三陰性轉移性乳癌治療的最新進展

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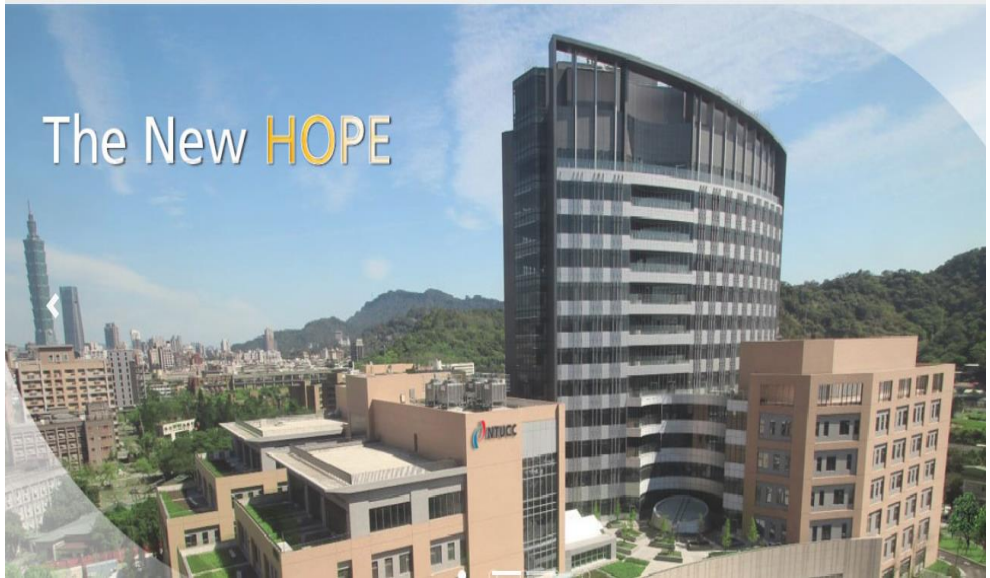
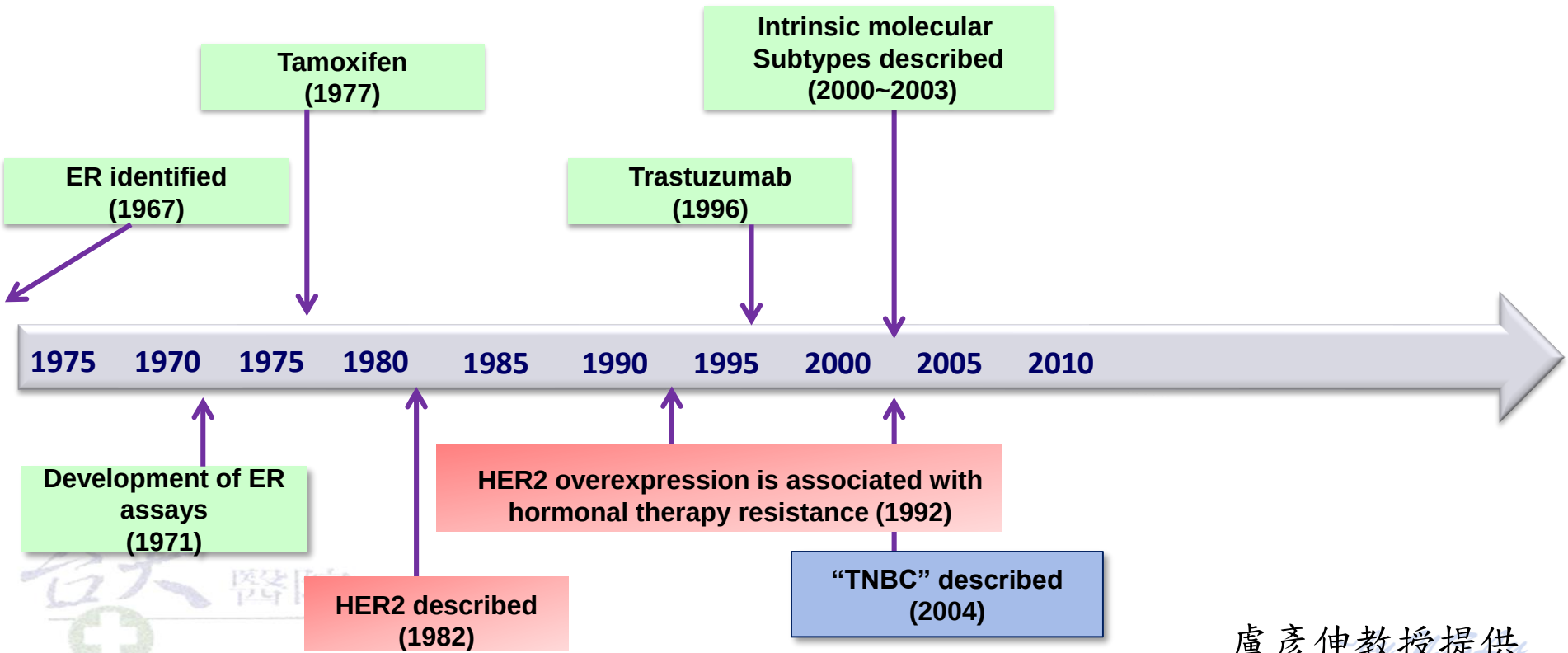


Historic Timeline of Therapies Specifically Targeting the ER Pathways for HR+ Breast Cancer



盧彥伸教授提供

何謂三陰性(Triple-Negative)?

- Estrogen receptor (ER) — negative
- Progesterone receptor (PR) — negative
- Human Epidermal Receptor type 2 (HER2) — negative

TNBC Characteristics

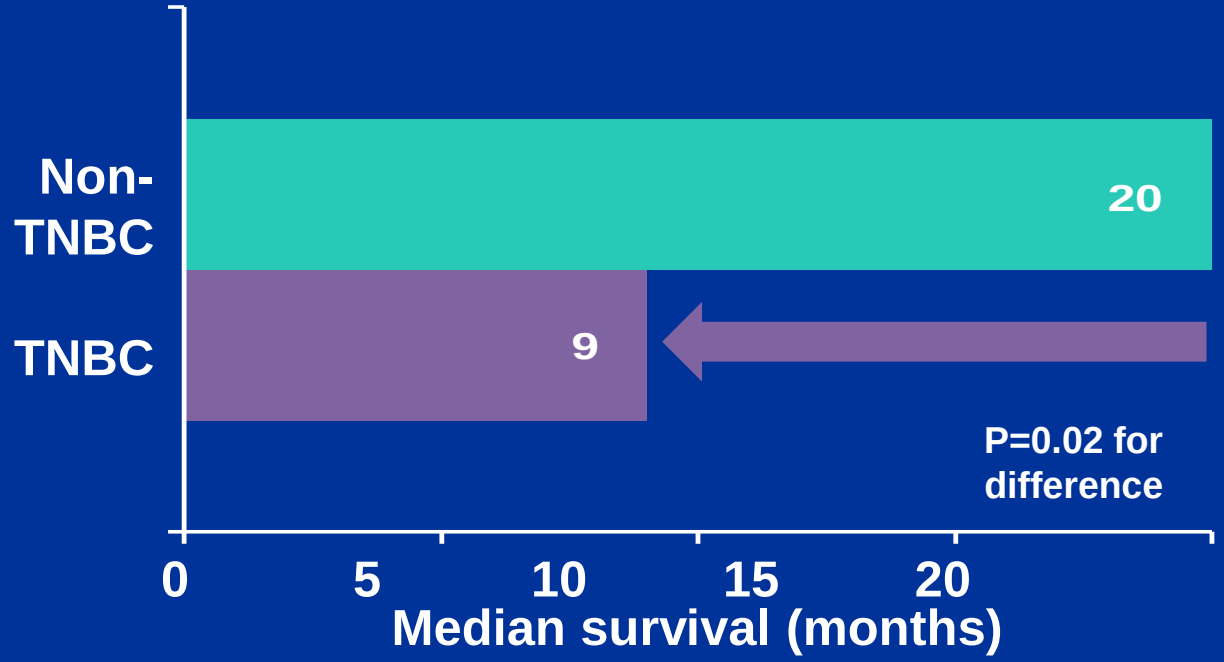
- ~15% of all breast cancers
- Younger age 較年輕
- High grade 高惡性度
- Higher recurrence rate 高復發率
- Higher disease burden

- **Higher chance of BRCA1 mutation**

For quite a long period,
we have only chemotherapies

TNBC Significantly Shortens Survival in Patients with Metastatic Disease

Significantly Shorter Survival Following Recurrence in Patients with TNBC[1]



HR for death 1.6 (95% CI 1.2–2.1) p=0.003

2007

HR = hazard ratio

1. Dent et al. Clin Cancer Res 2007

Chemotherapies

- Anthracyclines
  - Doxorubicin
  - Epirubicin
  - Liposomal doxorubicin
- Anti-microtubules
  - Paclitaxel
  - Docetaxel
  - Vinorelbine
  - Eribulin
- Topoisomerase II
  - etoposide

Bevacizumab

- Anti-metabolites
  - Fluorouracil
  - Capecitabine
  - Gemcitabine
  - Methotrexate
- Alkylating agents
  - Cyclophosphamide
  - Mitomycin C
- Platinum
  - cisplatin
  - carboplatin

TNBC: Lack of specific weapons

ER/PR(+) disease

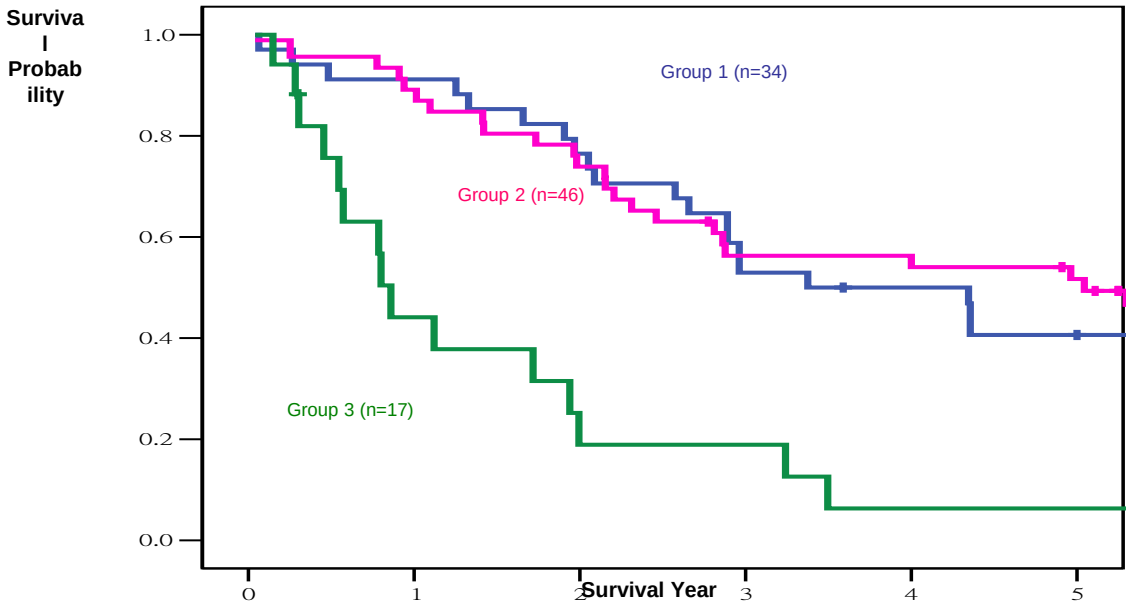
- Endocrine therapy
  - Tamoxifen, LHRHa
  - Aromatase inhibitors
  - Fulvestrant
  - Progesterone derivatives
- Targeted therapies
  - mTOR inhibitors
  - CDK4/6 inhibitors
  - PI3K inhibitors

HER2(+) disease

- Trastuzumab
- Lapatinib
- Pertuzumab
- T-DM1
- Ongoing, such as neratinib, tucatinib

TNBC— Worse Outcome

台大醫院第四期乳癌五年存活率



2006-2008 NTUH BC patients stage IV, N=97	
Gr 1	ER (+)/HER2(-)
Gr 2	HER2 (+)
Gr 3	Triple negative

Finally, some advances in TNBC!

Recent Progress

- Targeted therapy (2018)
  - **PARPi for *gBRCA1/2* mutations**
- 1st immunotherapy (2019)
  - **Atezolizumab (anti-PDL1)**
- ADC in development
  - **sacitumumab govitecan**

PARP INHIBITORS

The battles between DNA repair machinery and DNA damage inducers

Endogenous factor,
ex, normal replication

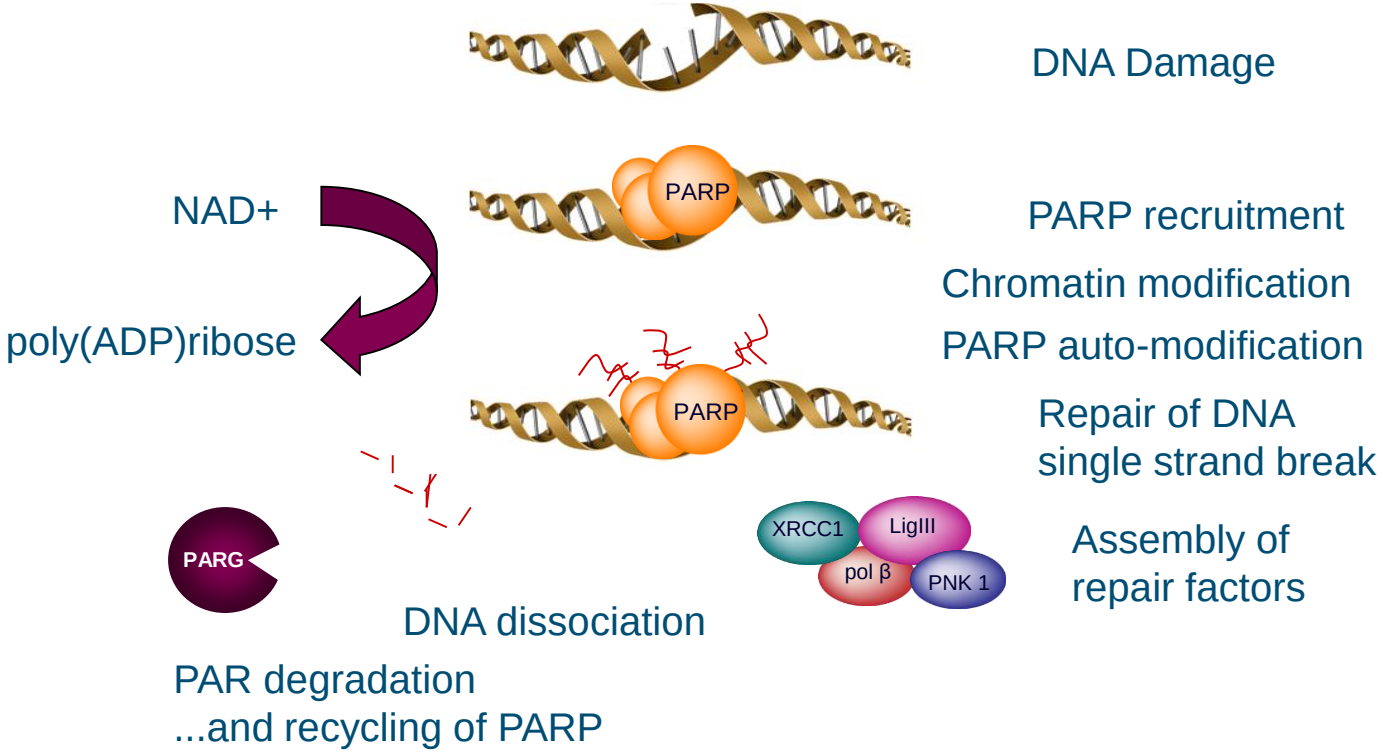
Exogenous factor, ex,
chemo, xRT, UV, toxin

Cell survival
or
Cell death

DNA repair:
BER, NER, HRR, MMR, NHEJ, etc

Adapted from Jackson and Bartek, Nature 2009

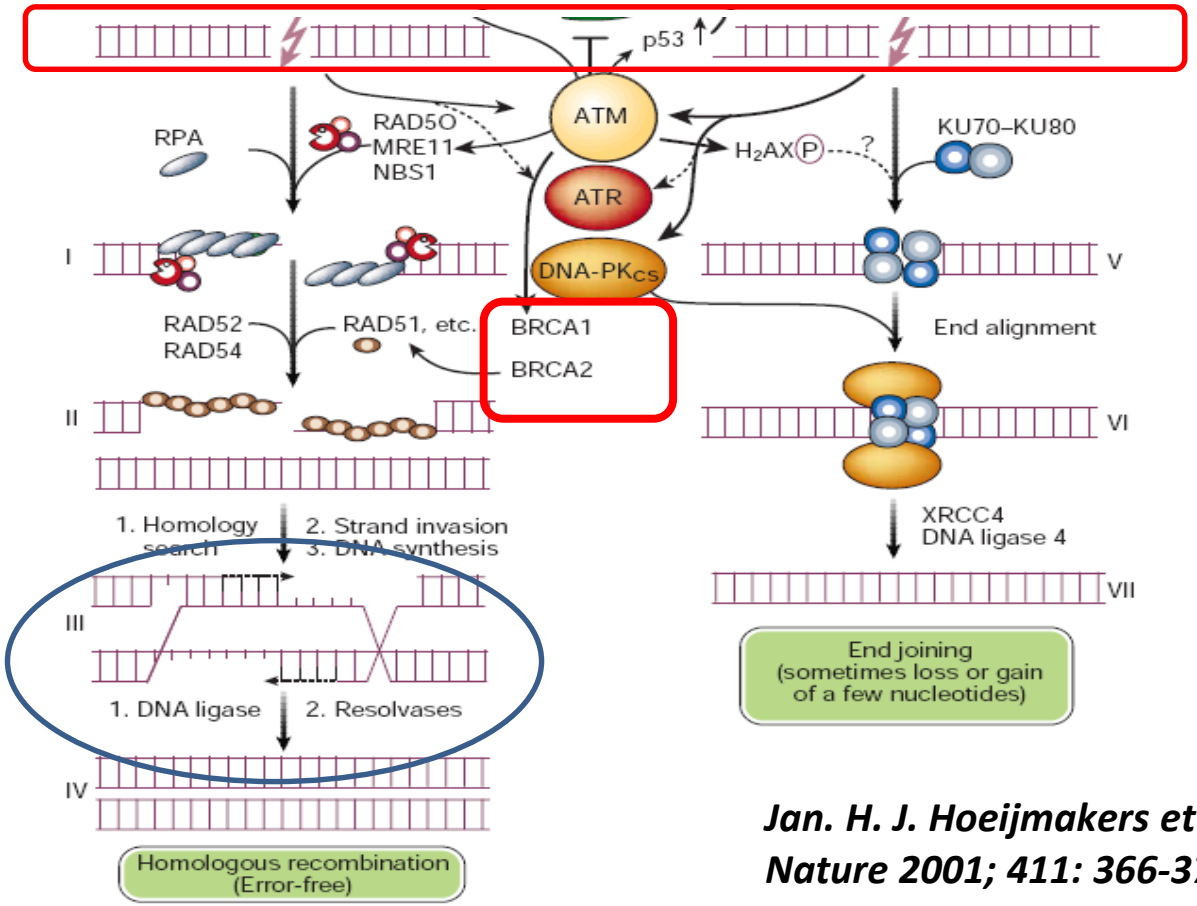
PARP, a key player in ssDNA break (BER)



BRCA1 and BRCA2 play a key role in HRR (DSB) pathway

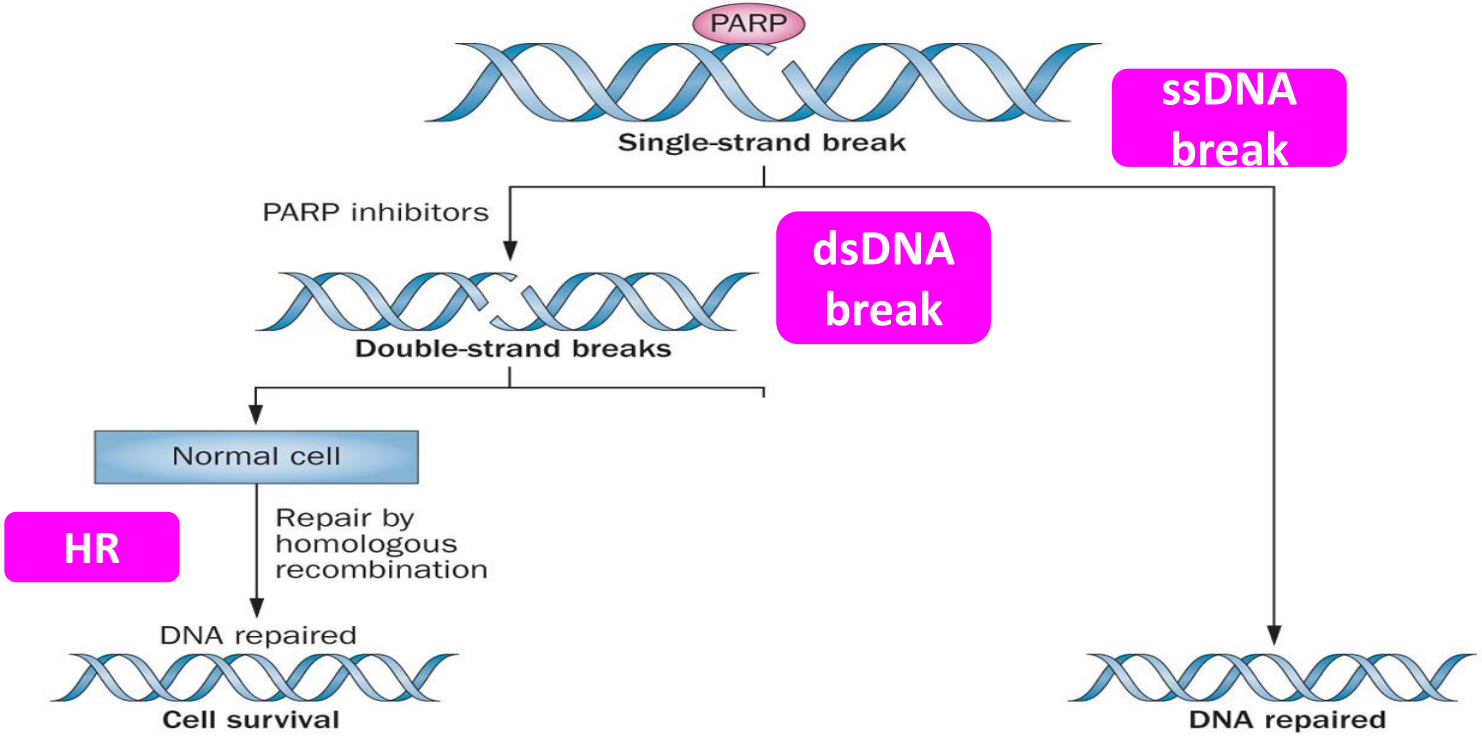
HRR

NHEJ



Jan. H. J. Hoeijmakers et al,
Nature 2001; 411: 366-374

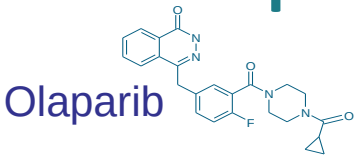
PARP inhibitors and Synthetic Lethality

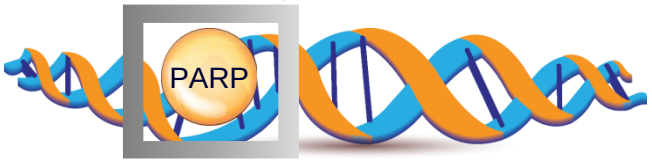


Sonnenblick, A. *et al.* (2014) An update on PARP inhibitors—moving to the adjuvant setting *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2014.163

nature REVIEWS CLINICAL ONCOLOGY

Olaparib, the first approved PARPi in treating BC





Trapped PARP on single-strand breaks

Increase in double-strand breaks in replicating cells

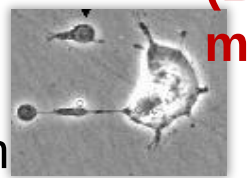
Double-strand breaks

HR Deficient cancer cell

E.g. with **non-functioning BRCA (BRCA1/2 mutation)**

Normal cell

DNA damage accumulation and cell death



Repair by homologous recombination

OlympiAD is a Phase III study investigating olaparib vs TPC in g*BRCA*m HER2-negative metastatic breast cancer[1]

Germline BRCA mutation

and taxane

HER2 negative (TNBC or ER/PR+)

in the advanced setting

Prior Anthra + Taxane
≦ 2L Chemo for MBC
≥ 1L ET for ER(+)

FSI May 2014[3]

Global Study in 19 countries and approximately 141 sites[1]

Randomise 2:1
N=302[4]

Stratification by[2]

- *Prior chemotherapy regimens for metastatic breast cancer*
- *Hormonal receptor (HR) status*
- *Prior platinum therapy*

Olaparib
300mg**po* bid

Treatment of Physician's Choice
(TPC)
Capecitabine or Eribulin or Vinorelbine

Primary endpoint
- PFS (RECIST 1.1, Independent Review)

Secondary endpoints
- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad g*BRCA*m status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

1. https://clinicaltrials.gov/ct2/show/NCT02000622; 2. Robson et al. Poster OT1-1-04, San Antonio Breast Cancer Symposium 2014; 3. AZ data on file (2017),
4. Robson et al. N Engl J Med. 2017; 377:523-533

Patient Characteristics

	Olaparib (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
BRCA mutation status, n (%)		
BRCA1	117 (57)	51 (53)
BRCA2	84 (41)	46 (47)
Both	4 (2)	0
Hormonal receptor status, n (%)		
ER and/or PgR positive	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

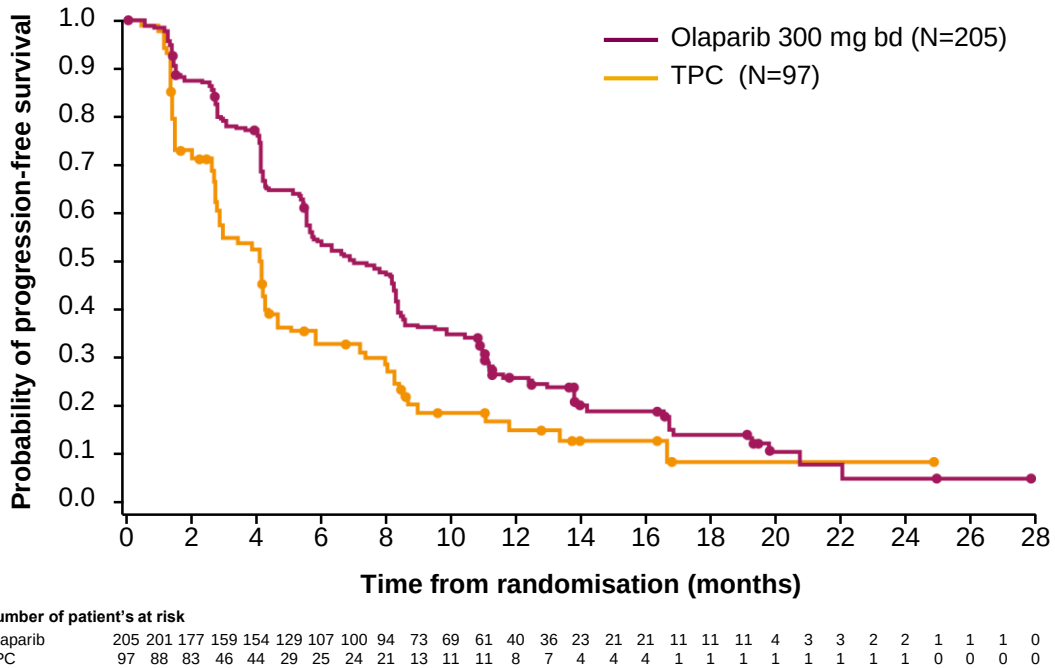
Patient Characteristics

		Olaparib (205), n (%)	TPC (97), n (%)
ECOG	0	148 (72.2)	62 (63.9)
No. of Met sites	1	46(22.4%)	25 (25.8%)
	≥ 2	159 (77.6%)	72 (74.2%)
Sites of mets	Bone/local	16 (7.8%)	6 (6.2%)
	CNS	17 (8.3%)	8 (8.2%)
De novo stage IV MBC		26 (12.7%)	12(12.4%)
Progression at randomization		159 (77.6%)	73 (75.3%)

Data Cutoff: 9th December 2016

1 Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

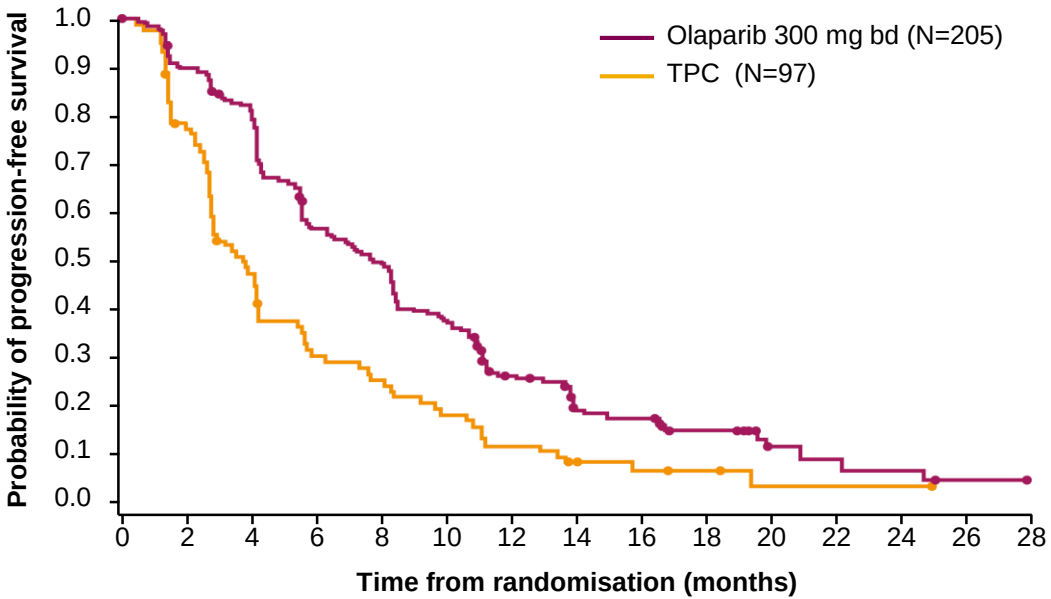
Primary endpoint: PFS assessed by BICR



	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	**7.0**	**4.2**
	HR = 0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

1. Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

Investigator-assessed PFS: consistent and supportive



Number of patient's at risk

Olaparib	205	201	181	165	162	153	111	105	93	75	74	61	42	30	25	23	23	13	13	12	5	4	4	3	3	1	1	1	0
TPC	97	87	68	46	40	31	25	24	21	18	15	13	10	5	5	5	4	3	3	2	1	1	1	1	1	0	0	0	0

	Olaparib	TPC
n	205	97
Events (%)	165 (80.5)	80 (82.5)
Median (m)	**7.8**	**3.8**
	HR=0.50 95%CI 0.36, 0.68 p<0.0001	

In this Asian subpopulation, PFS by BICR was prolonged in patients receiving olaparib compared with those treated with TPC

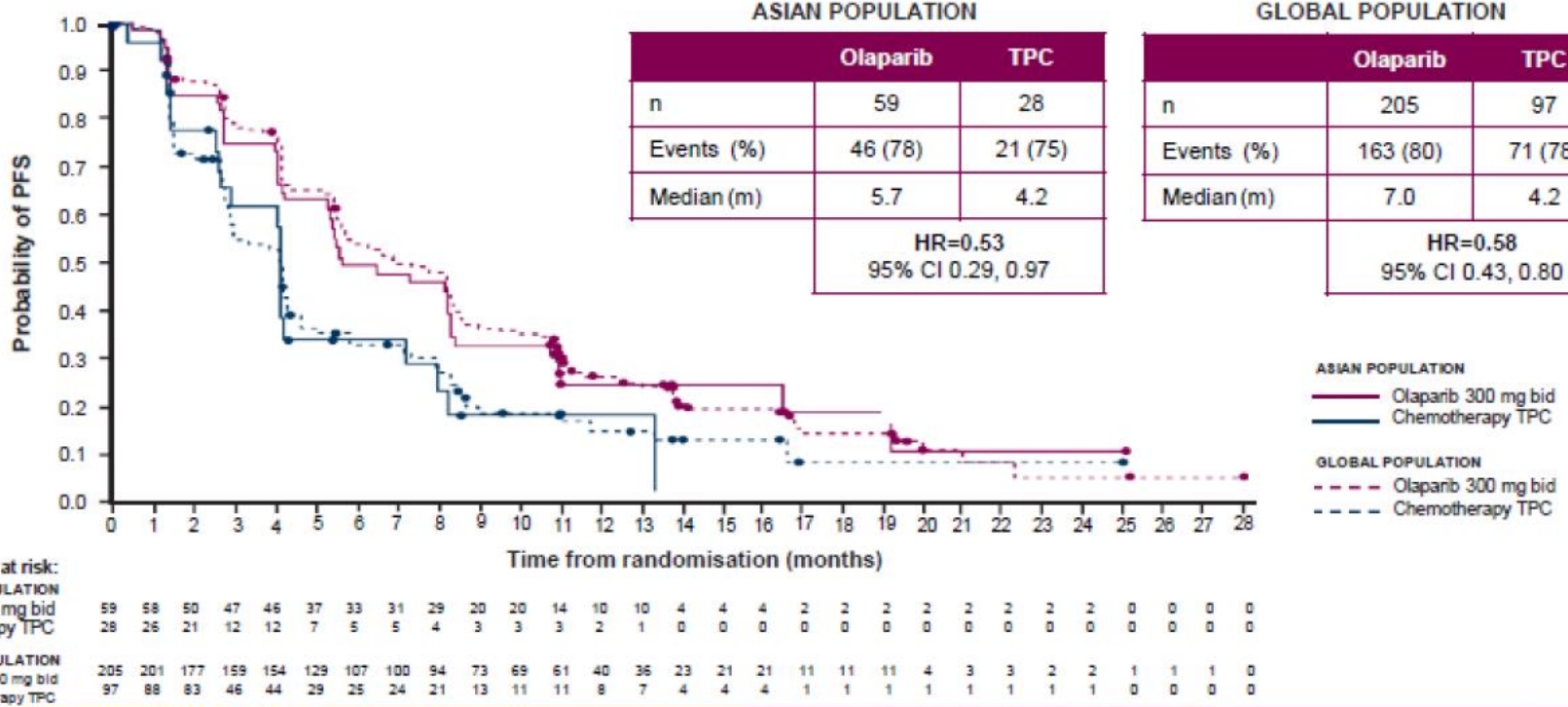
Data in Asian patients was similar to that observed in the global population (median 7.0 vs 4.2 months; HR 0.58; 95% CI 0.43, 0.80).[1]

ASIAN POPULATION

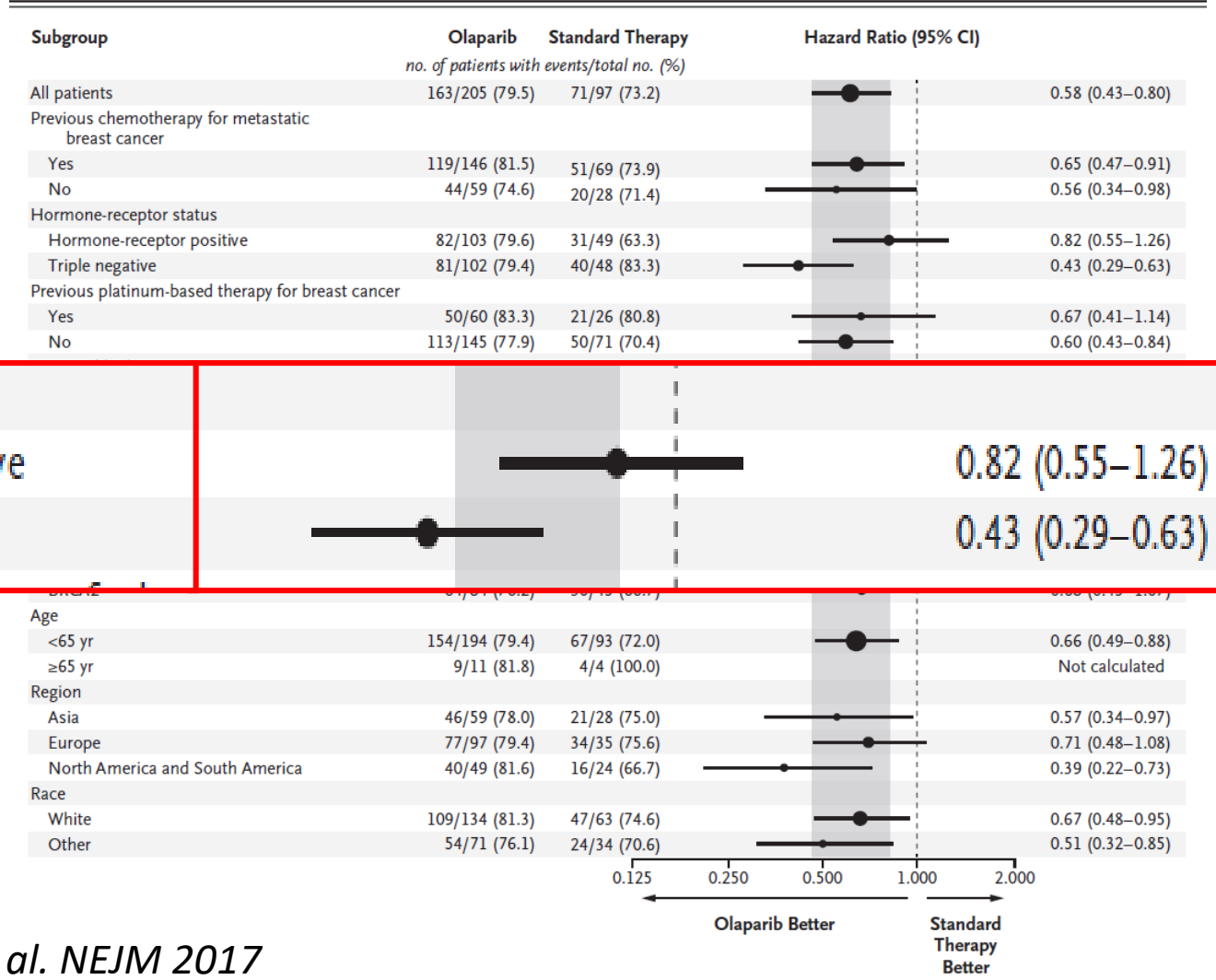
	Olaparib	TPC
n	59	28
Events (%)	46 (78)	21 (75)
Median (m)	5.7	4.2
	HR=0.53 95% CI 0.29, 0.97	

GLOBAL POPULATION

	Olaparib	TPC
n	205	97
Events (%)	163 (80)	71 (78)
Median (m)	7.0	4.2
	HR=0.58 95% CI 0.43, 0.80	



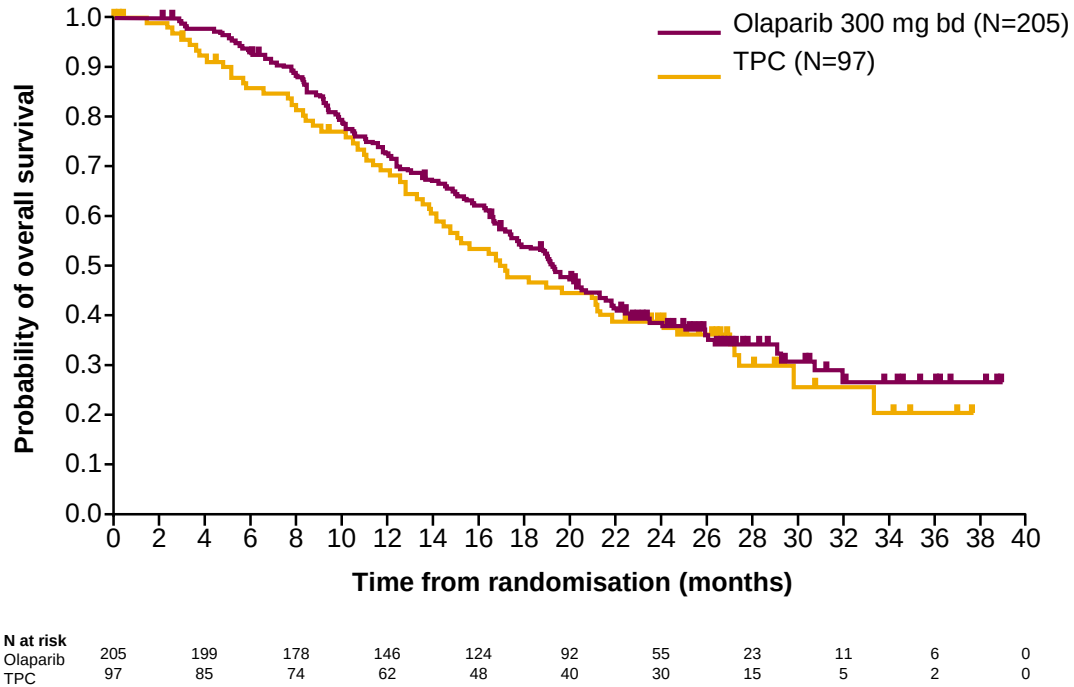
PFS: Subgroup analysis



Hormone-receptor status
Hormone-receptor positive 0.82 (0.55–1.26)
Triple negative 0.43 (0.29–0.63)

Robson et al. NEJM 2017

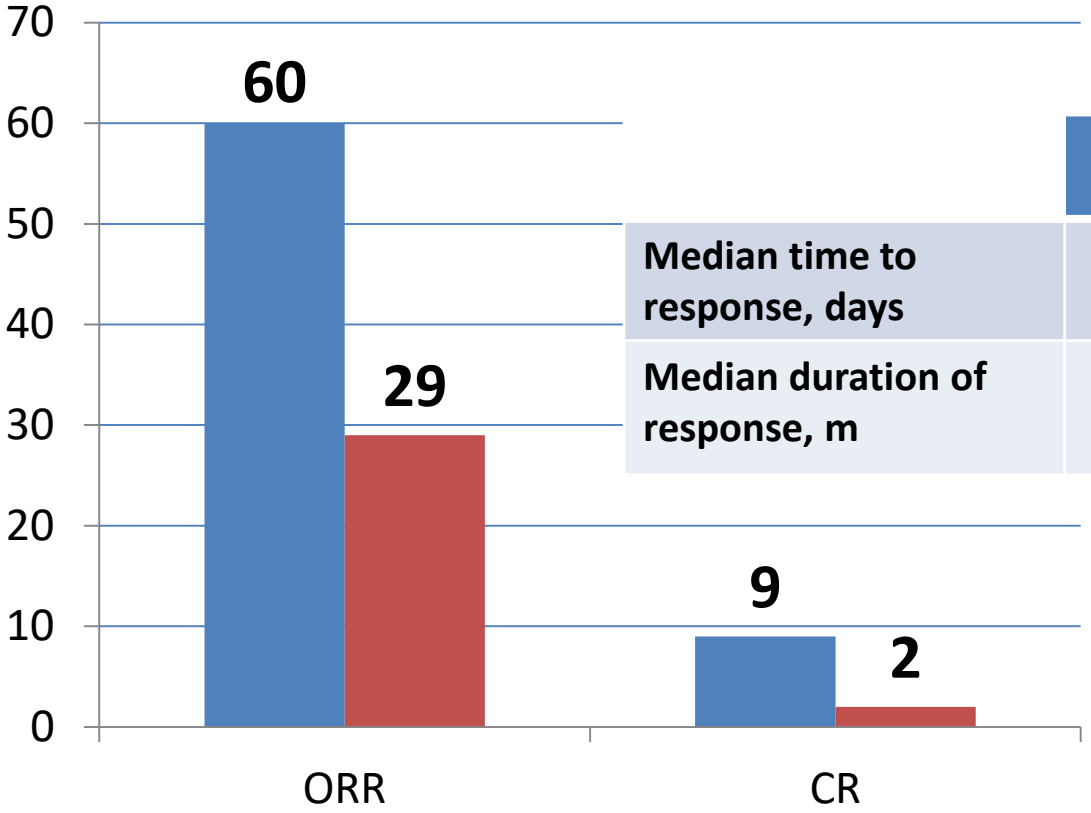
No significant difference in OS so far



	Olaparib	TPC
n	205	97
Events (%)	130 (63)	62 (64)
Median (m)	**19.3**	**17.1**
	HR = 0.90 95% CI (0.66, 1.23) p=0.513	
Survival at 6m (%)	93.1	85.8
Survival at 18m (%)	54.1	48.0

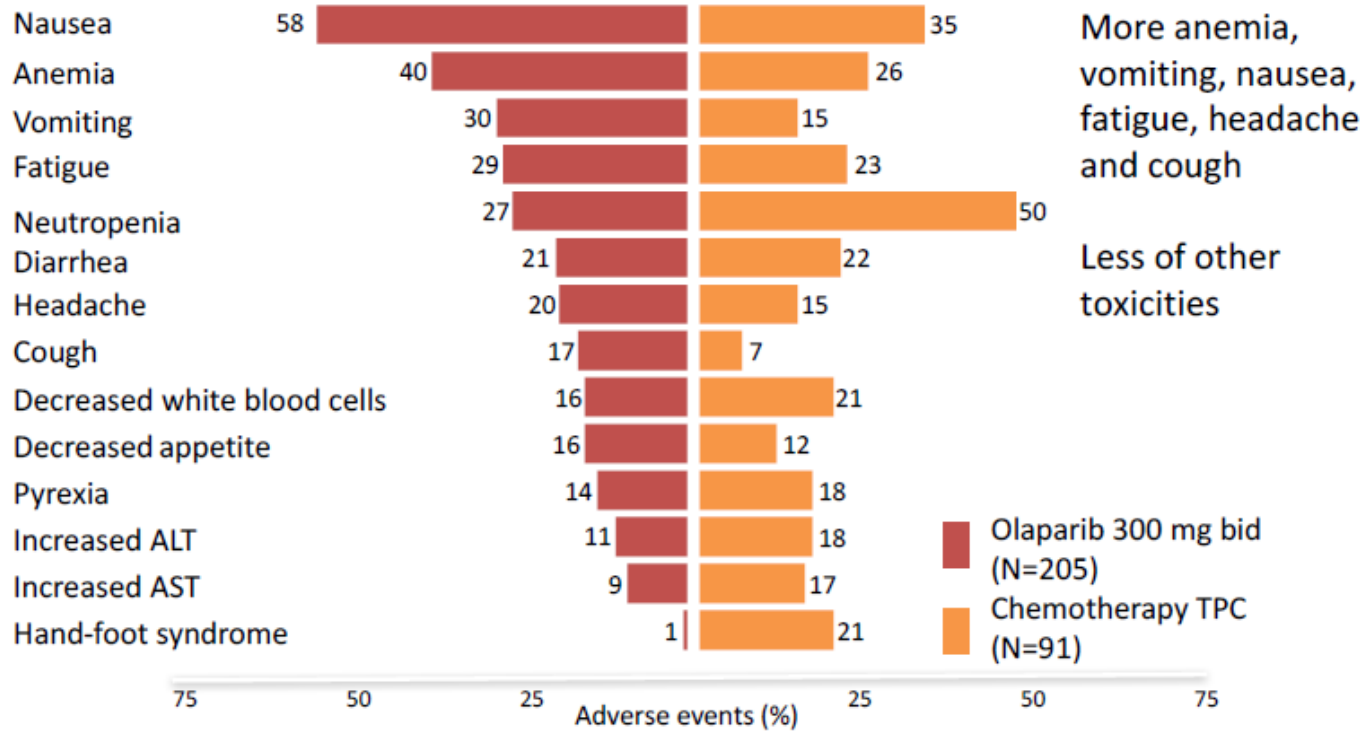
1. Robson et al. AACR, 2018

Objective Response by BICR



	Olaparib (n=167)	C/T TPC (n=66)
Median time to response, days	47	45
Median duration of response, m	6.4 (2.9-9.7)	7.1 (3.2-12.2)

OLYMPIAD: Adverse events (any grade) in ≥15% of patients



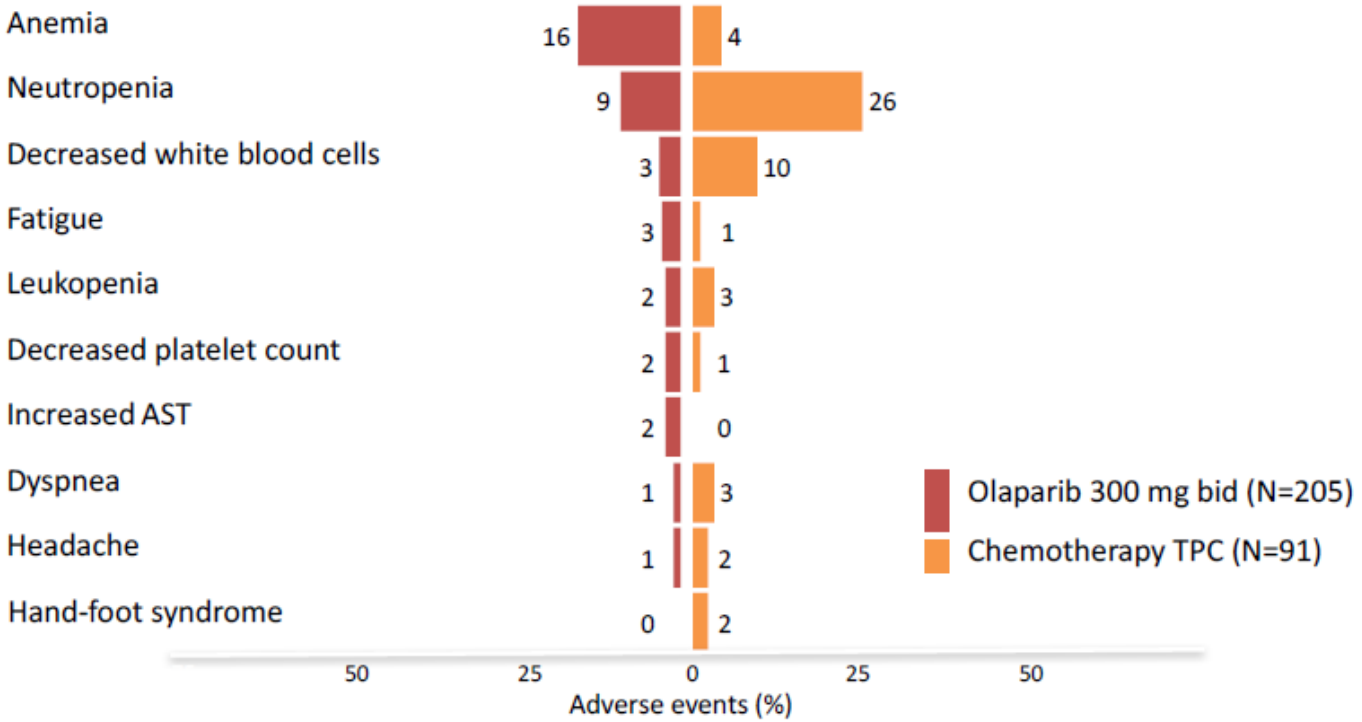
More anemia, vomiting, nausea, fatigue, headache and cough

Less of other toxicities

Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Robson, NEJM 2017

Grade ≥3 AE in ≥ 2% patients in either arm

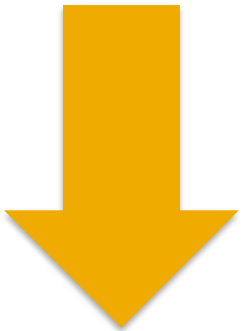


Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Robson et al. NEJM 2017

TEAEs led to discontinuations in 5% of patients treated with olaparib[1]

Additionally 36% in the olaparib group received dose interruptions and 25% received dose reductions due to TEAEs[1]



	Olaparib (N=205) n (%)	TPC (N=91) n (%)
Dose interruption	74 (36.1)	26 (28.6)
Dose reduction	52 (25.4)	28 (30.8)
Mean daily dose in mg	571.5	NA
Treatment discontinuation	10 (4.9)	7 (7.7)

Adapted with permission[1]

TEAE=treatment-emergent adverse event
Data Cutoff: 25 September 2017

1. Robson et al. AACR, 2018

Study Design: EMBRACA

gBRCAm (+)

HER2(-)

Prior Anthra + Taxane

≤ 3L Chemo for MBC

no active CNS mets

R 2:1

Talazoparib 1mg 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

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.
*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.
www.clinicaltrials.gov (NCT01945775)

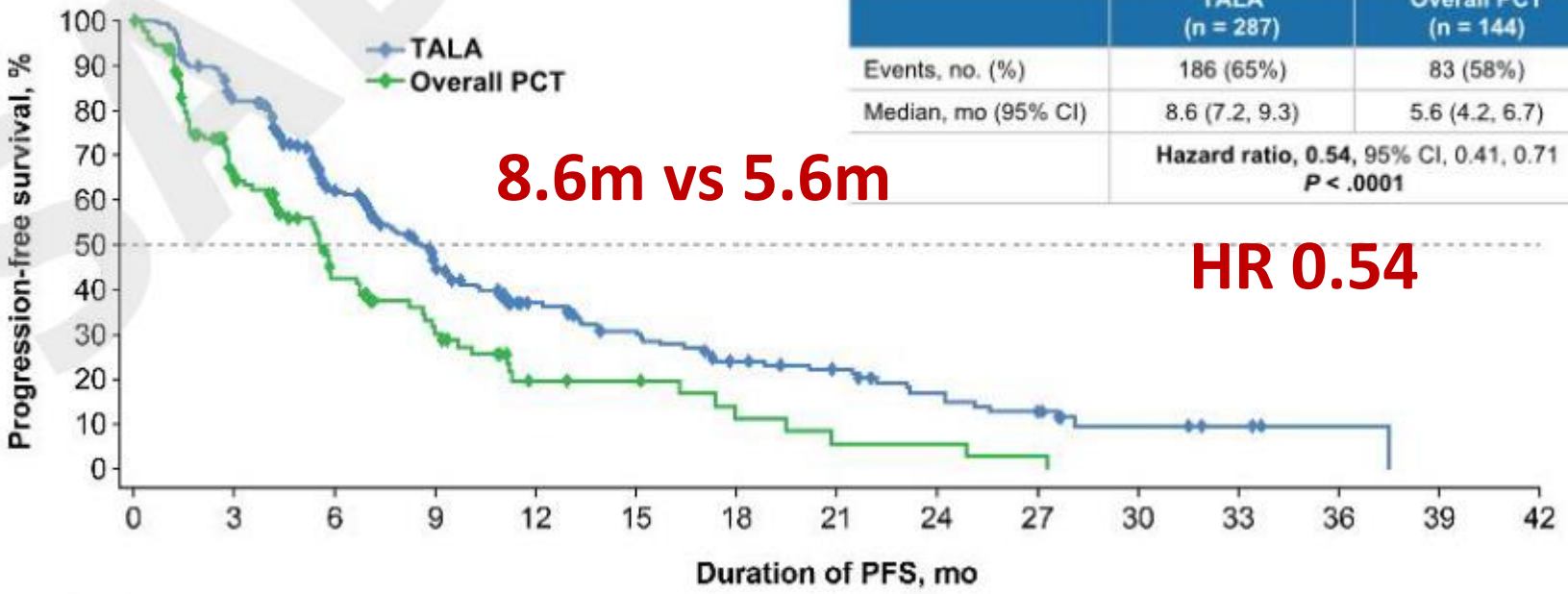
Litton et al. SABCS 2017

Primary Endpoint: PFS by Blinded Central Review

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

8.6m vs 5.6m

HR 0.54



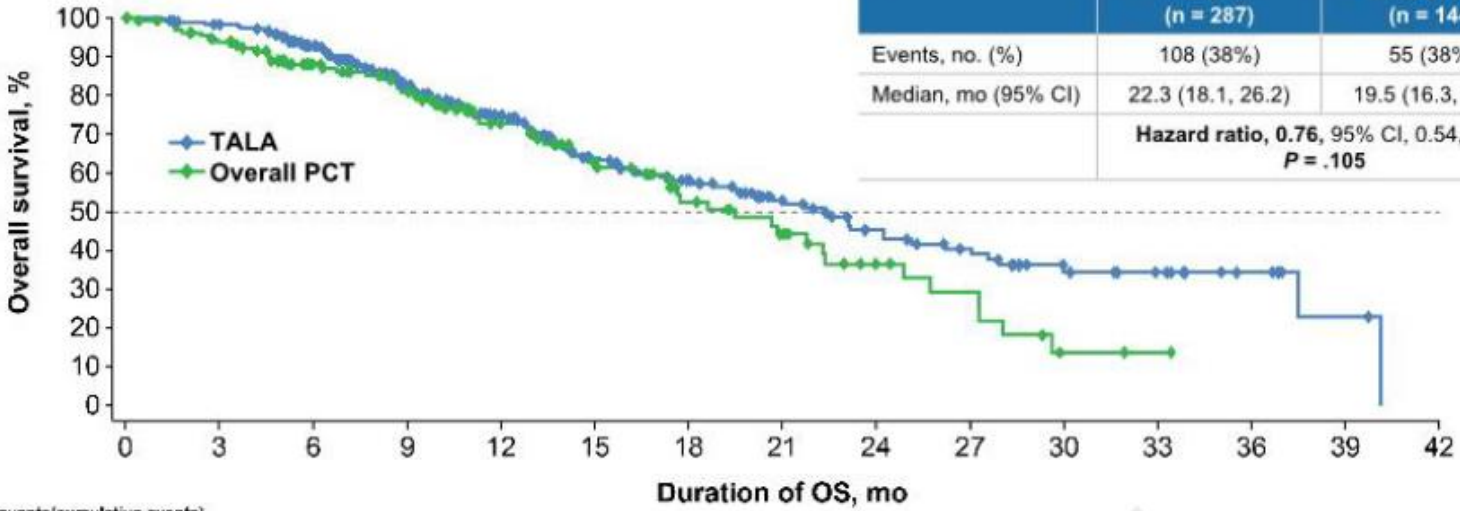
No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	18 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	88 (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)

Litton et al. SABCS 2017 1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

Interim OS Analysis: Secondary Endpoint

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 ***P* = .105**	



No. at risk (events/cumulative events)

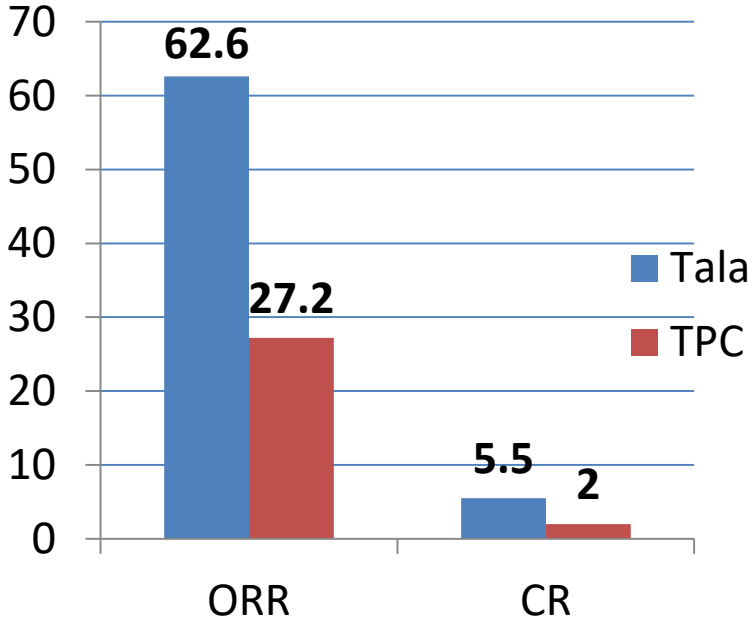
TALA	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (5/55)	52 (6/81)	38 (7/88)	30 (1/102)	18 (1/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	144 (0/0)	119 (5/5)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (1/46)	11 (3/49)	8 (2/51)	2 (1/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/56)

Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

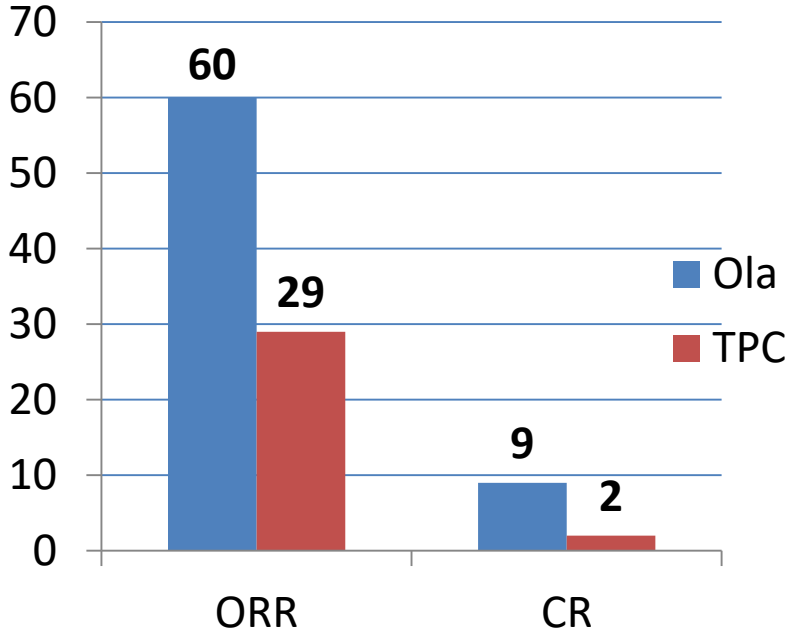
Litton et al. SABCS 2017

Objective Response by BICR

EMBRACA

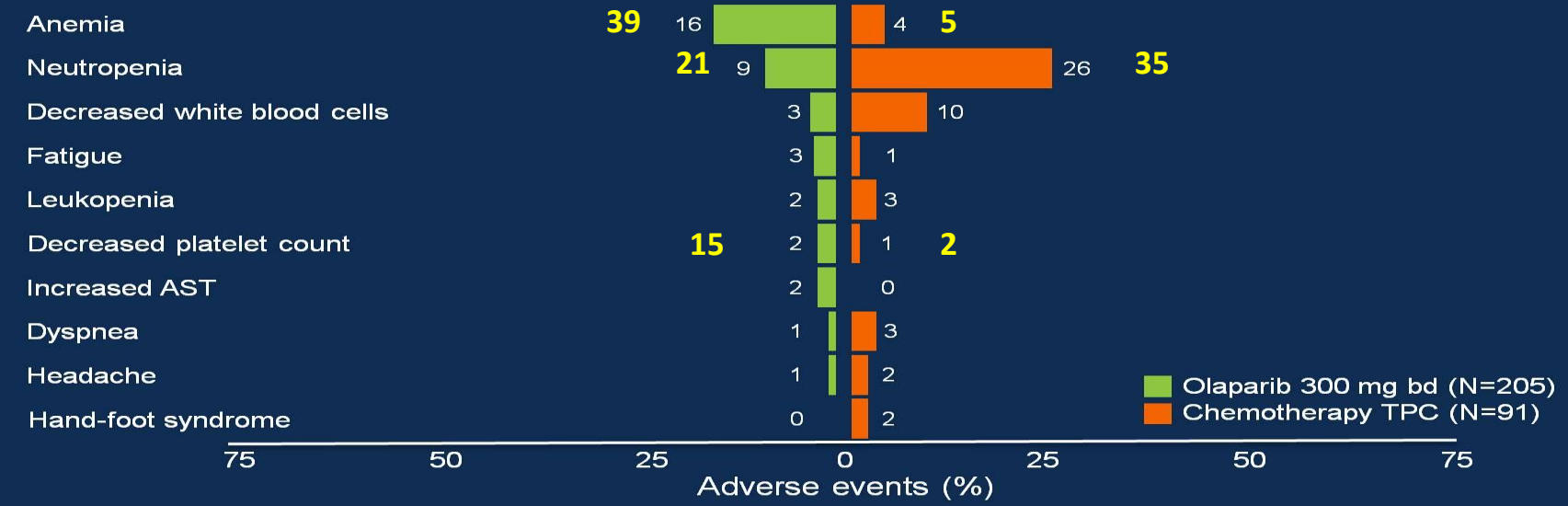


OlympiAD



Robson et al. NEJM 2017, Litton et al. NEJM 2018

Grade ≥3 adverse events in ≥2% patients in either arm



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Presented By Mark Robson at 2017 ASCO Annual Meeting

Tolerance profile of talazoparib

	Talazoparib (N=286)	TPC (N=126)
Dose modification (interruption/reduction)	66%	60%
Median dose intensity	87.2%	NA
Grade ¾ SAE	25.5%	25.4%
Drug related SAE	9.1%	8.7%
Permanent discontinuation due to AE	5.9%	8.7%

Litton JK et al. NEJM 2018

NCCN Guidelines Version 1.2019
Invasive Breast Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b]

HER2-Negative

Preferred regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin

- PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2* mutation)[d]
  - Olaparib[d] (category 1)
  - Talazoparib[d] (category 1)
- Platinum (option for patients with triple-negative tumors and germline *BRCA1/2* mutation)[d]
  - Carboplatin
  - Cisplatin
- Atezolizumab + albumin-bound paclitaxel (option for patients with PD-L1-positive TNBC)[e]

Other recommended regimens[c]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in certain circumstances[c]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[f]

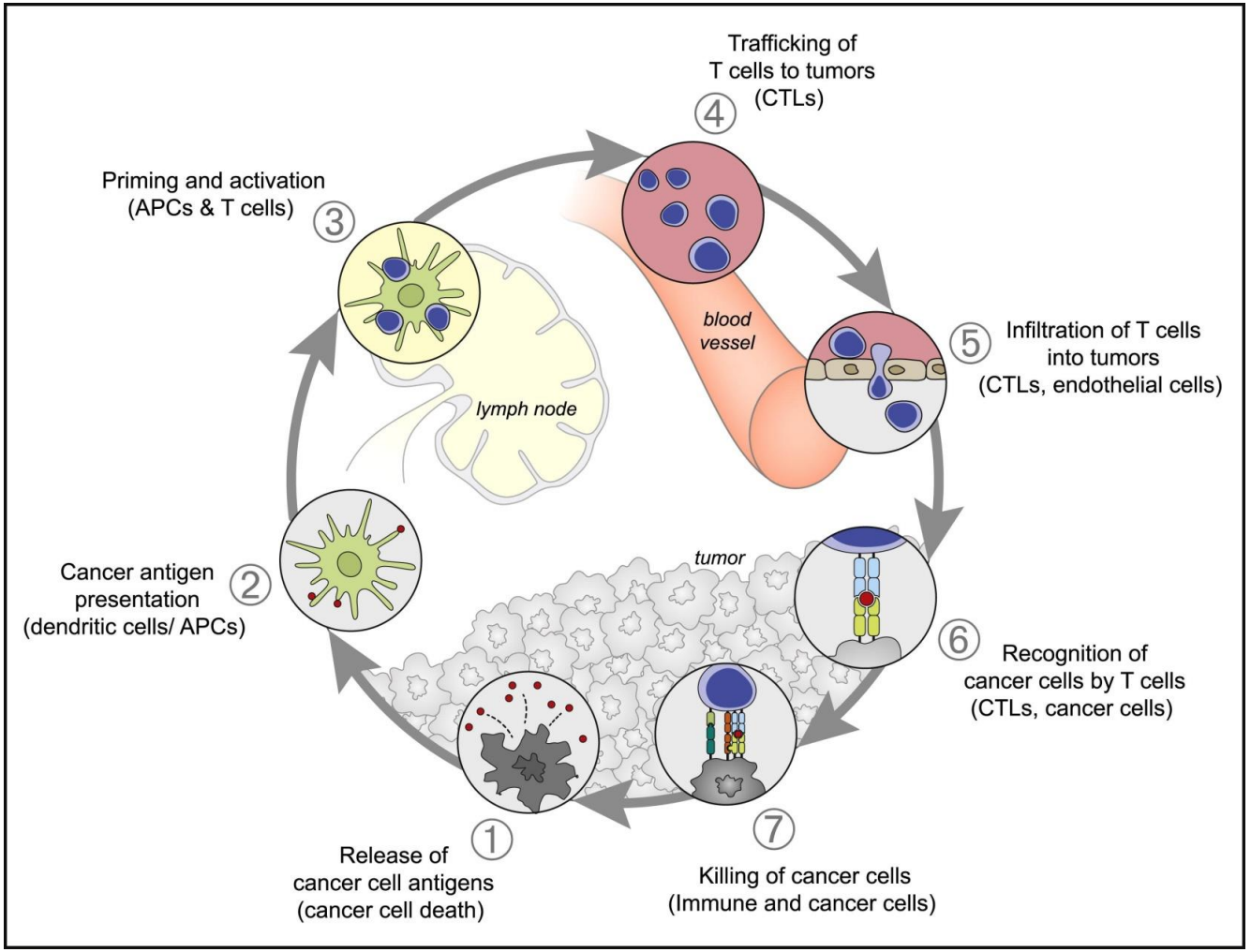
HER2-Positive[g]

Preferred regimens

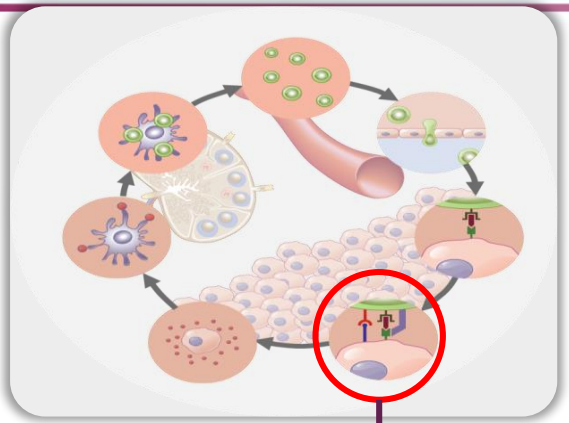
- Pertuzumab + trastuzumab + docetaxel (category 1)[h]
- Pertuzumab + trastuzumab + paclitaxel[g]

Other recommended regimens:

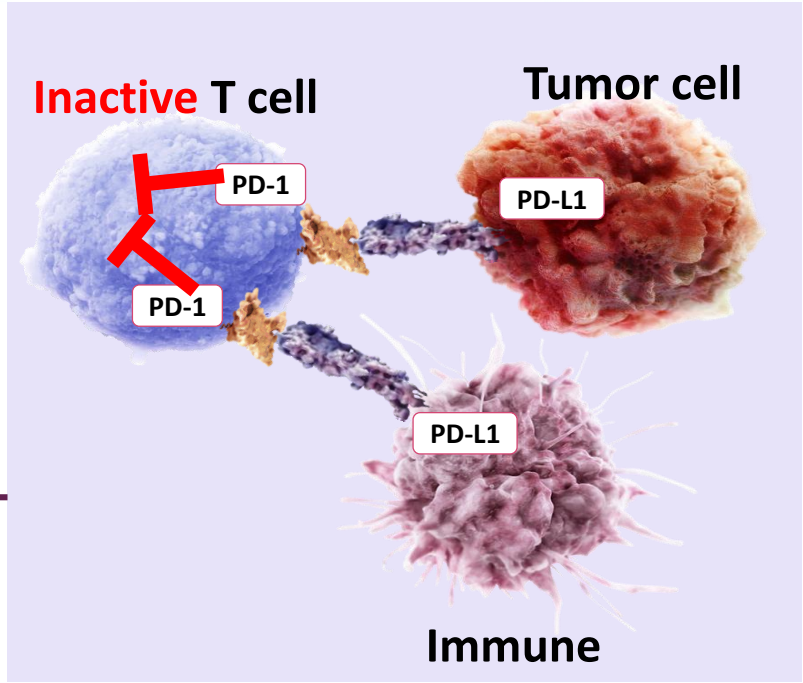
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[h] ± carboplatin
- Trastuzumab + docetaxel[h]
- Trastuzumab + vinorelbine[h]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[h,i,j]


Trafficking of
T cells to tumors
(CTLs)
4
Priming and activation
(APCs & T cells)
3
blood
vessel
5
Infiltration of T cells
into tumors
(CTLs, endothelial cells)
lymph node
tumor
Cancer antigen
presentation
(dendritic cells/ APCs)
2
6
Recognition of
cancer cells by T cells
(CTLs, cancer cells)
1
Release of
cancer cell antigens
(cancer cell death)
7
Killing of cancer cells
(Immune and cancer cells)

Binding of PD-L1 to PD-1 can lead to the inhibition of T-cell activity



Tumor

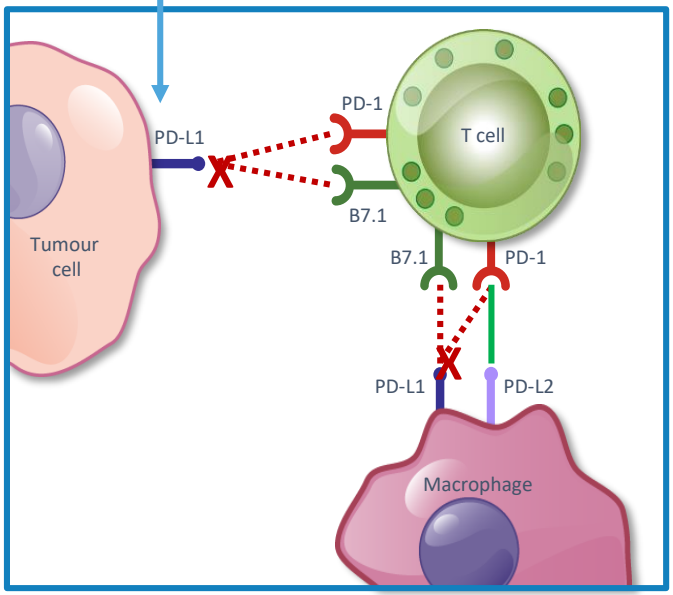


1.Chen, et al. *Clin Cancer Res* 2012
2.Herbst, et al. *Nature* 2014
3. Powles, et al. *Nature* 2014

Immune checkpoints inhibitors targeting PD-L1 and PD-1

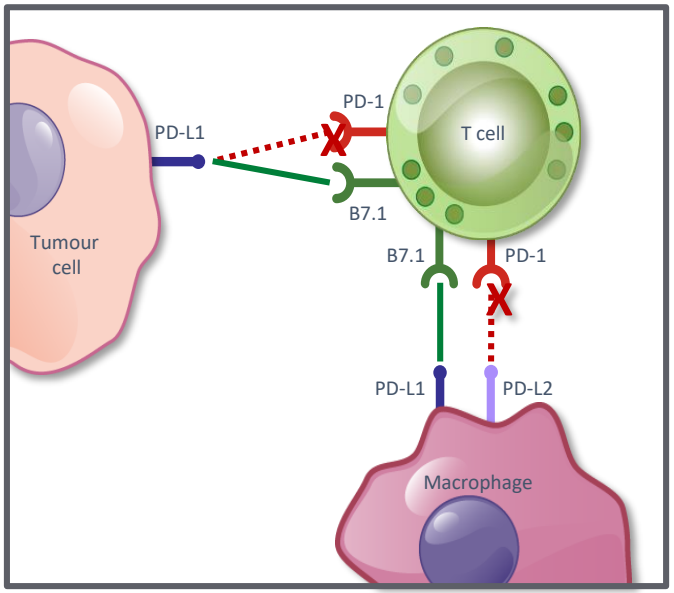
Anti-PDL1

Targeting PD-L1 can block co-inhibitory signalling between the TC and both PD-1 and B7.1, preventing down-regulation of T-cell activity[1–3]



Anti-PD1

Targeting of PD-1 blocks co-inhibitory signalling between the TC and PD-1, sparing the interaction between the TC and B7.1[1–3]



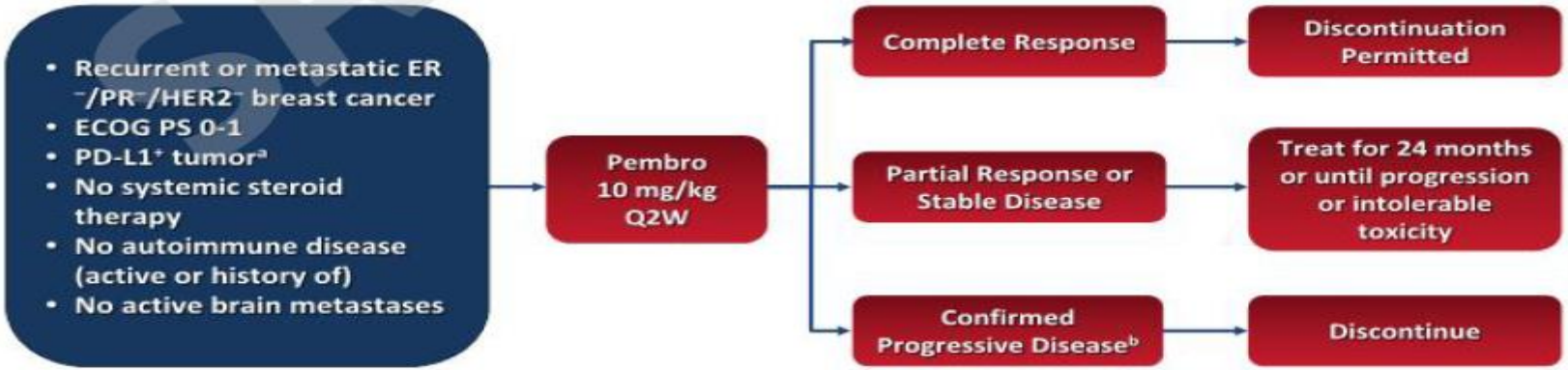
1.Chen, et al. Clin Cancer Res 2012;

2. Paterson, et al. J Immunol 2011;

3. Yang, et al. J Immunol 2011;

Pembrolizumab (anti-PD1 Ab)

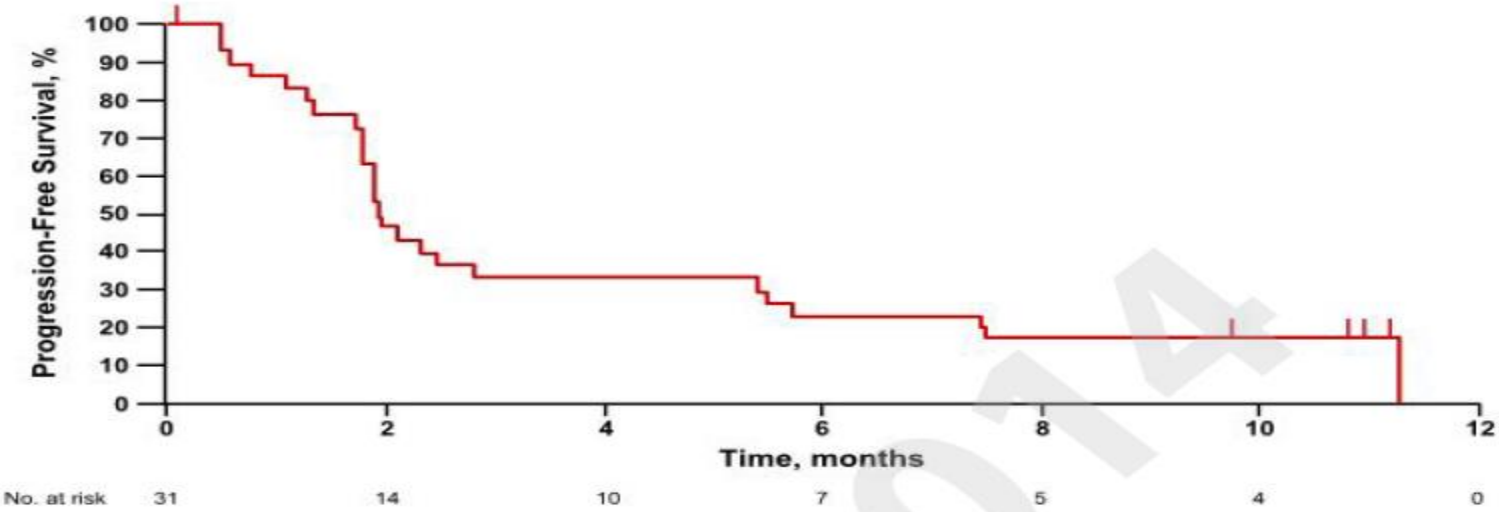
Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

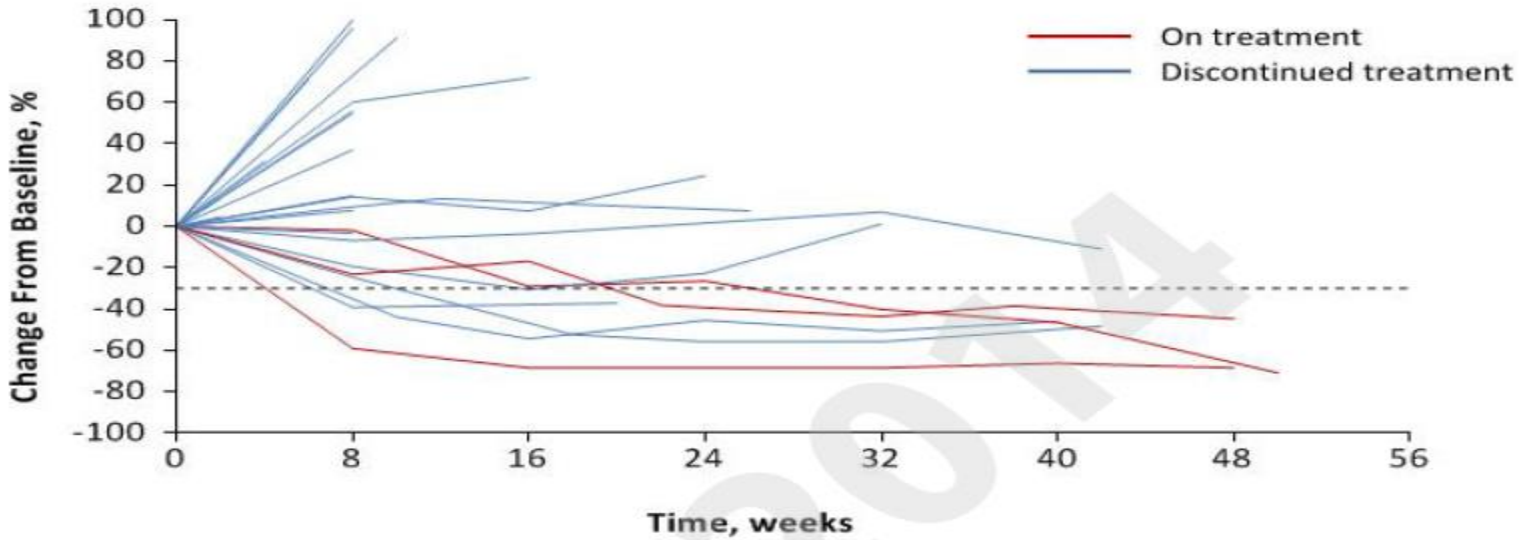
Kaplan-Meier Estimate of PFS (RECIST v1.1, Central Review)



- Median PFS: 1.9 months (95% CI, 1.7-5.4)
- PFS rate at 6 months: 23.3%

Analysis cut-off date: November 10, 2014.

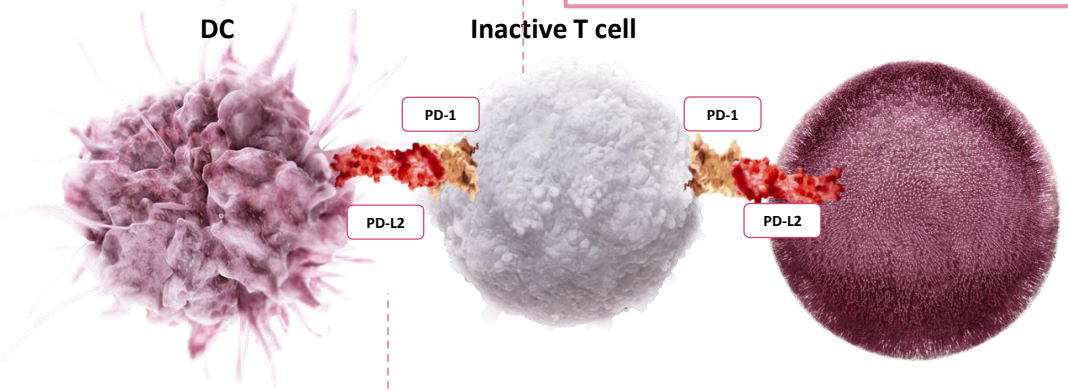
Change From Baseline in Target Lesions Over Time (Central Review)



Analysis cut-off date: November 10, 2014.

atezolizumab (anti-PDL1 Ab)

The interaction of PD-L2 and PD-1 may preserve immune homeostasis in normal tissues



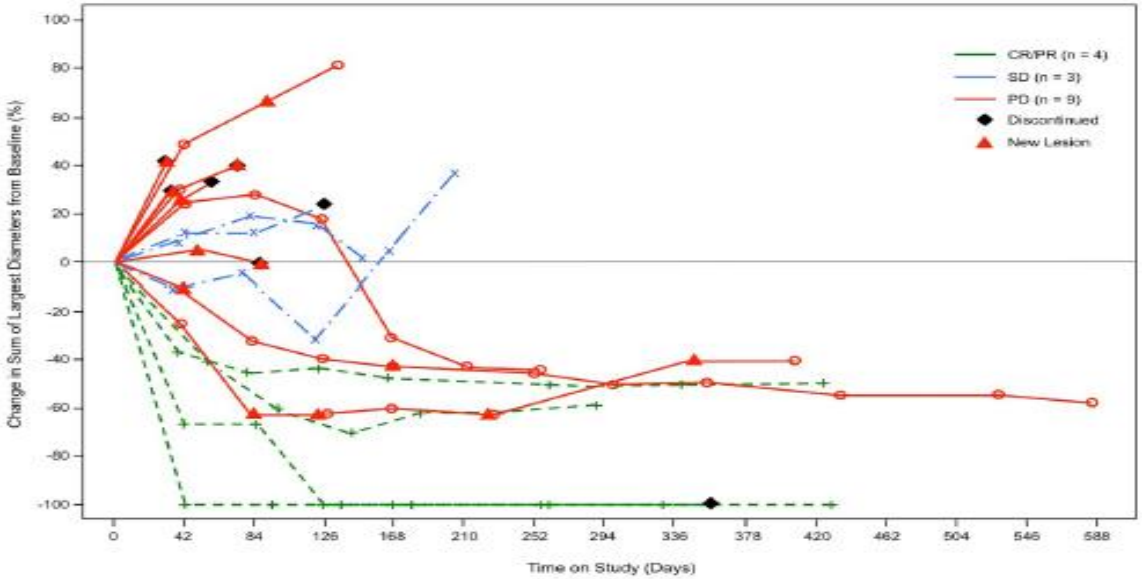
PD-L2 is primarily expressed on both immune and epithelial cells in normal tissues

TECENTRIQ can preserve immune homeostasis in normal tissue by sparing the interaction of PD-L2 (on normal tissue) with PD-1 (on T cells)

1.Latchman, et al. Nat Immunol 2001;
2.Brown, et al. J Immunol 2003;
3.Matsumoto, et al. Biochem Biophys Res Commun 2008;
4.Akbari, et al. Mucosal Immunol 2010
5.Chen, et al. Clin Cancer Res 2012;
6.Schmid, et al. J Clin Oncol 2016

MPDL3280A: Tumor Burden Over Time

Efficacy-evaluable population with TNBC

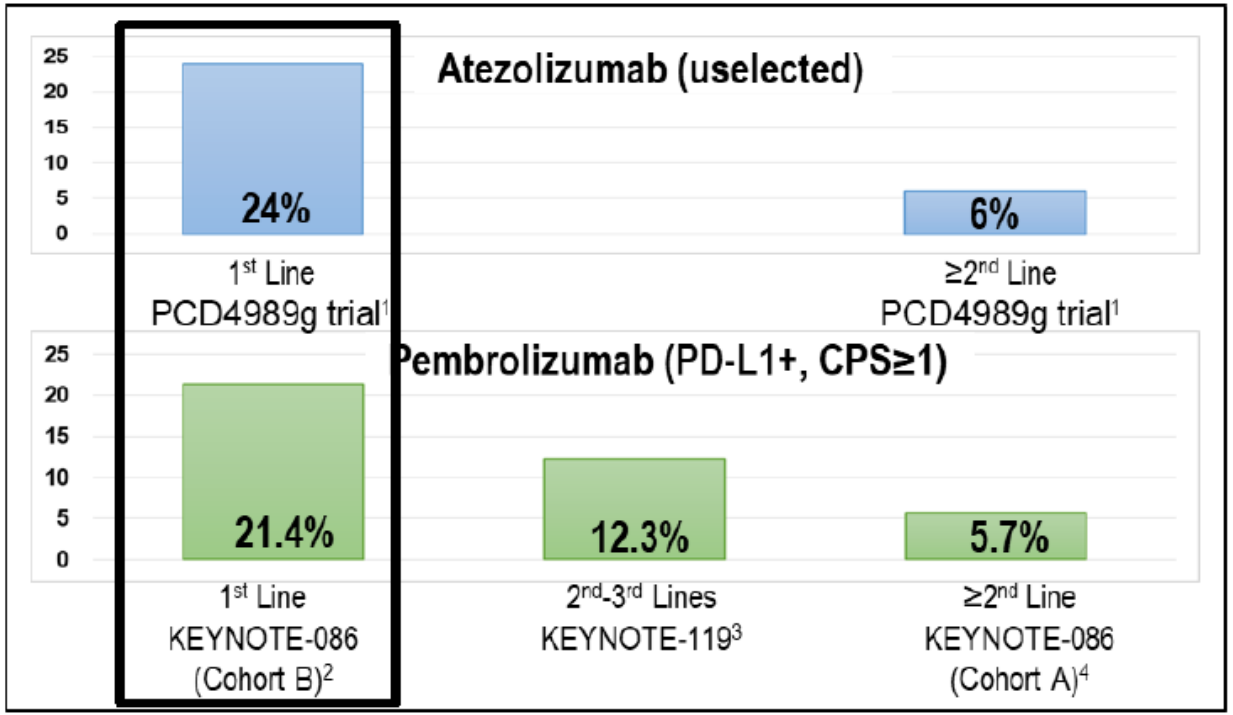


- Median duration of response has not yet been reached (range: 18 to 56+ wks)
- Median duration of survival follow-up is 40 wks (range: 2+ to 85+ wks)

Investigator-assessed confirmed ORRs per RECIST v1.1.
Efficacy population includes patients dosed by July 21, 2014; clinical data cutoff, December 2, 2014.
New lesions at consecutive visits for the same patient might be the same lesion.

Emens LA, et al. AACR 2015.

SHOULD WE GIVE IMMUNE CHECKPOINTS INHIBITORS IN FIRST LINE OR SUBSEQUENT LINES OF TREATMENT?



[1]Emens L JAMA Oncol 2018; [2]Adams S Ann Oncol 2019; [3]Cortes J ESMO LBA21; [4]Adams S Ann Oncol 2019

IMpassion130: Phase III atezolizumab study in mTNBC

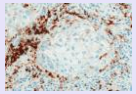
Multicentre, international, double-blind, placebo-controlled, randomised trial in more than 900 patients with advanced TNBC

Key IMpassion130 eligibility criteria[a]:

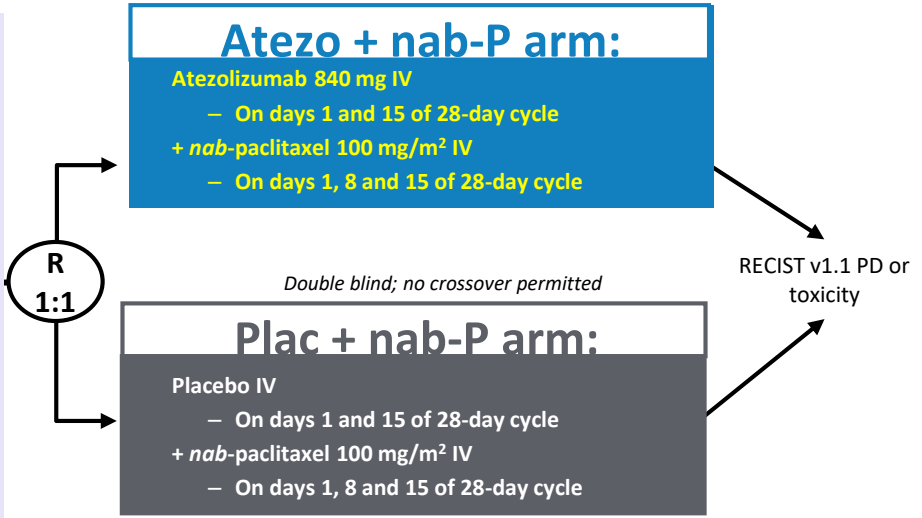
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]



- PD-L1 IHC centralised
- PD-L1 on IC and TC
- VENTANA SP142 IHC assay



- 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, tumour-infiltrating immune cell; TFI, treatment-free interval.
[a] ClinicalTrials.gov: NCT02425891.
[b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status).
[d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Baseline characteristics were well balanced between treatn

IMpassion130 included younger patients with good functional status, which is representative of the advanced TNBC population

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018.

[a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm

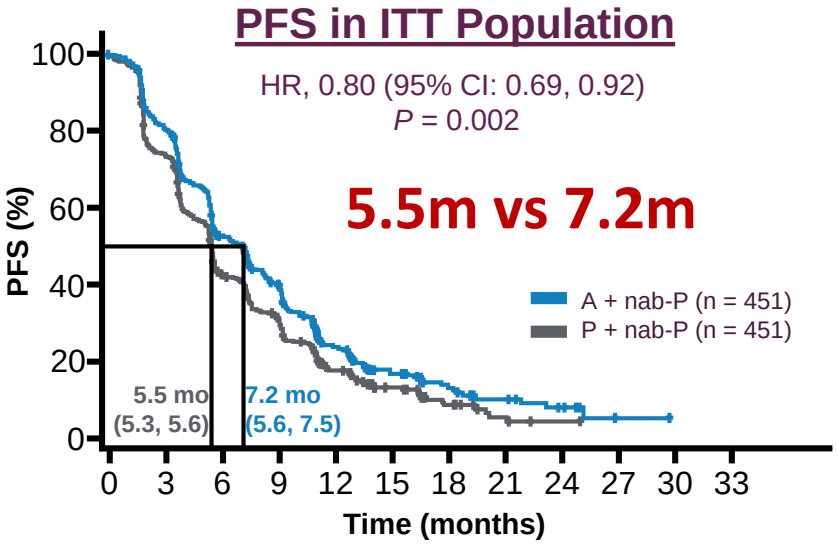
[b] Of n = 450 in each arm.

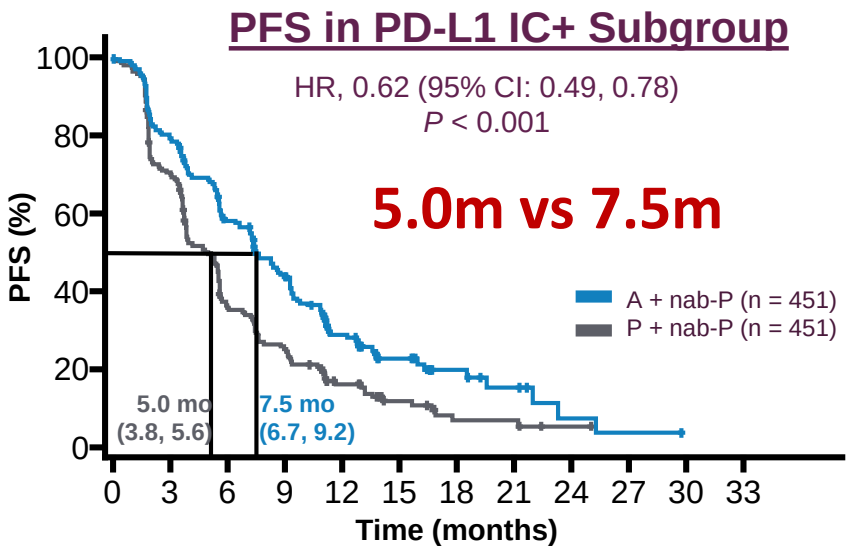
[c] ECOG PS before start of treatment was 2 in 1 patient per arm.

[d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

Schmid P, et al. N Engl J Med. 2018;379:2108-2121

Primary endpoints: PFS



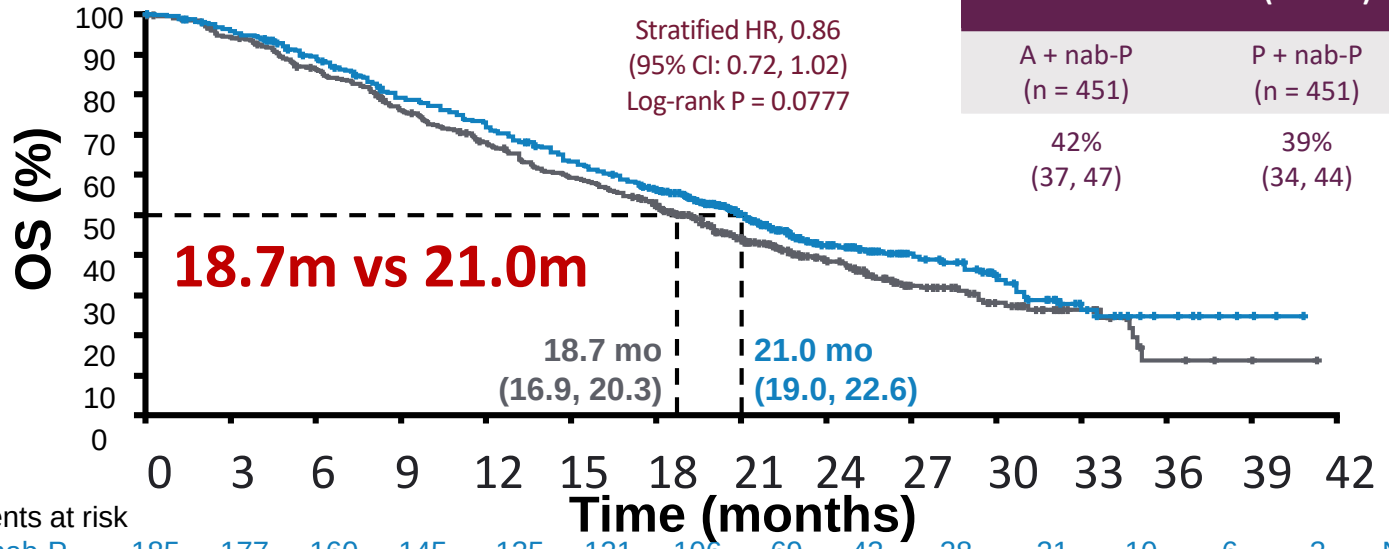


- Atezolizumab + nab-paclitaxel resulted in statistically significant PFS benefit in the ITT and PD-L1+ populations[1]
- Based on these data,[2] atezolizumab + nab-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

* TECENTRIQ is indicated for the treatment of PD-L1 population according to Tecentriq prescribing information in Taiwan.

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

Primary endpoints: OS in ITT population



24-Month OS Rate (95% CI)	
A + nab-P (n = 451)	P + nab-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

A + nab-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + nab-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

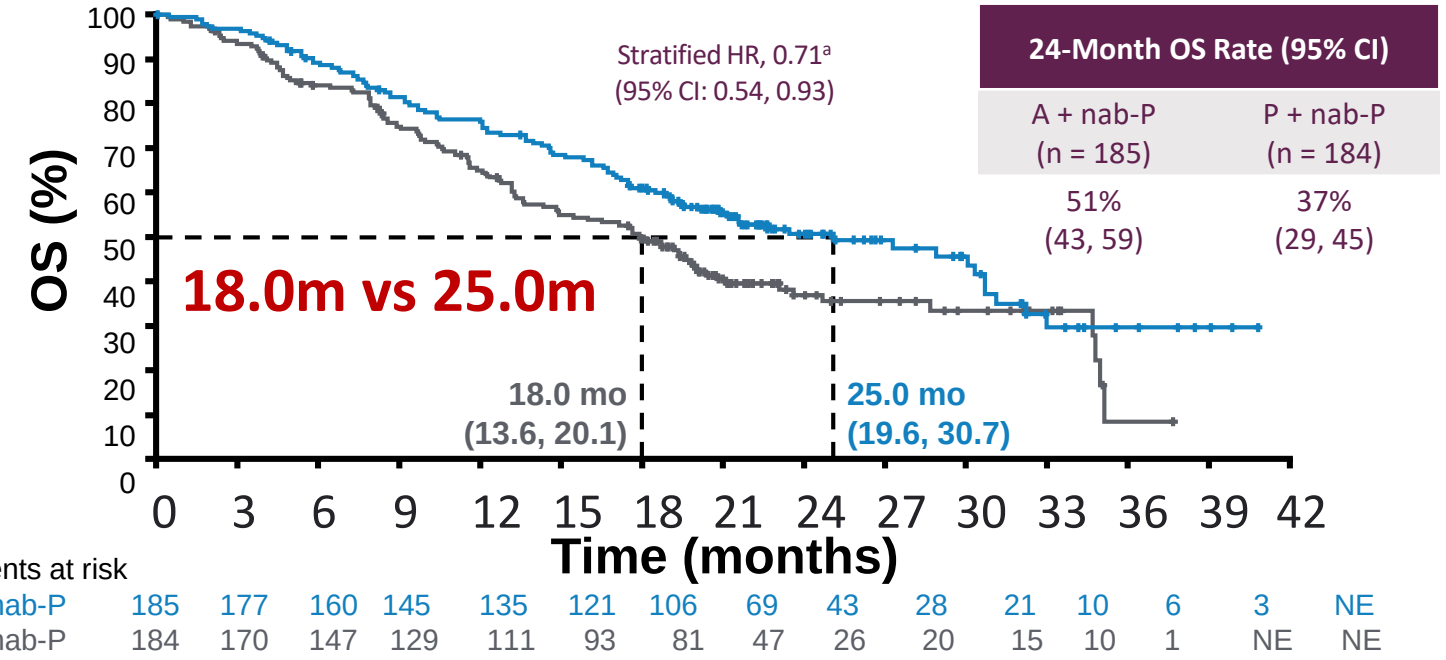
* TECENTRIQ is indicated for the treatment of PD-L1 population according to Tecentriq prescribing information in Taiwan.

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

Data cut off: January 2, 2019

Emens, et al. ASCO 2019 (Mpassion 130 Updated OS)

Primary endpoints : OS in PD-L1(+) population



24-Month OS Rate (95% CI)	
A + nab-P (n = 185)	P + nab-P (n = 184)
51% (43, 59)	37% (29, 45)

Patients at risk

A + nab-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + nab-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

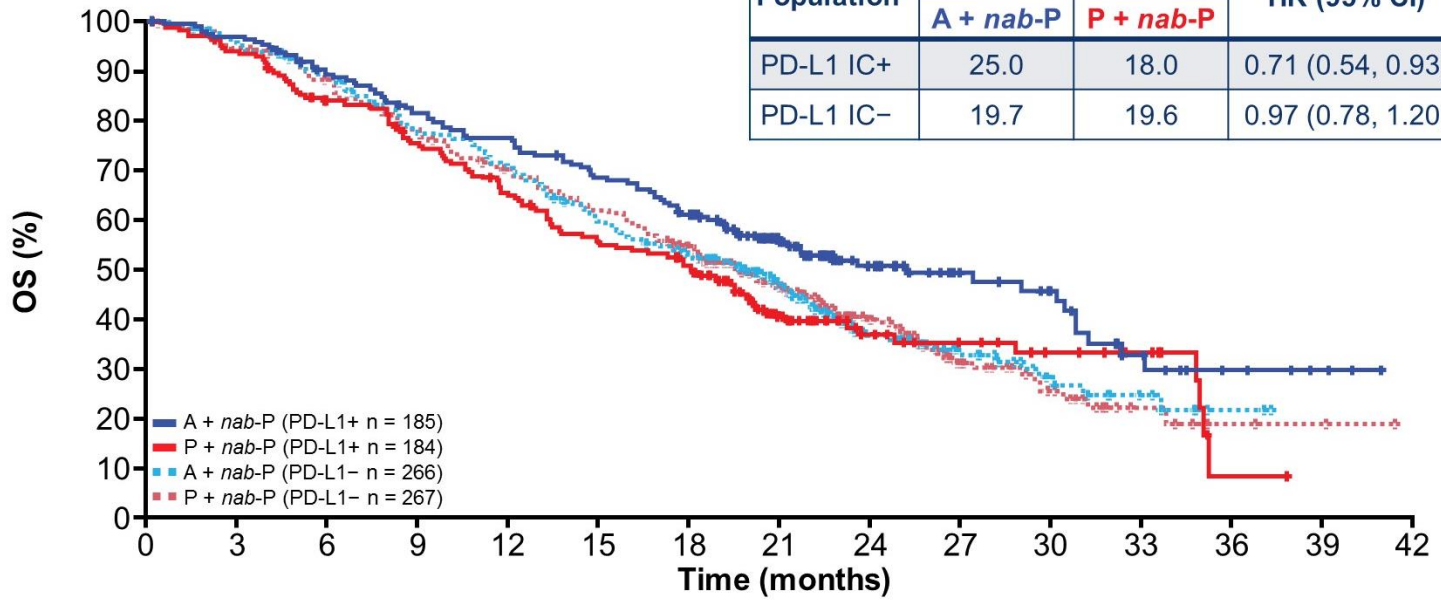
[a] Not formally tested due to pre-specified hierarchical analysis plan.
Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.

Data cut-off: January 2, 2019

Emens, et al. ASCO 2019 (Mpexcion 130 Updated OS)

Positive PD-L1 expression drove OS benefit with TECENTRIQ + nab-pac

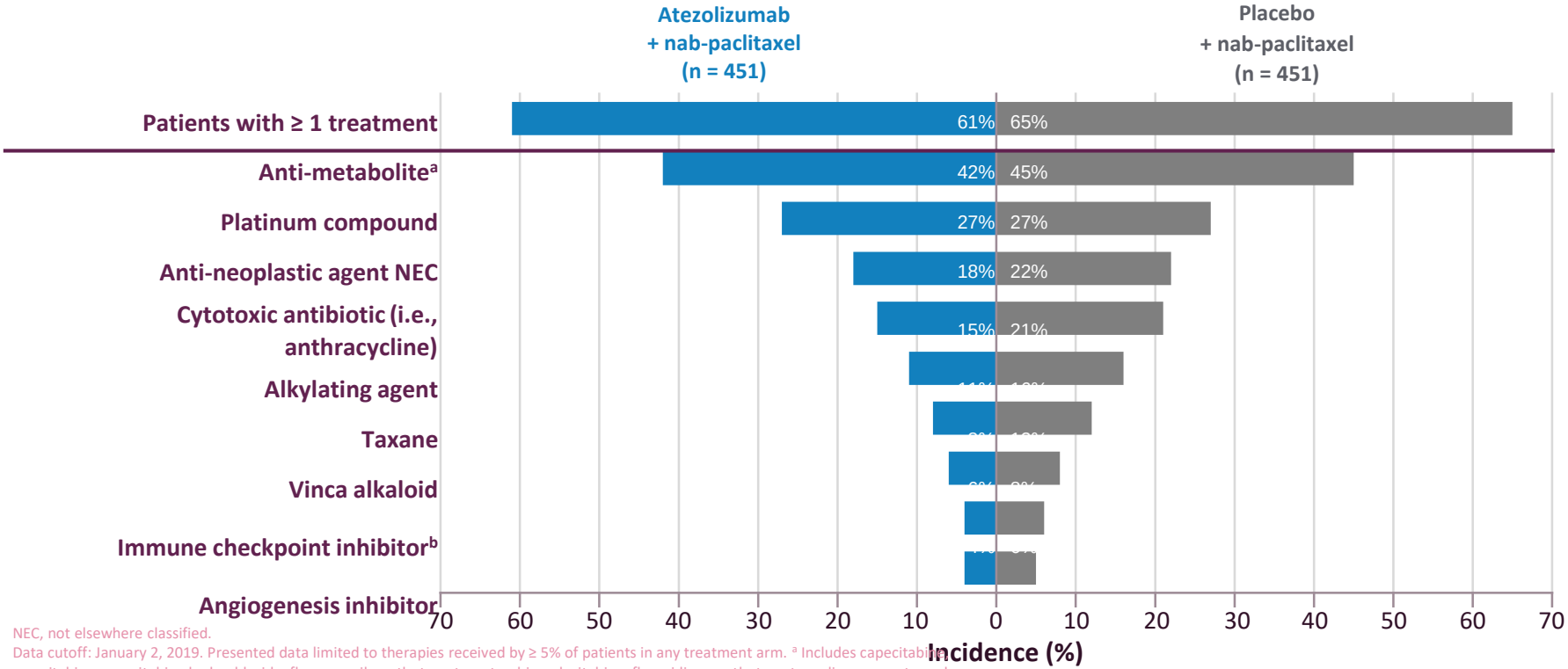
Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Data cut off: January 2, 2019

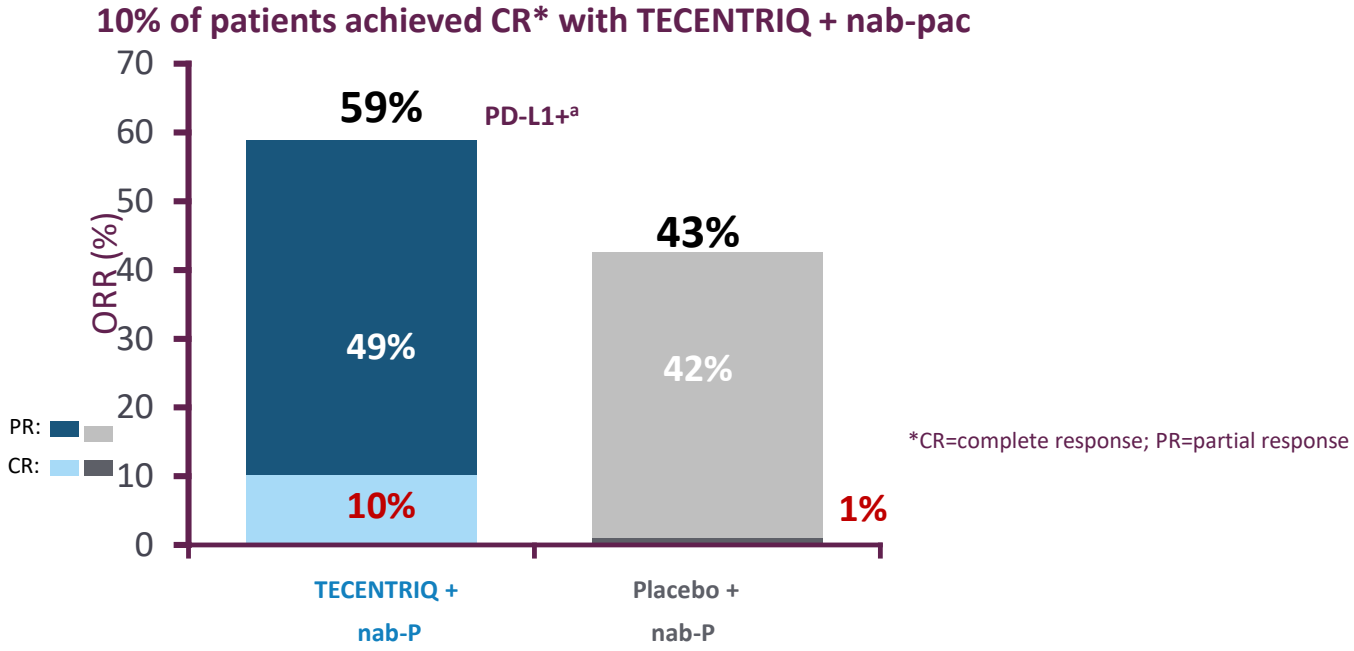
Emens, et al. ASCO 2019 (IMpassion 130: Updated OS)

Subsequent Therapies



NEC, not elsewhere classified.
Data cutoff: January 2, 2019. Presented data limited to therapies received by ≥ 5% of patients in any treatment arm. [a] Includes capecitabine, gemcitabine, gemcitabine hydrochloride, fluorouracil, methotrexate, cytarabine, decitabine, floxuridine, methotrexate sodium, pemetrexed, tegafur. [b] Includes monoclonal antibodies targeting PD-L1, PD-1 and CTLA-4.

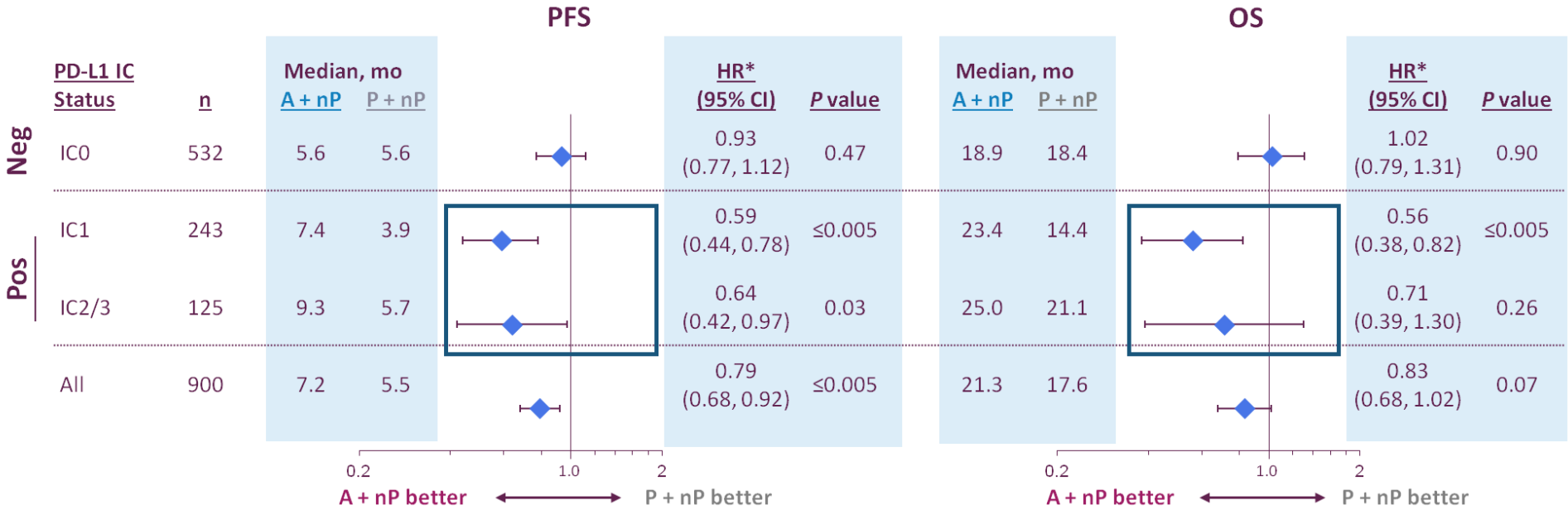
Secondary endpoints
1L PD-L1+ TNBC atezolizumab+ nab-pac ORR



*CR=complete response; PR=partial response

No. of ongoing responses, n (%)[b]	39 (36)	19 (24)
DOR, median (95% CI), months	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)

Consistent clinical benefit with atezolizumab+ nab-paclitaxel was observed across all PD-L1 IC+ subgroups



- Emens, et al. SABCS 2018 (Abstract GS1-04)

Safety summary

AE, n (%)	Atezo + nab-P (n = 452)	Plac + nab-P (n = 438)
All-cause AEs		
Any grade	449 (99%)	429 (98%)
Grade 3-4	220 (49%)	185 (42%)
Grade 5	6 (1%)	3 (1%)
Treatment-related AEs		
Any grade	436 (96%)	410 (94%)
Grade 3-4	**179 (40%)**	**132 (30%)**
Grade 5[a]	**3 (1%)[a]**	**1 (< 1%)[a]**
Any grade serious AEs		
Serious AEs regardless of attribution	103 (23%)	80 (18%)
Treatment-related serious AEs	56 (12%)	32 (7%)
Any-grade AEs leading to any treatment discontinuation	**72 (16%)**	**36 (8%)**
Leading to atezo or plac discontinuation	29 (6%)	6 (1%)
Leading to nab-P discontinuation	72 (16%)	36 (8%)
Any-grade AEs leading to any dose reduction or interruption	**212 (47%)**	**177 (40%)**
Leading to atezo or plac dose interruption	139 (31%)	103 (24%)
Leading to nab-P dose reduction or interruption	195 (43%)	172 (39%)

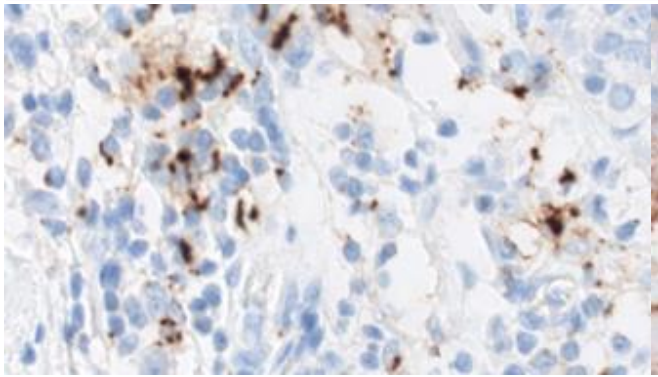
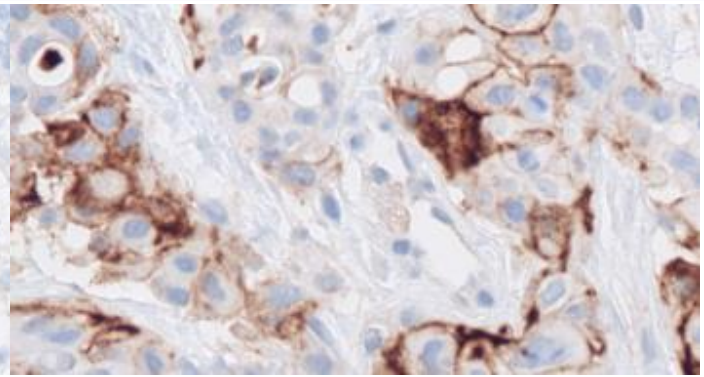
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

AESIs suggestive of potential immune-related aetiology

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- 1 grade 5 AESI per arm (both treatment related):
  - **Atezo + nab-P: autoimmune hepatitis**
  - **Plac + nab-P: hepatic failure**
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - **Atezo + nab-P: 17%**
  - **Plac + nab-P: 4%**
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - **Atezo + nab-P: 3%**
  - **Plac + nab-P: < 1%**
- Hepatitis rates were balanced

Examples using the VENTANA PD-L1 IHC (SP142) assay

PD-L1 IHC (SP142) Assay by VENTANA Medical Systems	
PD-L1 on IC	PD-L1 on TC
	

Emens, et al. SABCS 2018 (Abstract GS1-04)

IMpassion130: PD-L1 expression on IC with SP142

PD-L1 IC staining criteria		Scoring algorithm in IMpassion130
IC score	% of tumour area occupied by PDL1–expressing IC of any intensity	
IC3	**≥10%**	
IC2	**≥5% and <10%**	**PD-L1 positive**
IC1	**≥1% and <5%**	
IC0	<1%	PD-L1 negative

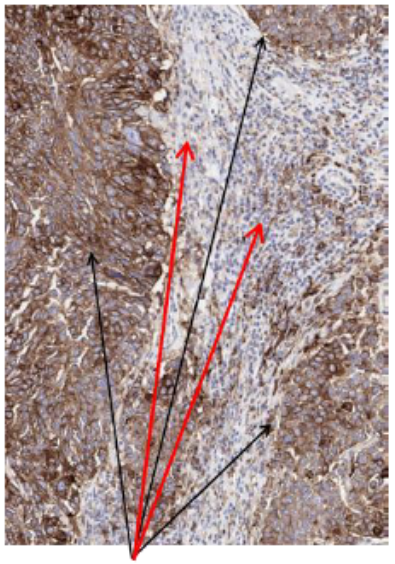
There are more than 1 PDL1 IHCs

- Measure of PD-L1 expression: combined positive score (CPS)

$$\text{CPS} = \frac{\text{\# PD-L1–staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

- Assessed centrally in newly obtained core or excisional biopsy from metastatic, not previously irradiated, tumor lesion using PD-L1 IHC 22C3 pharmDx (Agilent Technologies)

- Positive PD-L1 expression: CPS ≥10 and CPS ≥1



PD-L1 positive cells (Tumor Cells, Immune Cells)

Balar AV et al. Presented at ESMO 2016; Oct 7-11, 2016; Copenhagen, Denmark. Abstr. LBA32-PR.

BARCELONA 2019 ESMO congress

Performance of PD-L1 immunohistochemistry assays in unresectable locally advanced or metastatic triple-negative breast cancer: post hoc analysis of IMpassion130

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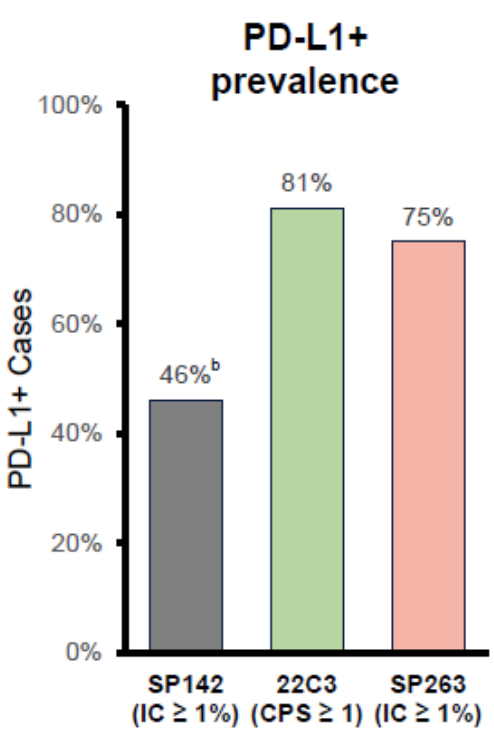
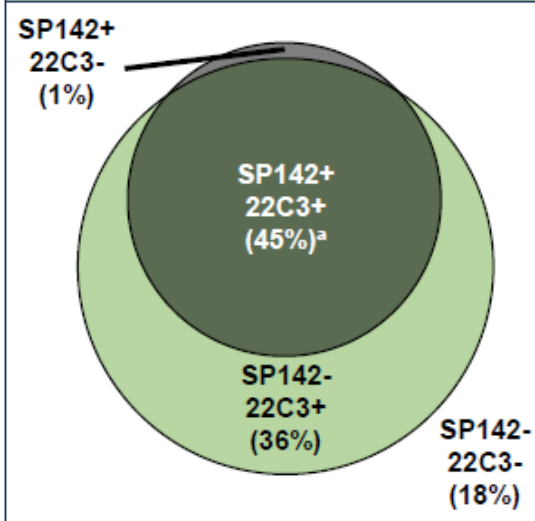
PD-L1 IHC assays: prevalence and analytical concordance

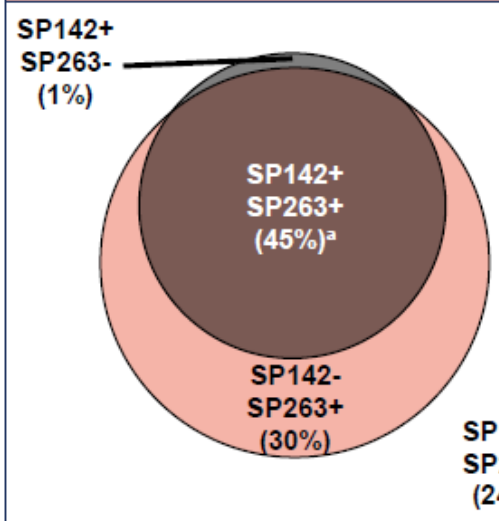


SP142 (IC 1%) and 22C3 (CPS 1)



OPAc	64%
PPA	98%
NPA	34%

SP142 (IC 1%) and SP263 (IC 1%)



OPAc	69%
PPA	98%
NPA	45%

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA *and* NPA required for analytical concordance.

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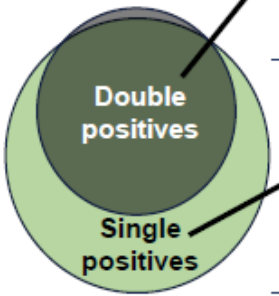
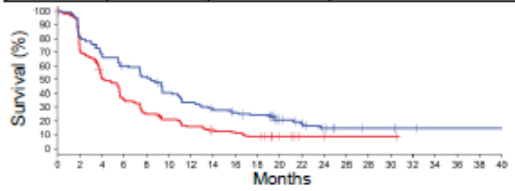
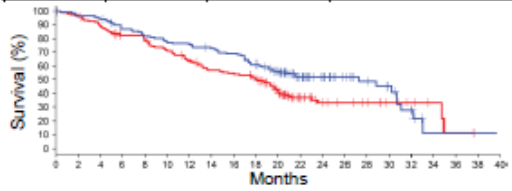
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

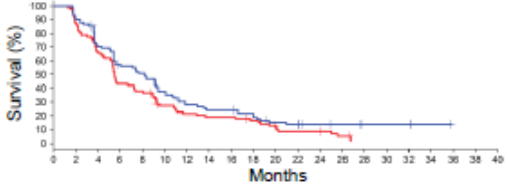
Clinical outcomes in BEP subpopulations defined by SP142 (IC 1%) and 22C3 (CPS 1)

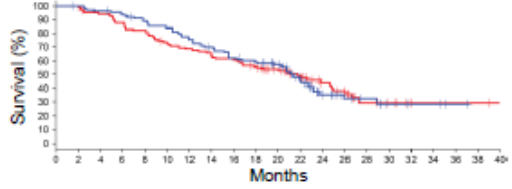


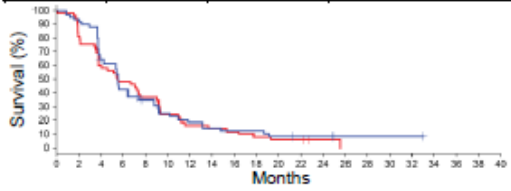
Population	Median PFS, mo			HR (95% CI)	Median OS, mo			HR (95% CI)
	A + nP	P + nP	Δ		A + nP	P + nP	Δ	
SP142+ 22C3+ (45%; 279/614)	8.3	3.9	4.4	0.60 (0.46, 0.78)	27.3	18.0	9.3	0.71 (0.52, 0.98)
SP142- 22C3+ (36%; 218/614)	7.3	5.6	1.7	0.81 (0.61, 1.09)	21.3	21.8	−0.5	0.92 (0.64, 1.31)
SP142- 22C3- (18%, 111/614)	5.5	5.6	−0.1	1.00 (0.66, 1.51)	14.7	19.6	−4.9	1.08 (0.67, 1.76)

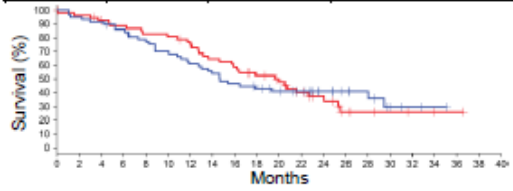












Double positive: SP142 IC ≥ 1%, 22C3 CPS ≥ 1; single positive: SP142 IC < 1%, 22C3 CPS ≥ 1; double negative: SP142 IC < 1%, 22C3 CPS < 1.
HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

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ANTIBODY-DRUG CONJUGATE

EMBRACE Study

Patients (n=762)

- Locally advanced or metastatic breast cancer
- 2 - 5 prior chemotherapies (**≥ 2** for advanced disease)
- **Prior anthracycline and taxane**
- Progression on or within 6 months of last chemotherapy

RANDOMIZED 2:1

Stratified by HER2 status, prior capecitabine therapy, and geographical region

Eribulin
1.4 mg/m^2 IV over 2-5 min, Day 1,8 q21 days

Treatment of Physician's choice
- Any monotherapy (cytotoxic, hormonal, biological); or
- Palliative treatment; or
- Radiotherapy

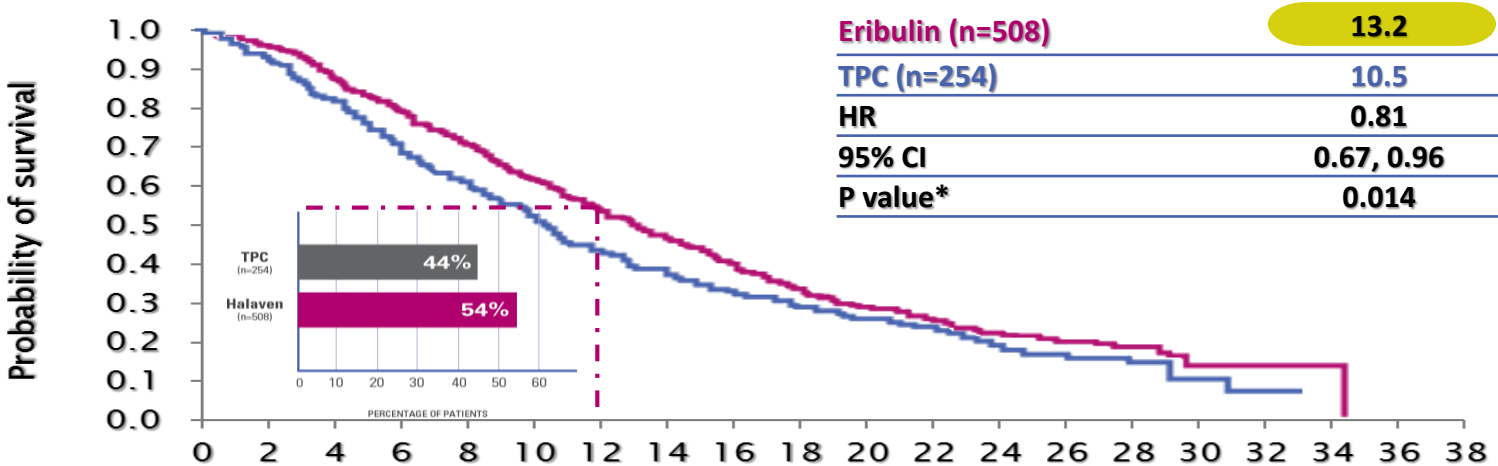
Primary Endpoints: Overall Survival
Secondary Endpoints: PFS, overall response rate, duration of response, safety

EMBRACE = Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin; PFS, progression-free survival; HER2 = human epidermal growth factor receptor 2; IV = intravenous

Cortes J *et al. Lancet* 2011; 377: 914–23.

EMBRACE: OS Updated Analysis[1,2]

	Medium OS, months
Eribulin (n=508)	13.2
TPC (n=254)	10.5
HR	0.81
95% CI	0.67, 0.96
P value*	0.014



Number at risk

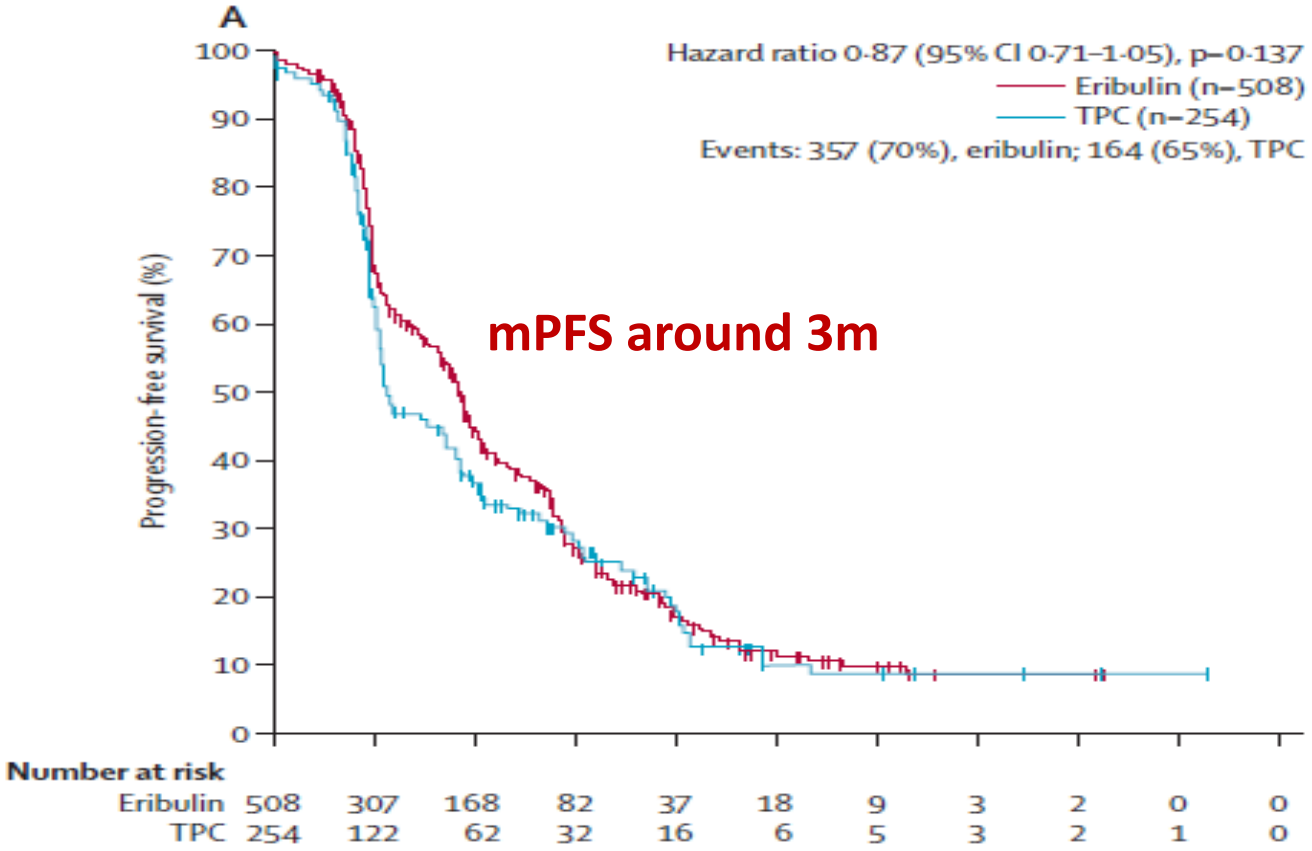
Eribulin	508	491	452	406	362	312	274	234	194	142	113	83	54	38	25	11	6	2	0
TPC	254	237	206	178	154	134	106	93	82	61	51	41	26	16	12	5	2	0	0

Analysis occurred at 589 events (deaths), representing 77% of the ITT population *Nominal P value from stratified log-rank test

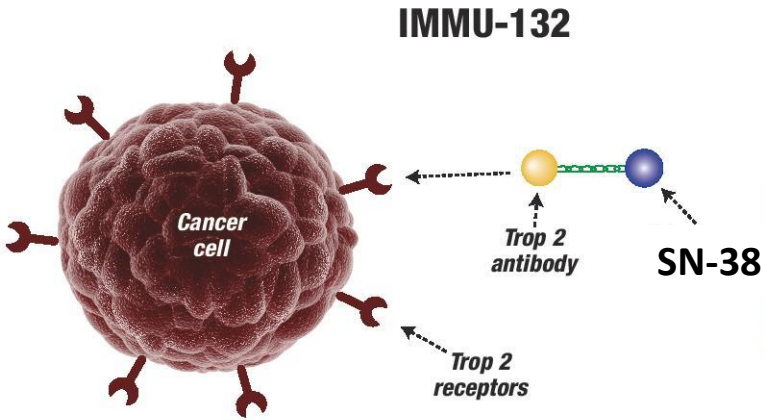
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; TPC = treatment of physician's choice

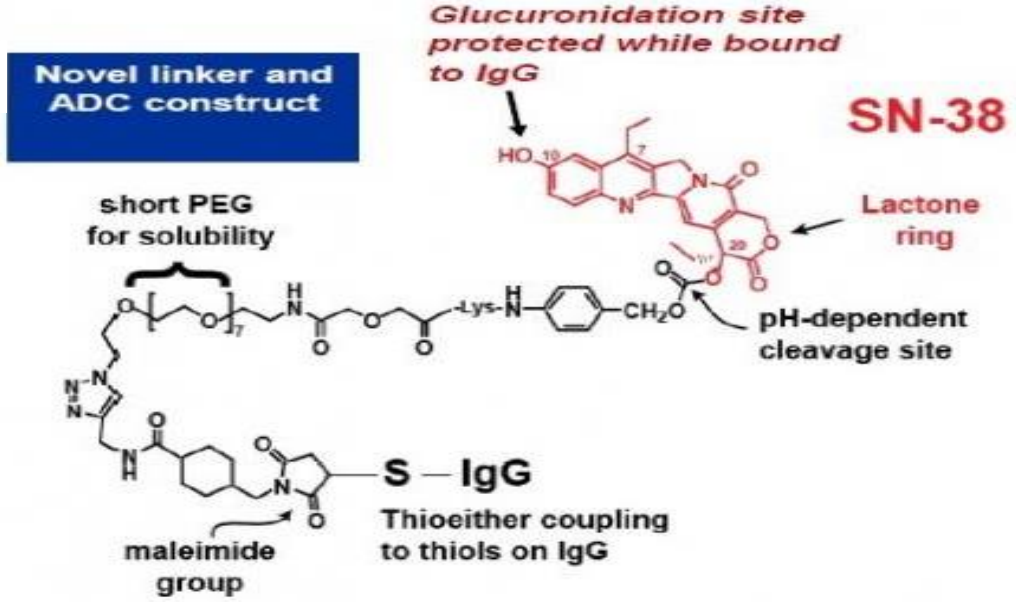
1. Cortes J *et al. Lancet*. 2011; 377: 914–23. 2. Twelves C *et al. Cancer Res* 2010; 70(24):Abstract # P6-14-8.

PFS results in EMBRACE trial



Anti-Trop2 ADC (sacitumumab govitecan)





Safety and Efficacy of Anti-Trop-2 Antibody Drug Conjugate, Sacituzumab Govitecan (IMMU-132), in Heavily Pretreated Patients with TNBC

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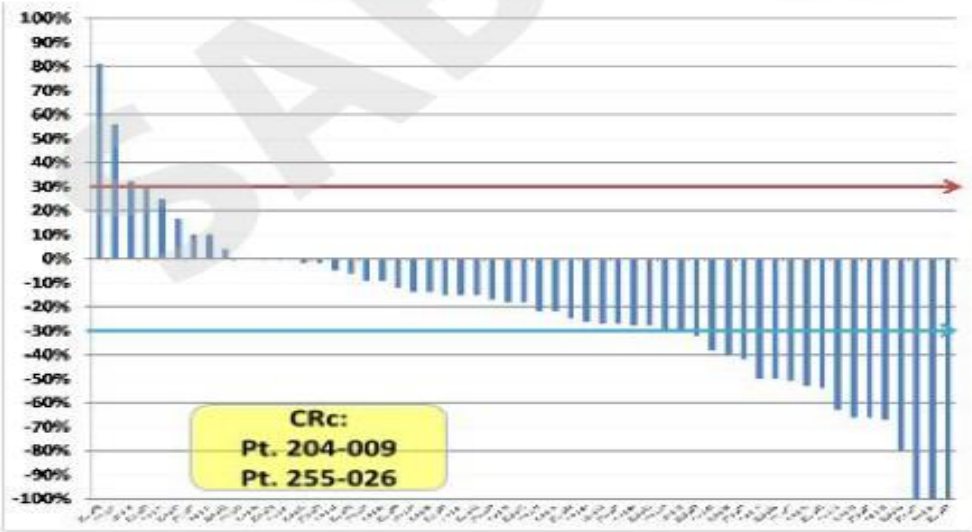
[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]University of Colorado Cancer Center, Aurora, CO; [3]Vanderbilt-Ingram Cancer Center, Nashville, TN; [4]Indiana University Health Center for Cancer Care, Goshen, IN; [5]UF Health Cancer Center, Orlando, FL; [6]Weill Cornell Medicine, New York, NY; [7]Helen F. Graham Cancer Center & Research Institute, Newark, DE; [8]Baylor Sammons Cancer Center, Texas Oncology, Dallas, TX; [9]Columbia University Medical Center, New York. NY; [10]Houston Methodist Cancer Center, Houston, TX; [11]O'Neal-Sokol Breast Cancer Research Foundation of Alabama Endowed Professorship, University of Alabama at Birmingham, Birmingham, Al; [12]Memorial Sloan Kettering Cancer Center, New York, NY; [13]Immunomedics, Inc., Morris Plains, NJ

SABCS 2015 PD3-06

Best Response by RECIST 1.1 (% Change From Baseline)

Post-Taxane; ≥2 Prior Lines, 10 mg/kg QW

10 Nov 2015



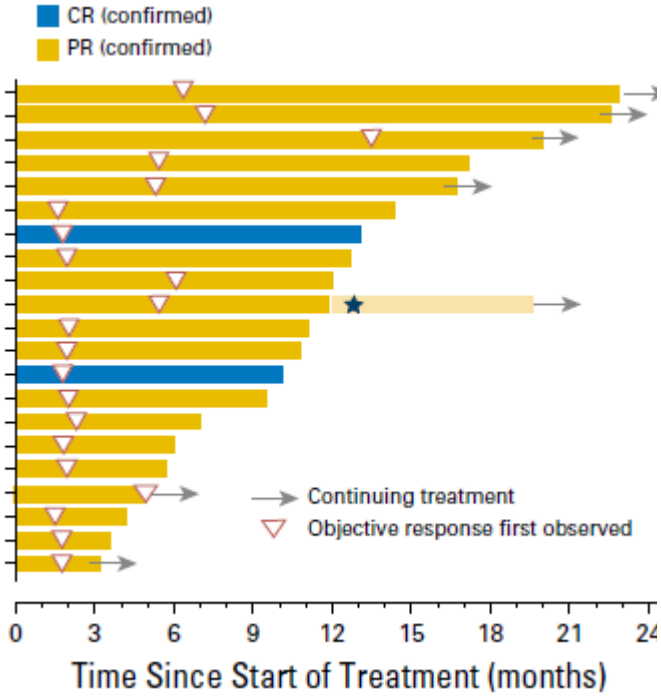
Median # prior therapies (range): 5 (2 – 12)

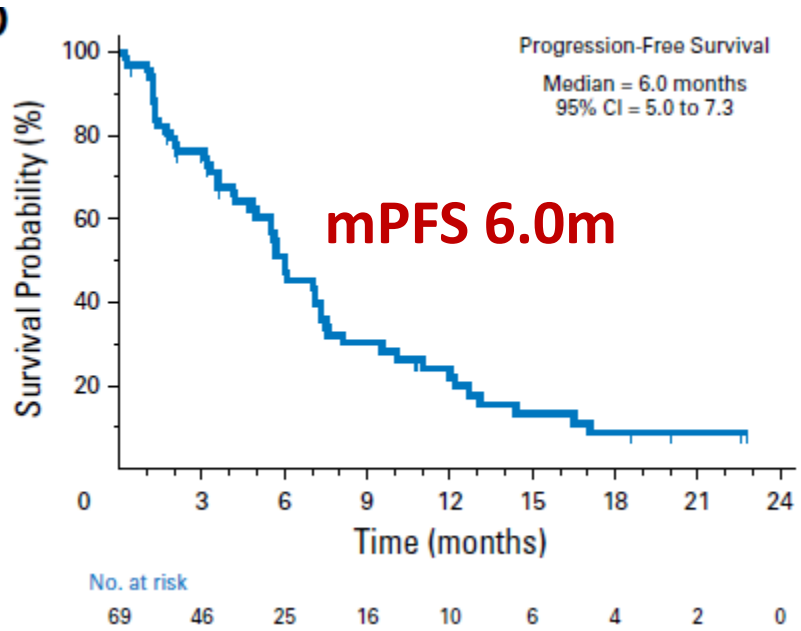
ORR (18/58) = 31%
- 2 confirmed CR
- 16 PR (12 confirmed)
- 24 Stable Disease
  - 5 Confirmed SD
  - 9 ≥ 20% regression
- 16 progressive disease
  - *8 pts with PD could not be included in the graph due to new lesion (1) or progression of NTL (7) and 3 pts with PD, but without available measurement of TL.

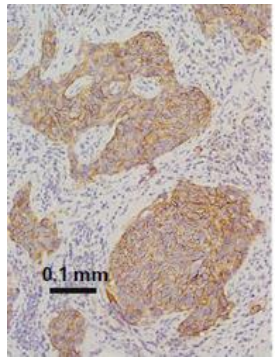
CBR (CR+PR+SD≥6 Mos) = 45%
CBR (CR+PR+SD≥4 Mos) = 53%

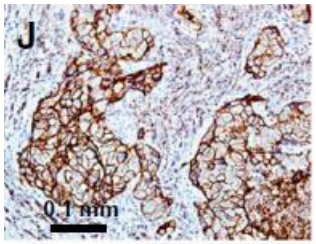
60 patients: 2 excluded because <3 doses
58 assessable patients
47 patients represented in graph; *11 of 16 pts with PD not shown

FDA Approved fast track status



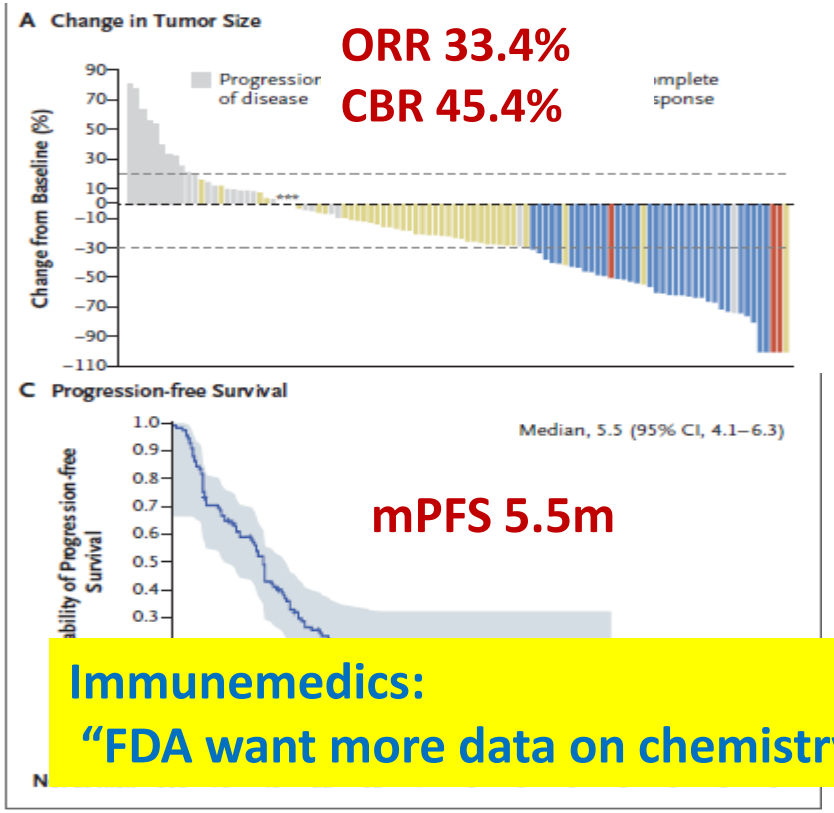


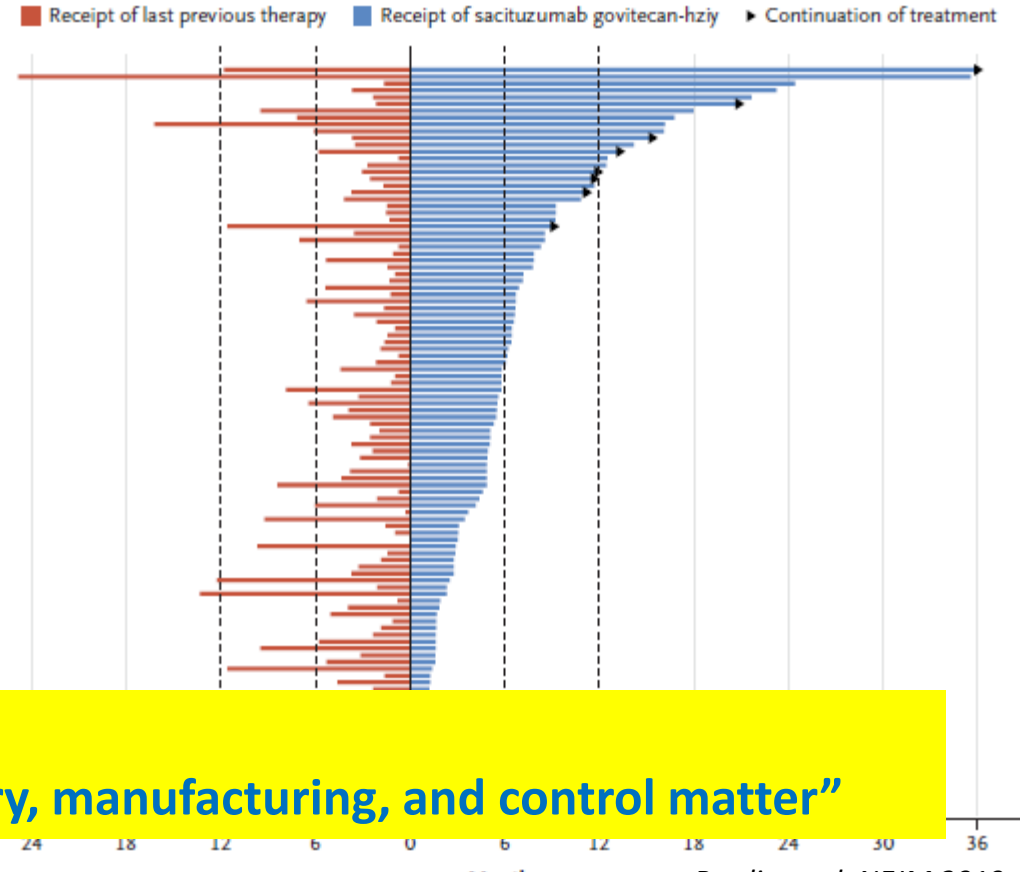




Bardia et al. JCO 2017

Benefit maintained in expanded cohort





Immunemedics:
"FDA want more data on chemistry, manufacturing, and control matter"

Bardia et al. NEJM 2019

mTNBC Confirmatory Study of Sacituzumab Govitecan vs. Physicians' Choice (ASCENT) is Well Underway

Amended ASCENT Phase 3 Study (under SPA): Overview

- First patient dosed in November 2017 in U.S.
- SPA protocol accepted by EU regulatory authority
- Clinical trial accruing globally

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed March 14, 2018.

Take home message

- **PARPi for *gBRCA1/2* mutations (not just TNBC)**
  - family history is the key, but generally higher in TNBC
  - With significant PFS benefit (~7m), ORR 60%, well tolerated
- **Atezolizumab (anti-PDL1) in combination with nab-paclitaxel**
  - 1st line setting, in PDL1(+) pts, IC ≥ 1% by SP142 assay
  - PFS (HR 0.6) and OS (HR 0.7) survival benefit
  - Also the 1st approved ICI in MBC
- sacitumumab govitecan: anti-Trop 2 ADC
  - Phase III ongoing
  - But promising phase 1 result with ORR 30%, PFS ~6months

Thanks For Your Attention!