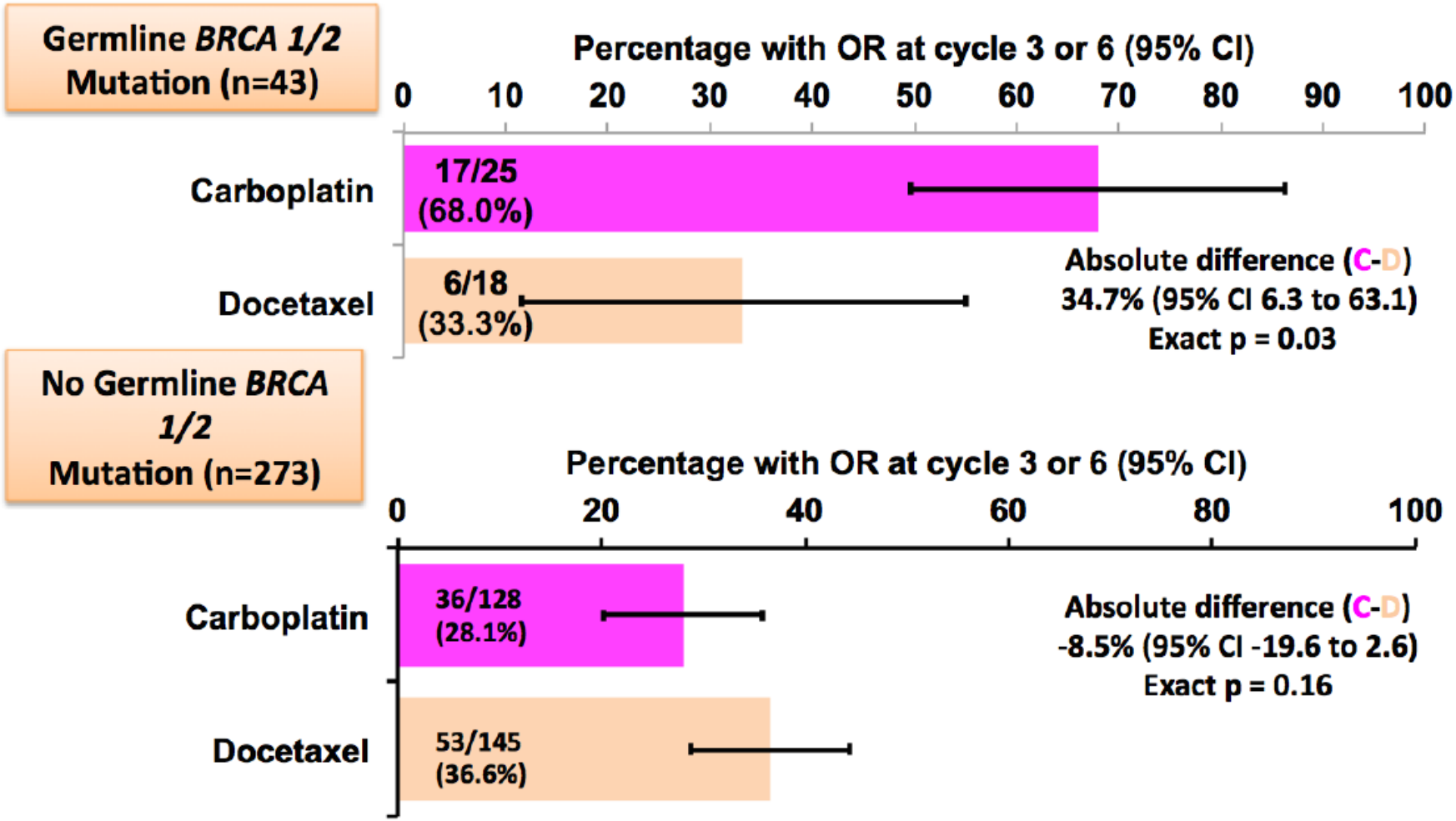
First-Line Platinum-based Chemotherapy

Objective Response Rate by *BRCA* Mutational Status



Interaction: randomised treatment & *BRCA 1/2* status: p = 0.01

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Tutt A et al, Nat Med 2018; [in press]

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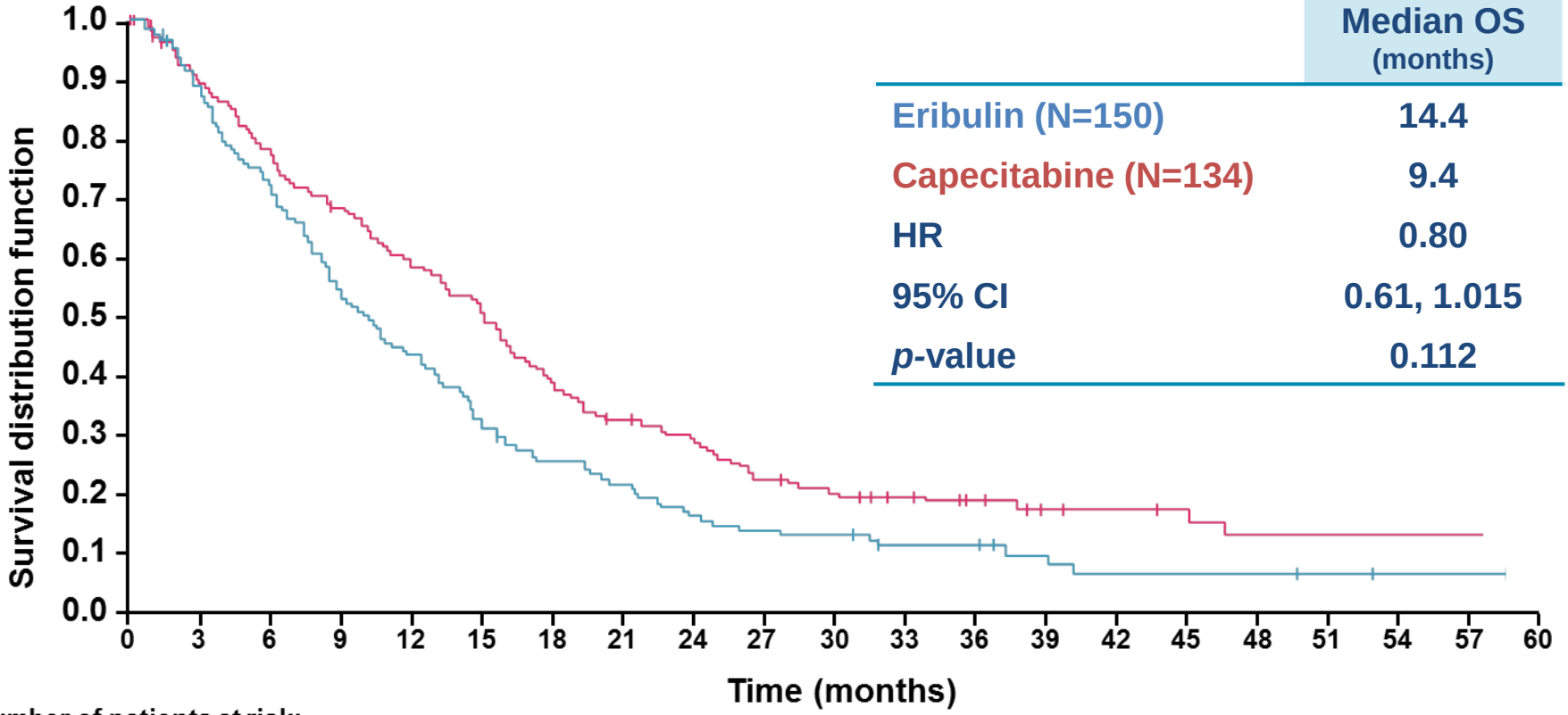
Eribulin 301 study : Overall survival in TNBC patients



	Median OS (months)
Eribulin (N=150)	14.4
Capecitabine (N=134)	9.4
HR	0.80
95% CI	0.61, 1.015
p-value	0.112

Number of patients at risk:

Eribulin	150	129	107	93	78	60	45	40	29	24	18	13	9	8	5	4	3	1
Capecitabine	134	113	88	63	47	32	26	19	15	14	8	6	3	3	3	2	1	1

CI=confidence interval
Pre-specified exploratory sub groups

1) Twelves C et al. Breast Cancer: Basic and Clinical Research 2016

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Bevacizumab for Metastatic TNBC

Trial / Arm	Median PFS (mo) in TNBC Subset
E2100	
Paclitaxel (n=110)	5.3
Paclitaxel + bev (n=122)	10.6
AVADO	
Docetaxel + placebo (n=52)	5.4
Docetaxel + bev 15 mg/kg (n=58)	8.2
RIBBON-1	
Taxane/anthracycline + placebo (n=46)	6.2
Taxane/anthracycline + bev (n=96)	6.5
Capecitabine + placebo (n=50)	4.2
Capecitabine + bev (n=87)	6.1
ATHENA	
Taxane-based regimen + bev (n=577)	7.2*

OS in TNBC population showed no difference between bev and non-bev treated groups (HR=0.96; 95% CI: 0.79-1.16)

Thomssen, et al. SABCS 2009. Abstract 6093. O'Shaughnessy J, et al. SABCS 2009. Abstract 207.

The patient received 5 months of taxane + bevacizumab. A CT scan showed one remaining lesion of the liver. What do you propose next?

1. Stop treatment and FU
2. Stop taxane and maintenance bevacizumab
3. Local therapy of the remaining lesion (oligometastatic disease)
4. Biopsy of the remaining lesion for biology analysis
5. 2 + 3
6. 2 + 3 + 4

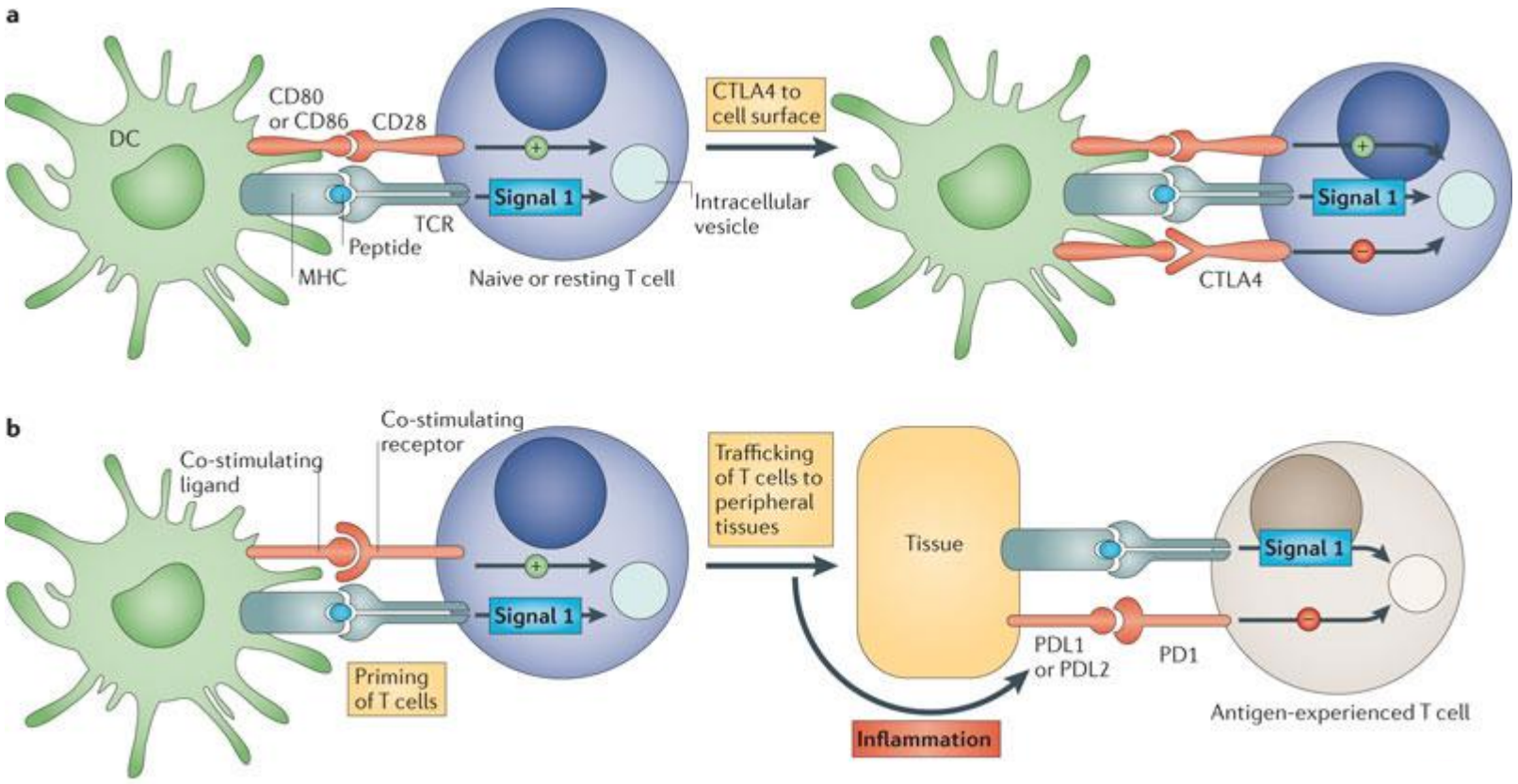
Oligometastatic Disease: Investigational Approach in MBC

Oligosensitive disease ≠ Oligoprogressive disease

If germline BRCA mutation was negative and PD-L1 positive, what do you propose?

1. Chemo + bevacizumab
2. Chemo + CPIs
3. Platinum-based therapy
4. Eribuline

Immune Checkpoints in Cancer



CTL4 immune checkpoint regulates initial T-cell response to antigen, whereas PD1 pathway regulates inflammatory responses in peripheral tissues by effector T cells

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Pardoll et al. Nature Reviews Cancer 2012

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Chemo ± CPIs in metastatic TNBC: A summary

PDL1+ subsets	IMpassion 131 (VIRTUAL ESMO congress 2020)	IMpassion 130 (MUNICH ESMO congress 2018)	KEYNOTE 355 (ASCO20 Virtual)
N	292	369	323 (2:1)
Minimum DFI	12m	12m	6m (20% < 12m)
> 3 involved sites	15%	20%	43% (≥ 3)
Chemo backbone	paclitaxel	nab paclitaxel	nab paclitaxel, paclitaxel, gem/carbo
Prior chemo for EBC	52% taxane	51% taxane	22% prior same class
No prior chemo	29% de novo	35% chemo-naive	32% de novo
PDL1+ rate	45% (SP142, IC≥1%)	41% (SP142, IC≥1%)	38% (22C3, CPS≥10)
	PFS ≈ OS ≤	PFS ↑ « OS ↑ »	PFS ↑

Question de corticoïdes?
Type de chimiothérapie ? Taxol vs Nab-paclitaxel ? Other?

Neoadjuvant Chemo-Immunotherapy in TNBC
A summary

	KN 522 Pembro / Placebo	Impassion 031 Atezo / Placebo
Patients	n= 602 (pCR Anal.)	n= 333 (after Amendment)
Carboplatin	**yes**	**no**
N+	51.7% / 51.3%	33.9% / 42.9%
T3/T4	26.0% / 25.6%	29.7% / 26.8%
PD-L1 pos.	83.3% / 81.6 % (CPS≥1)	45.2% / 47.3%(IC ≥ 1%)
Primary Endpoints	pCR in ITT, EFS	Co-Primary: pCR in ITT and PD-L1 pos.
pCR ITT	**64,8% / 51;2% Δ13;6%**	**57;6%/41.1% Δ16.5%**
pCR PD-L1pos.	**68.9% / 54.9% Δ 14%**	**68.8% / 49.3% Δ 19.5%**
pCR PD-L1neg.	**45.3% / 30.3% Δ 15%**	**47.7% / 34.3% Δ 13.3%**
LN+	**64.8% / 44.1% Δ 20.7**	**57.1% / 30.6% Δ 26.5%**
LN-	64.9% / 58.6% Δ 6.3	57.8% / 49.0% Δ 8.8%

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The patient received 6 months of carboplatin + gemcitabine + pembrolizumab (in a clinical trial) with partial response. What do you propose next?

1. Stop treatment and follow-up
2. Stop chemotherapy and maintainance pembrolizumab
3. Abraxane + atezolizumab in order to improve tumor response
4. capecitabine alone as maintenance

If germline BRCA1 mutation and PD-L1 were both positive, what do you propose as therapy?

1. Chemo + CPIs
2. PARP inhibitor alone (Olaparib or talazoparib)
3. Veliparib (PARP inhibitor) + carboplatin + paclitaxel
4. Chemo + bevacizumab
5. Perform oophorectomy + 1
6. Perform oophorectomy + 2 or 3

Managing BRCA – Mutated Positive MBC

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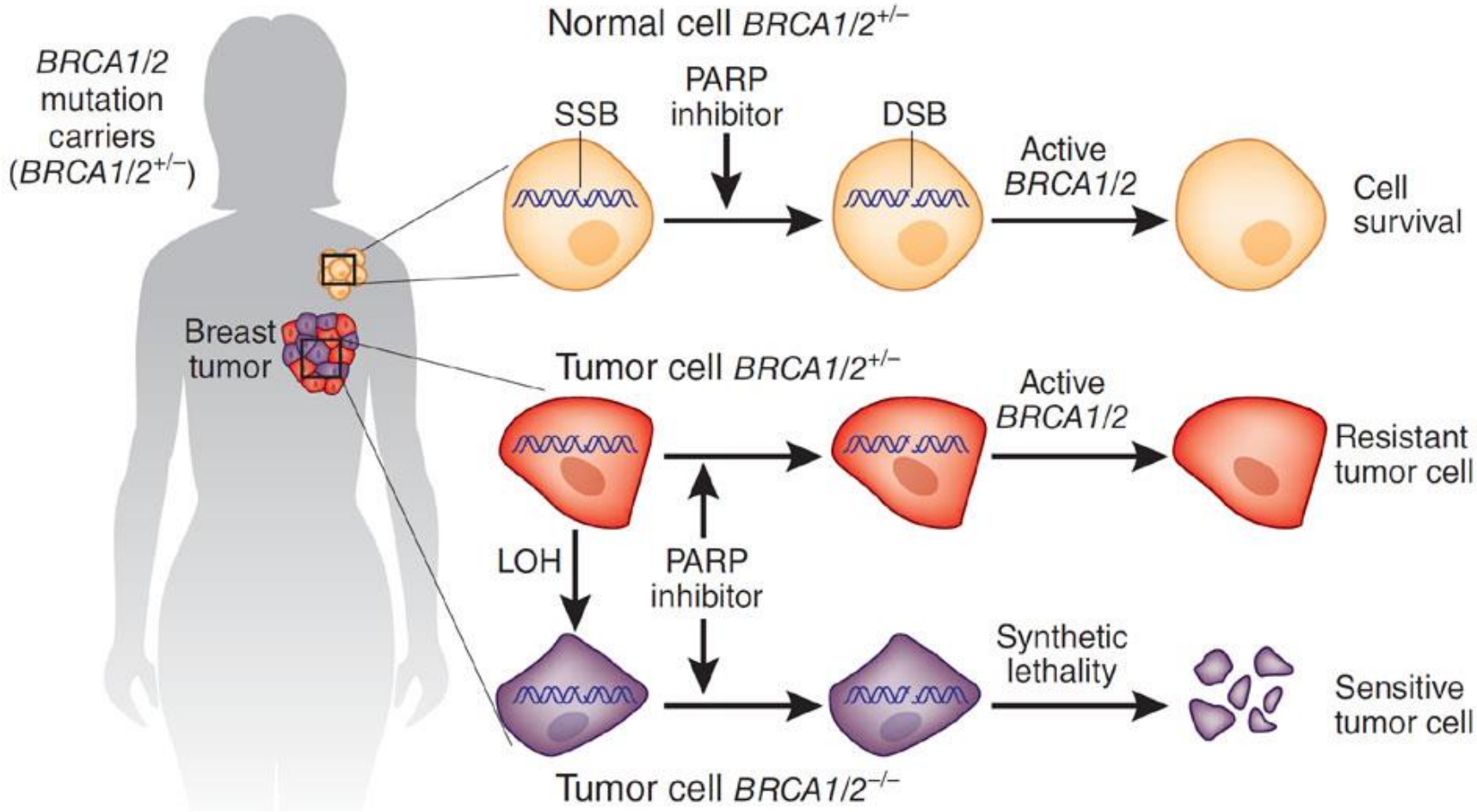
The concept of synthetic lethality



BRCA positive tumors: Role of PARP inhibitors in MBC HR + and TNBC

- Olaparib (OlympiAd trial)
- Talazoparib (EMBRACAtrial)
- Veliparib (BROCADE 3)

OLYMPIAD: STUDY DESIGN

HER2- MBC(N=302)

- ER+ and/or PR+ (HR+) or
- TNBC

- Deleterious or suspected deleterious g*BRCA* mutation
- ≤2 prior CT lines in metastatic setting
- Prior anthracycline and taxane
- HR+ disease progressed on ≥1 ET, or not suitable
- If prior platinum use
  - No evidence of progression under treatment
  - ≥12 months since (neo)adjuvant treatment

2:1

Olaparib
300 mg BID

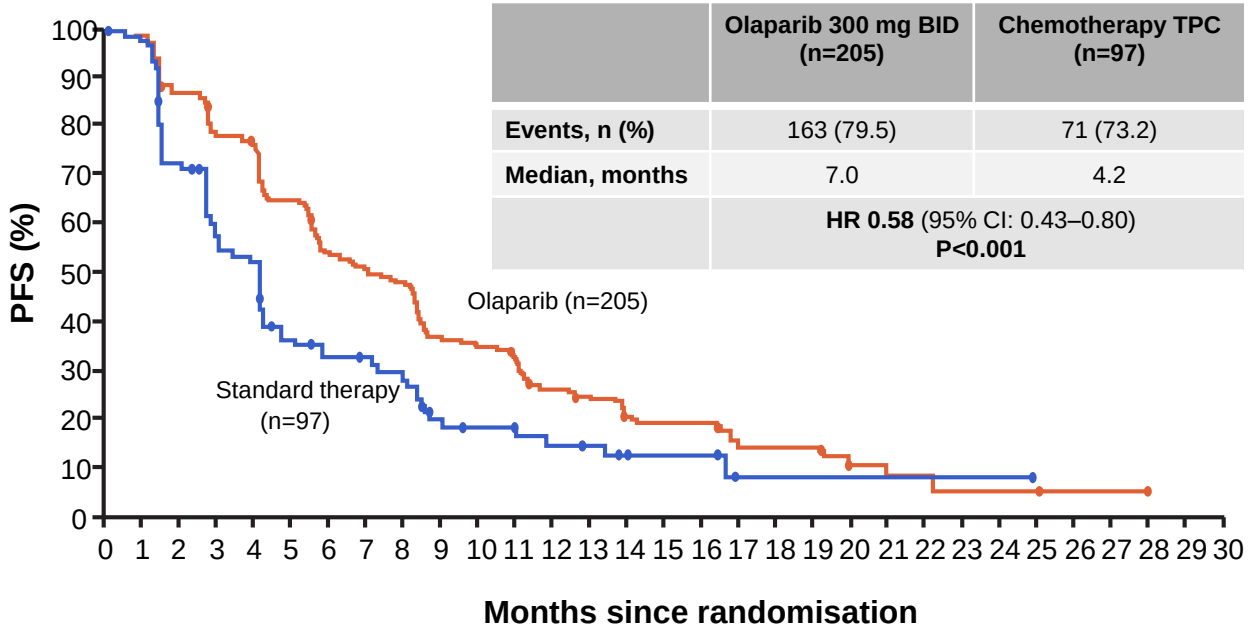
Chemotherapy TPC
- Capecitabine
- Eribulin
- Vinorelbine

- **Primary endpoint:** PFS (RECIST 1.1, BICR)
- **Secondary endpoints:** OS, time to second progression or death, ORR, global HRQoL (EORTC-QLQ-C30), safety and tolerability

Investigational drug: olaparib is not approved for use breast cancer in Europe.
BICR, blinded independent central review; BID, twice daily; EORTC; European Organisation for Research and Treatment of Cancer; ER, oestrogen receptor; g*BRCA*, germline *BRCA*; HRQoL, health-related quality of life; PR, progesterone receptor; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria In Solid Tumours; TPC, treatment of physician's choice

Robson M, et al. *N Engl J Med*. 2017;377:523–533.

OLYMPIAD: PFS (CENTRALLY EVALUATED)



	Olaparib 300 mg BID (n=205)	Chemotherapy TPC (n=97)
Events, n (%)	163 (79.5)	71 (73.2)
Median, months	7.0	4.2
	HR 0.58 (95% CI: 0.43–0.80) **P<0.001**	

No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Investigational drug: olaparib is not approved for use breast cancer in Europe.
Olaparib is approved by US FDA for the treatment of patients with deleterious or suspected deleterious g*BRCA* mutation, HER2- MBC who have previously been treated with CT in the neoadjuvant, adjuvant or metastatic setting. Patients with HR+ BC should have been treated with a prior ET or be considered inappropriate for ET
FDA, US Food and Drug Administration

Robson M, et al. *N Engl J Med*. 2017;377:523–533.

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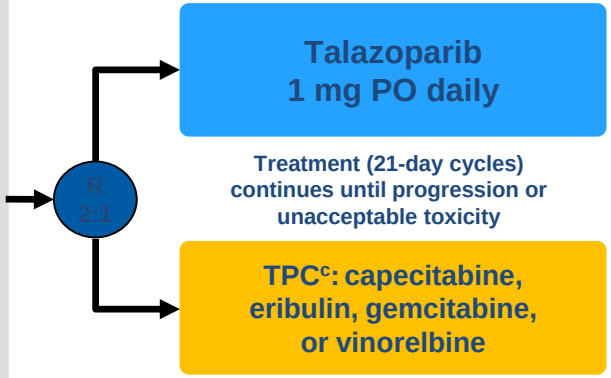
EMBRACA: STUDY DESIGN

Open-label, Phase III trial

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation (n=431)[a,b]

Stratification factors:

- Number of prior chemo regimens (0 or ≥1)
- TNBC or HR+
- History of CNS metastasis or no CNS metastasis



- **Primary endpoint:** PFS by blinded central review
- **Secondary endpoints:** OS, ORR, safety
- **Exploratory endpoints:** DoR for objective responders, QoL (EORTC QLQ-C30, QLQ-BR23)

Investigational drug: talazoparib is not approved for use in breast cancer in Europe.
[a]Additional inclusion criteria: no more than 3 prior cytotoxic CT regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or a anthracycline unless medically contraindicated; [b]HER2+ disease is excluded; [c] Physician's choice of therapy must be determined prior to randomisation
PO, by mouth

Litton J, et al. Presented at SABCS 2017. Abstract GS6-07.

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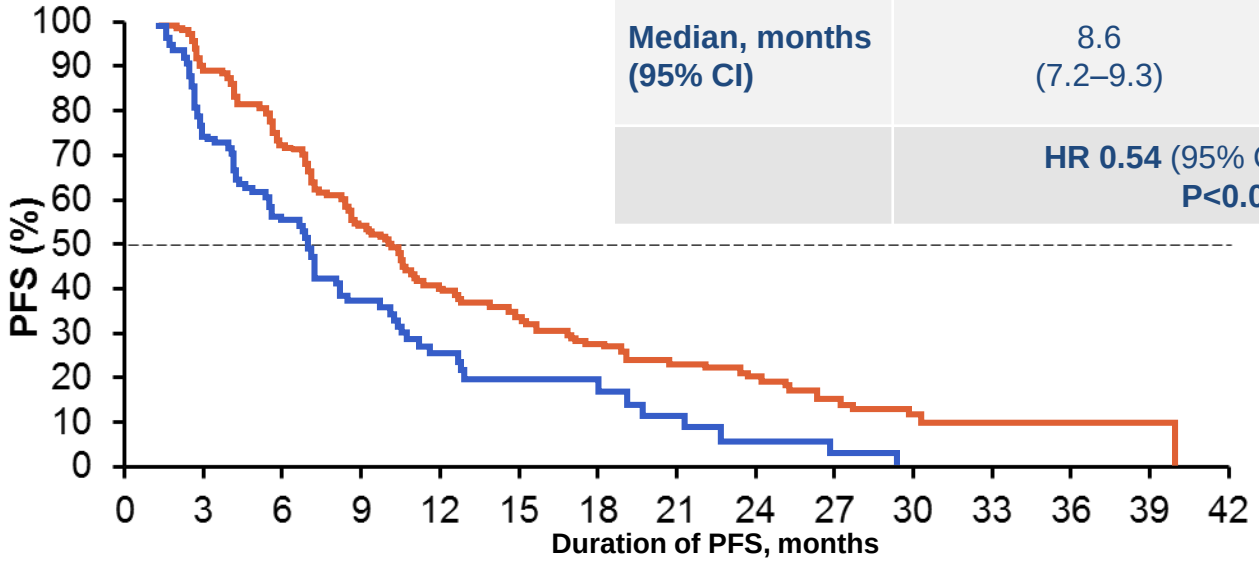
EMBRACA: PFS BY BLINDED CENTRAL REVIEW

	Talazoparib (n=262)	Overall TPC (n=114)
Events, n (%)	186 (65)	83 (58)
Median, months (95% CI)	8.6 (7.2–9.3)	5.6 (4.2–6.7)
	HR 0.54 (95% CI: 0.41–0.71) **P<0.0001**	



No. at risk (event/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/86)	0 (1/86)	287 (0/0)
TPC	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)	144 (0/0)

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Investigational drug: talozaparib is not approved for use in breast cancer in Europe.

Litton J, et al. Presented at SABCS 2017. Abstract GS6-07.

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Phase 3 study of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic g*BRCA*-associated breast cancer: BROCADE3

Véronique Diéras[1], Hyo S. Han[2], Bella Kaufman[3], Hans Wildiers[4], Michael Friedlander[5], Jean-Pierre Ayoub[6], Shannon L. Puhalla[7], Igor Bondarenko[8], Mario Campone[9], Erik H. Jakobsen[10], Mathilde Jalving[11], Cristina Oprean[12], Marketa Palácová[13], Yeon Hee Park[14], Yaroslav Shparyk[15], Eduardo Yañez[16], Matthew Dudley[17], Christine K. Ratajczak[17], David Maag[17], Banu K. Arun[18]

[1]Institut Curie, Paris, and Centre Eugène Marquis, Rennes, France; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Sheba Medical Center, Tel Hashomer, Israel; [4]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [5]Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia; [6]Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada; [7]UPMC Cancer Centers, Pittsburgh, PA, USA; [8]Dnipropetrovsk Medical Academy, City Hospital No.4, Dnipro, Ukraine; [9]Institut de Cancérologie de l'Ouest - Pays de la Loire, France; [10]Vejle Hospital/Lillebaelt Hospital, Vejle, Denmark; [11]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [12]University of Medicine and Pharmacy Timisoara; Oncomed SRL, Timisoara, Romania; [13]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [14]Samsung Medical Center, Seoul, Korea; [15]Lviv State Regional Treatment and Diagnostic Oncology Center, Lviv, Ukraine; [16]Universidad de la Frontera, Temuco, Chile; [17]AbbVie Inc., North Chicago, IL, USA; [18]The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

esmo.org

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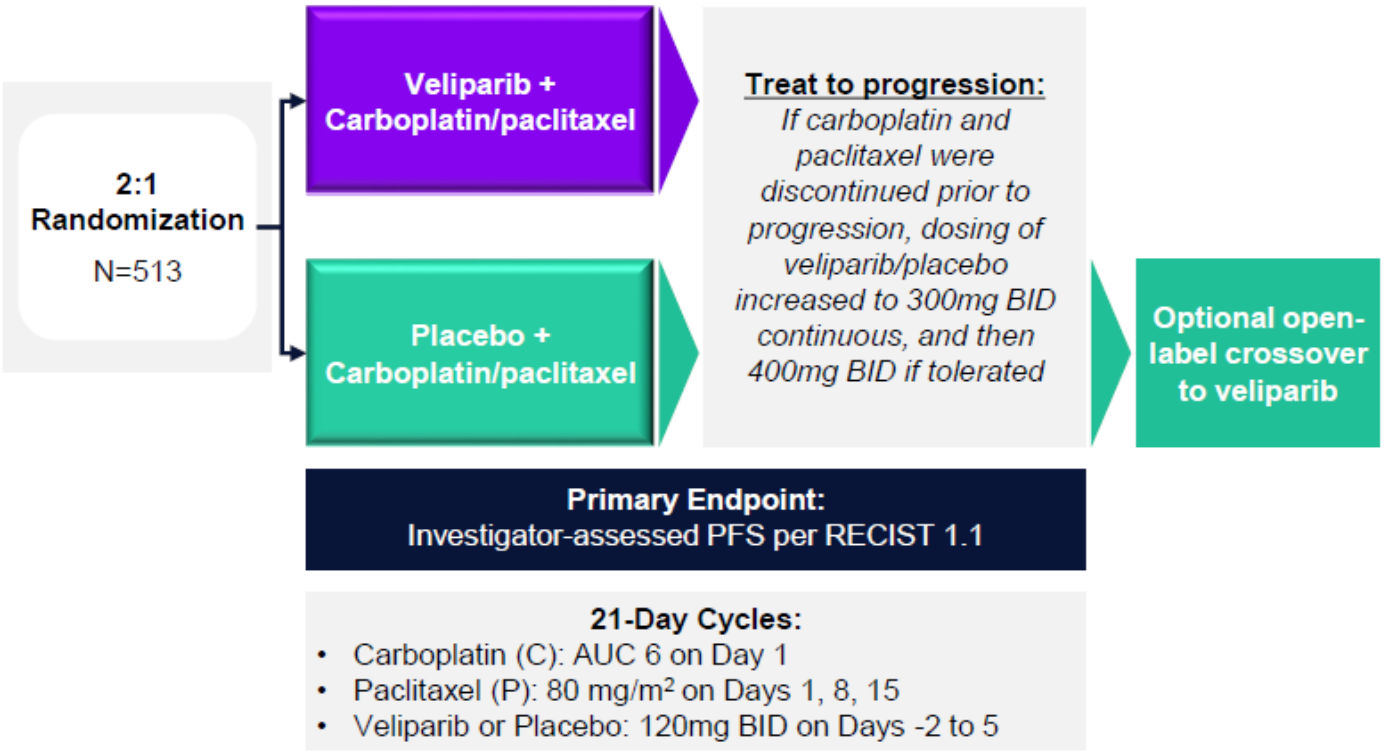
Study Design: BROCADE3 (NCT02163694)

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis



BARCELONA 2019 ESMO congress

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Diéras et al, ESMO 2019

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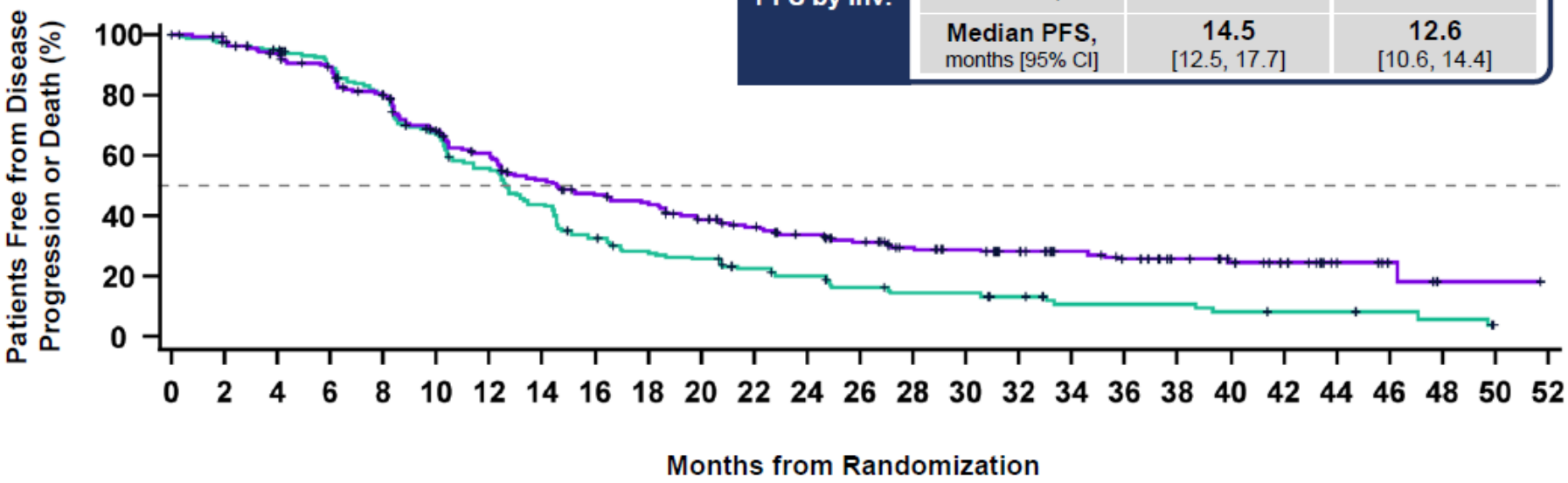
Primary Endpoint: PFS by Investigator Assessment

HR 0.705
[95% CI 0.566-0.877], p = 0.002

PFS by Inv.

	Veliparib + C/P	Placebo + C/P
PFS Events, n/N	217/337	132/172
Median PFS, months [95% CI]	**14.5** [12.5, 17.7]	**12.6** [10.6, 14.4]



No. at Risk

Control	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0
Veliparib	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0

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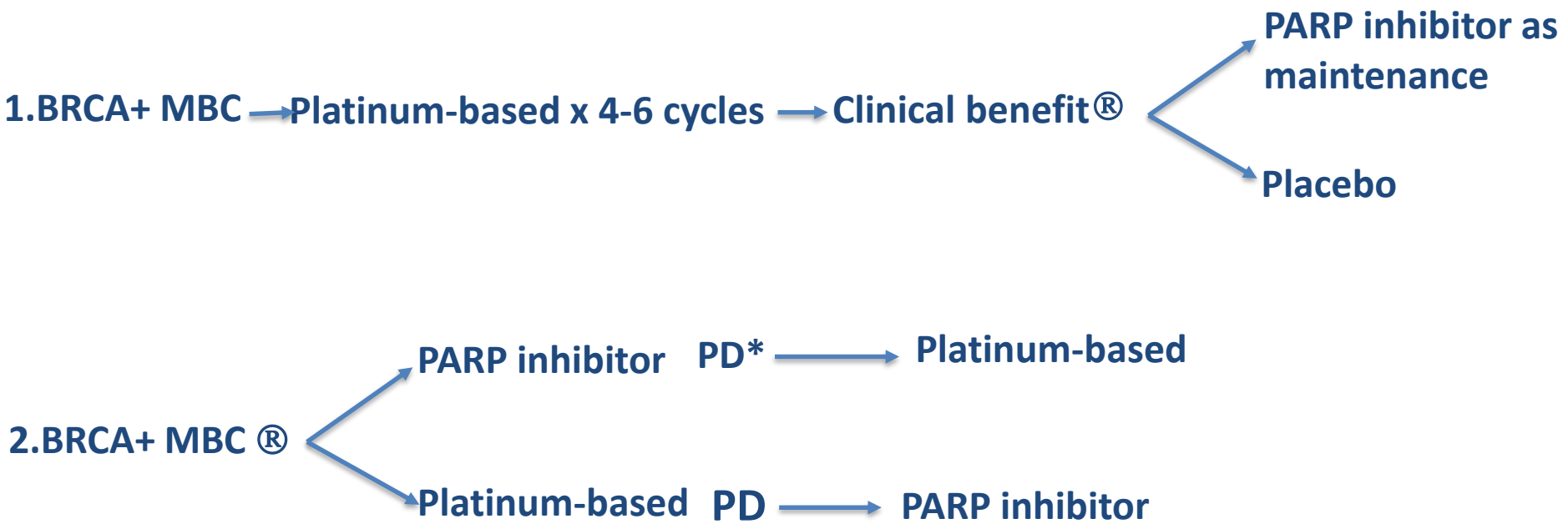
C/P: Carboplatin and Paclitaxel

Propositions for clinical trials design including platinum compounds and PARP inhibitors in BRCA+ metastatic breast cancer



* Progressive disease

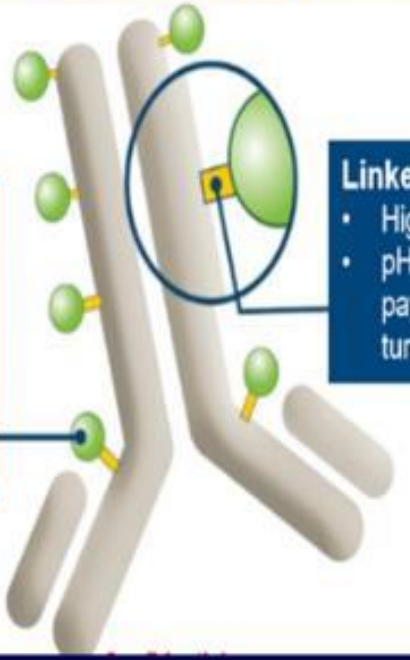
If the patient received for metastatic TNBC the following treatments: Taxane, capecitabine and eribuline ± biologicals; PS now is 2; multimetastatic disease but biological tests still normal: What do you propose?

1. Best supportive care
2. Clinical trial
3. Biopsy of one metastatic lesion and perform NGS
4. Sacituzumab govitecan
5. Vinorelbine or gemcitabine or eribuline

Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

5

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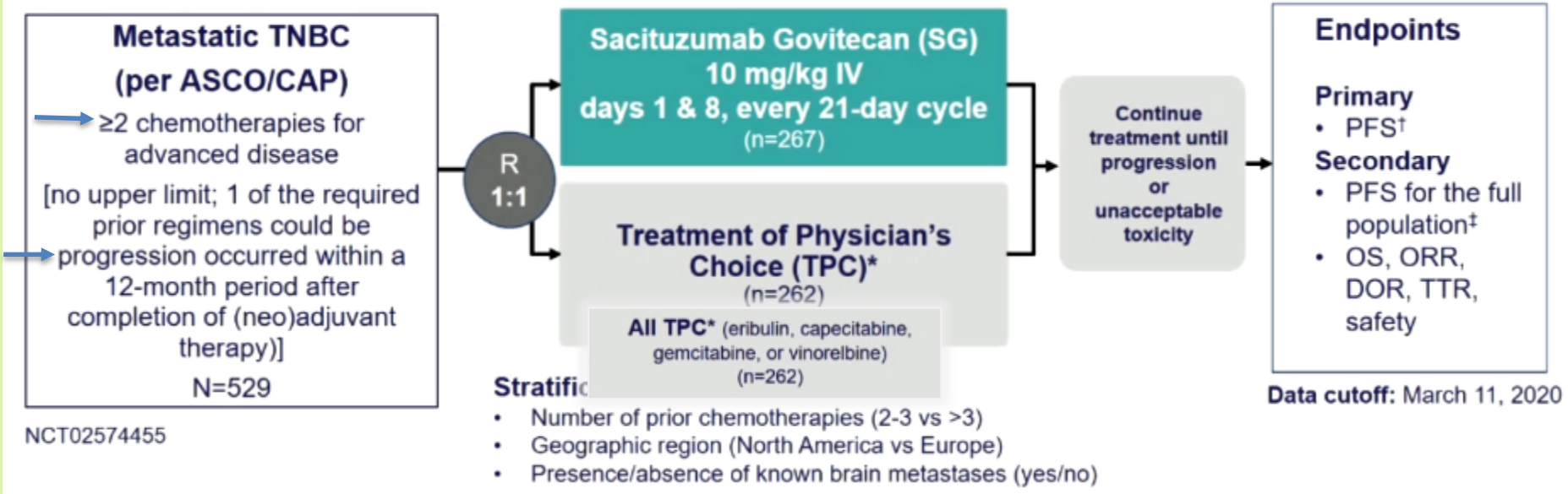
Clinical Trial

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Data cutoff: March 11, 2020

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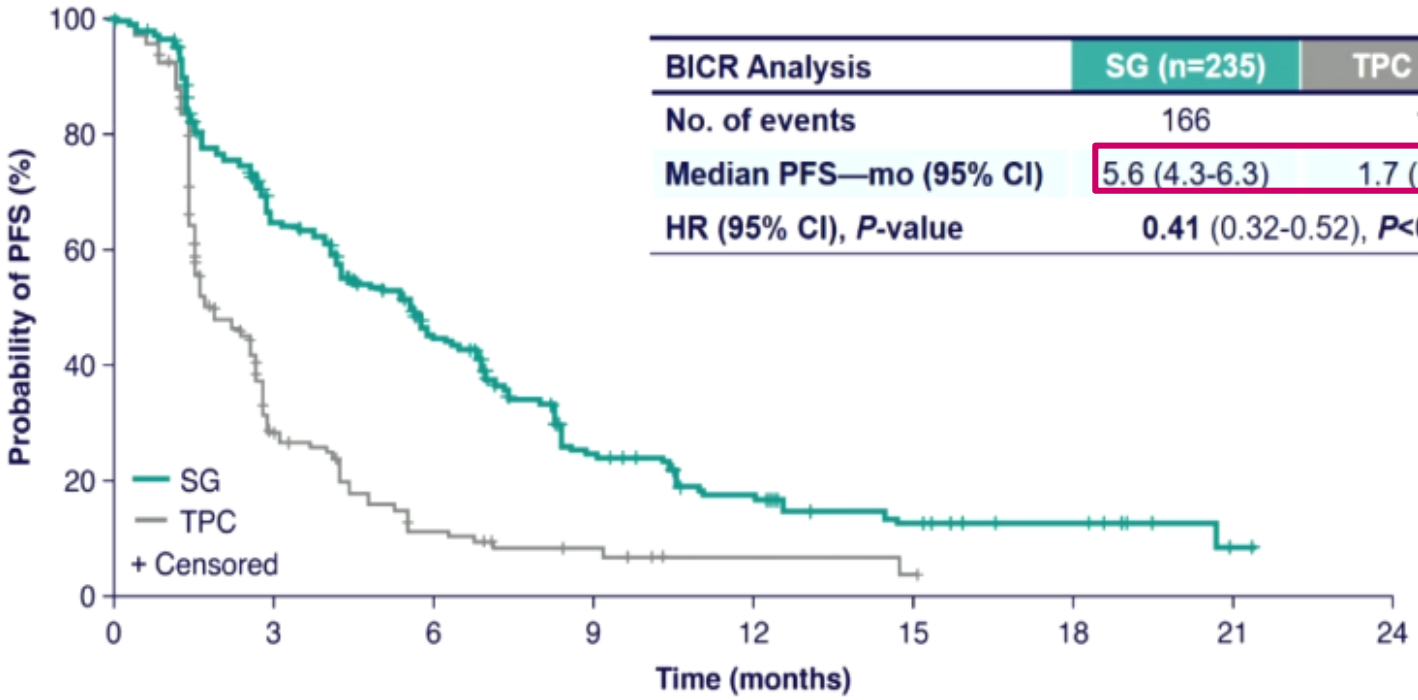
ASCENT Clinical Trial

(Sacituzumab Govitecan)

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

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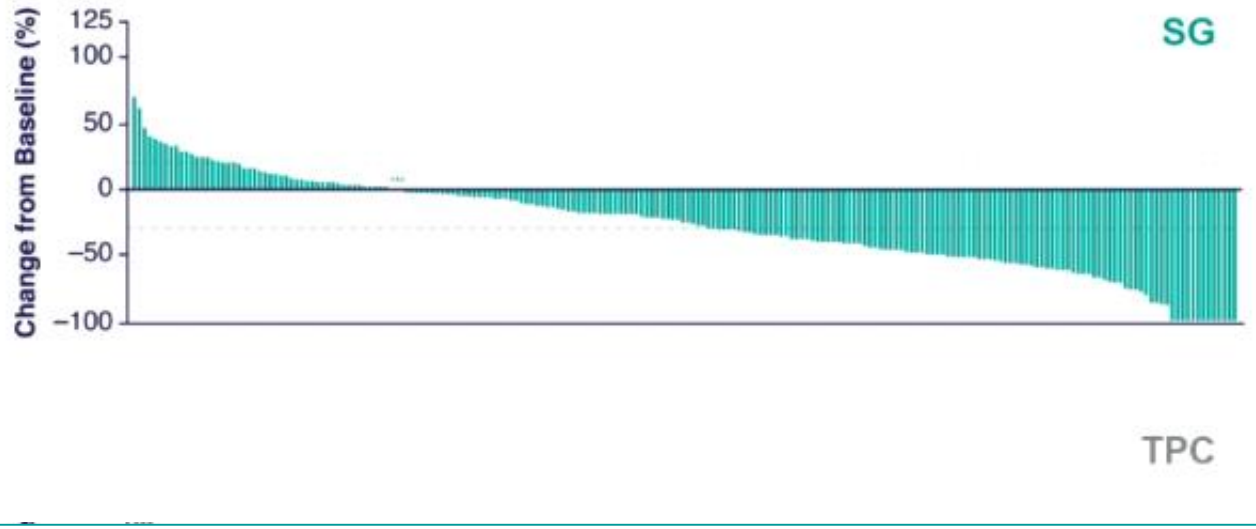
Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	

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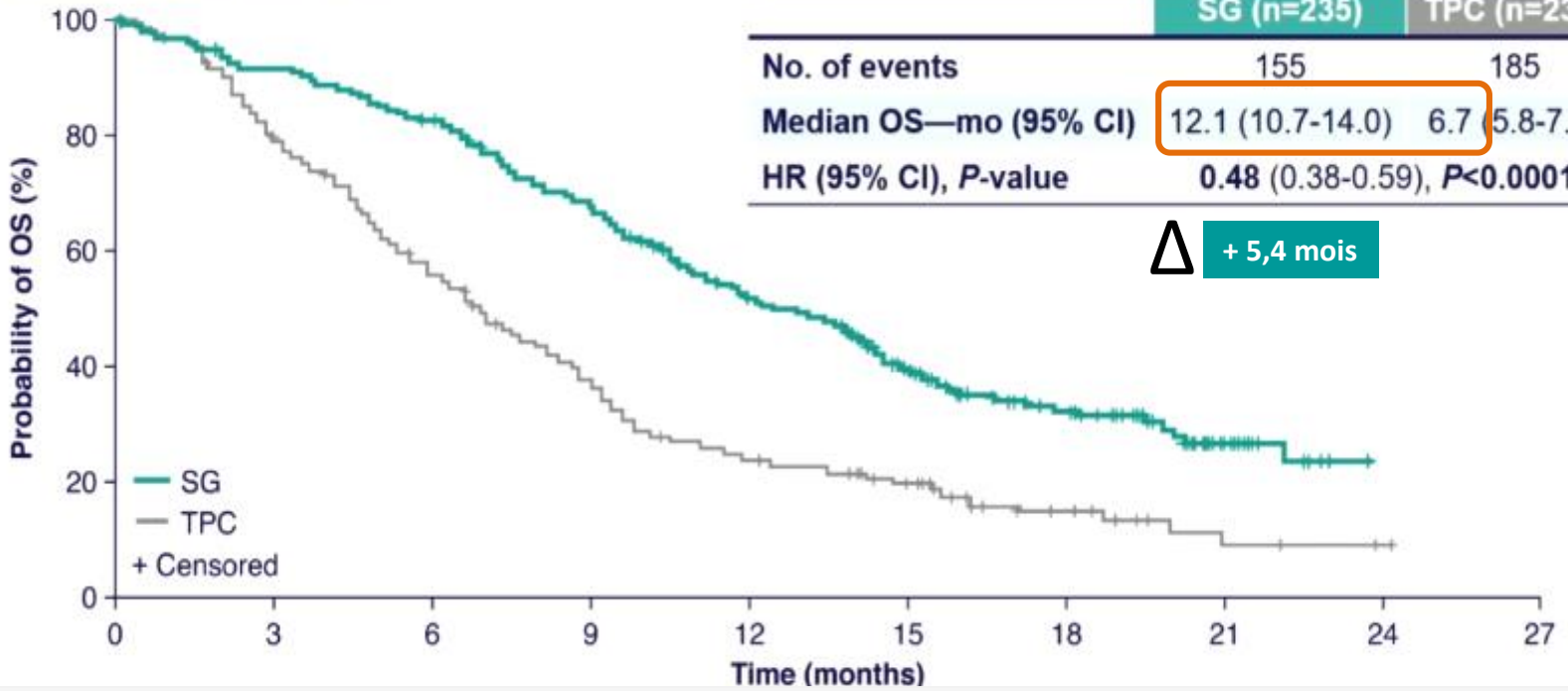
Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Δ + 5,4 mois

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(Sacituzumab Govitecan)

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

→ **Arrêt = 4,7 %**

TNBC: Conclusions (1)

- A group of TNBC benefits from chemotherapy based on anthracyclines and taxanes (and also from capecitabine and eribuline)
- Standard chemotherapy is revisited with the development of antibody-drugs conjugates (e.g. sacituzumab govitecan)
- *BRCA* mutated tumors: significant tumor responses to platinum and PARP inhibitors

TNBC: Conclusions (2)

- Immune checkpoint inhibitors + chemotherapy are active in 1st line TNBC, PD-L1 positive population.
- Chemotherapy + biologicals are needed in HR-, HER-2 ⊣, PD-L1 ⊣ tumors (quadruple negative)
- Genomic era: better understanding of the tumor heterogeneity and biology of tumor at baseline and at resistance which might lead to new targets and potentially to new active agents (challenge: studies design and pts accrual)

THANK YOU

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