13. Brustkrebs Kongress 2020

Köln und Niederrhein

18. Januar 2020

Brustzentrum Köln-Hohenlind

Kliniken Köln Beste Medizin für alle.

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DEUTSCHES KONSORTIUM

Zielgerichtete Therapien beim *BRCA*-assoziierten Mammakarzinom

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Zentrum Fam. Brust- und Eierstockkrebs

Uniklinik Köln

Köln, 18.01.2020

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DEUTSCHES KONSORTIUM Familiärer Brust- und Eierstockkrebs

PARP-Inhibitoren

- Wirkmechanismus
- OlympiAD

Zulassungsstudie Olaparib

- EMBRACA

Zulassungsstudie Talazoparib

- PARPi Zulassung und Kostenübernahme für die genetische Testung

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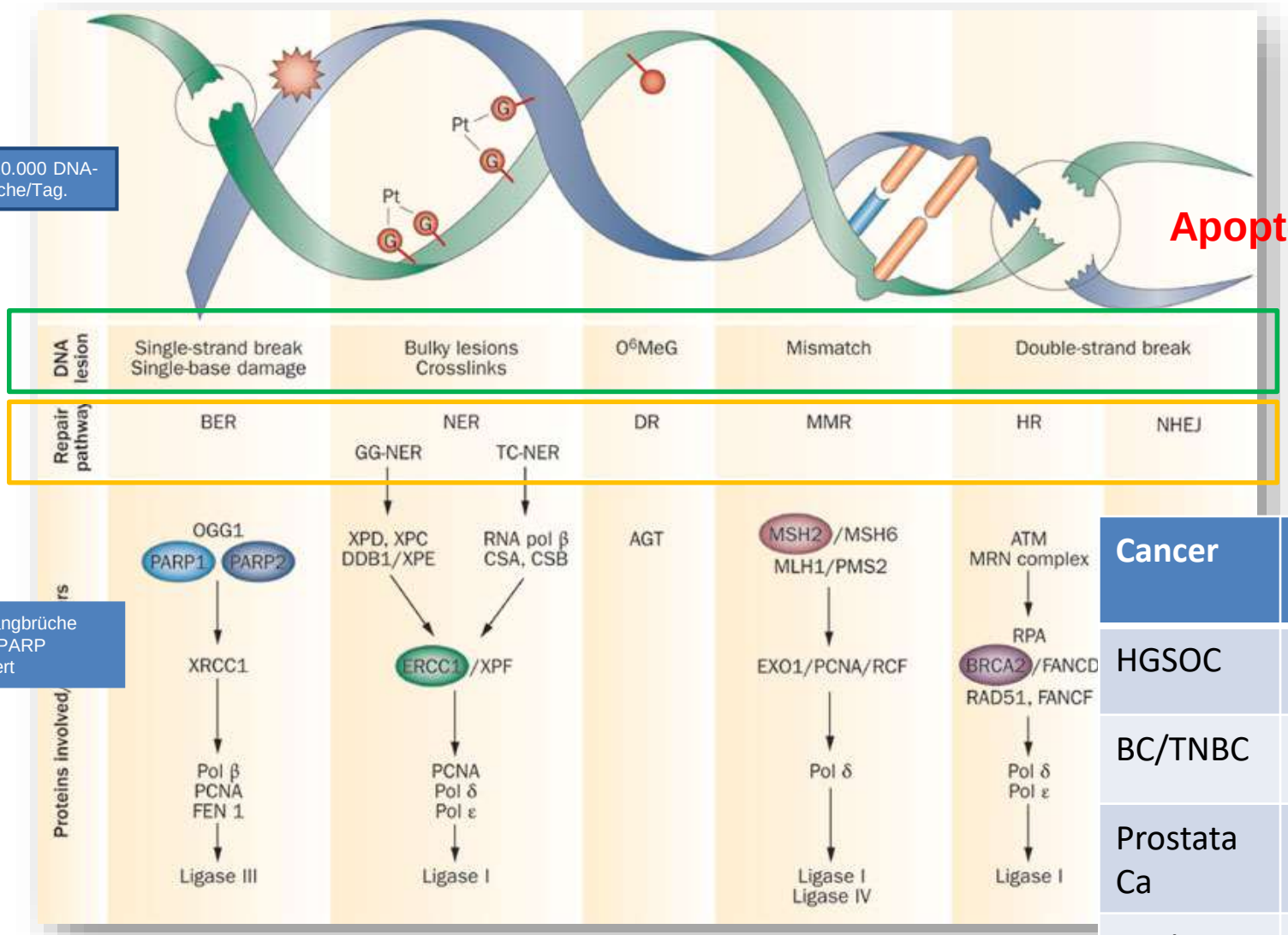
DEUTSCHES KONSORTIUM Familiärer Brust- und Eierstockkrebs

PARP-Inhibitoren

- Wirkmechanismus

DNA Reparaturwege

Bis zu 10.000–20.000 DNA-Einzelstrangbrüche/Tag.



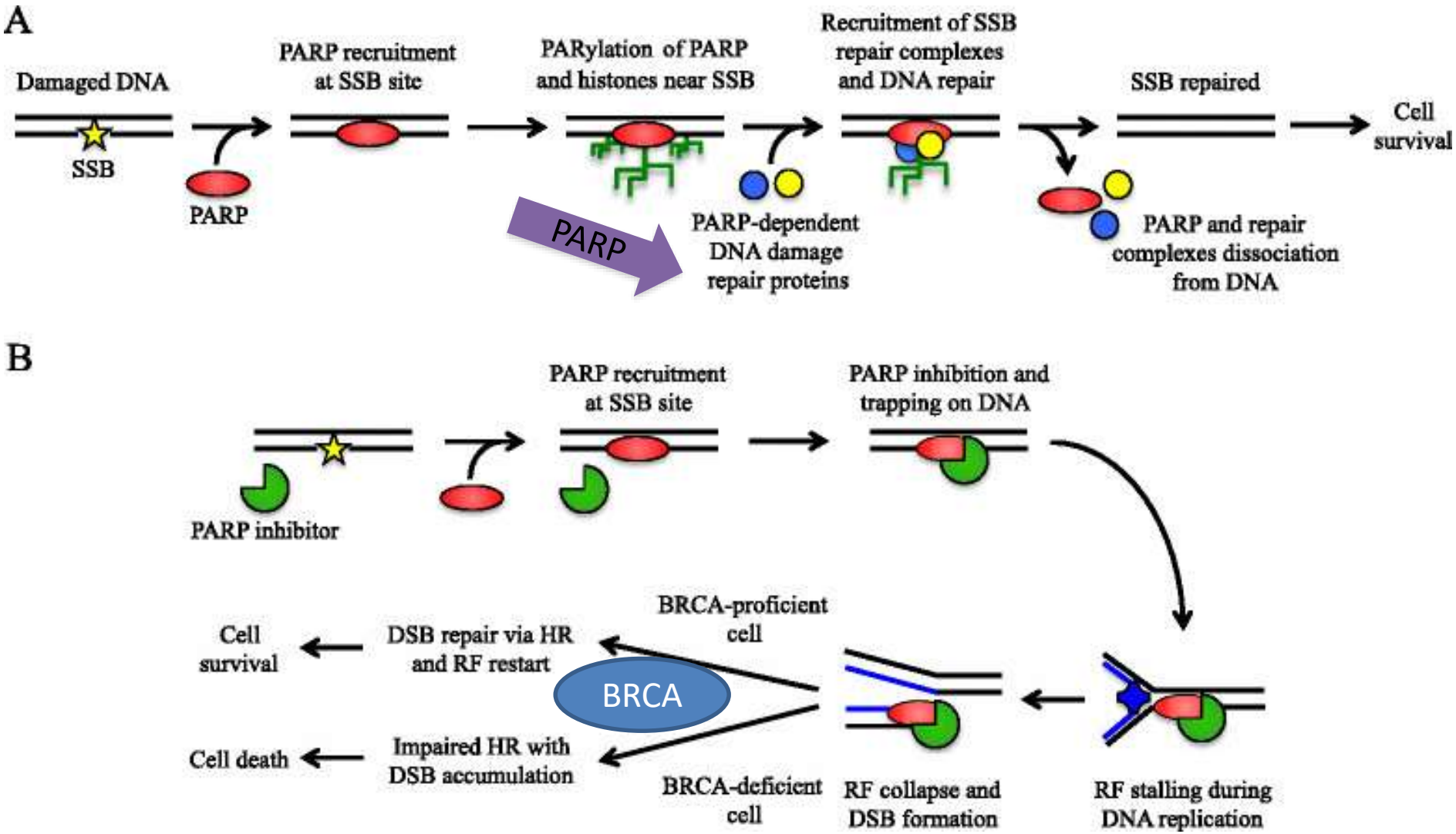
Apoptose

DNA-Einzelstrangbrüche
Werden durch PARP
Enzyme repariert

Cancer	HRD (%) t/g
HGSOC	~50%
BC/TNBC	~10-20%
Prostata Ca	~10-20%
Pankreas Ca	~10-20%

Postel-Vinay, S. *et al.* (2012) *Nat. Rev. Clin. Oncol.*

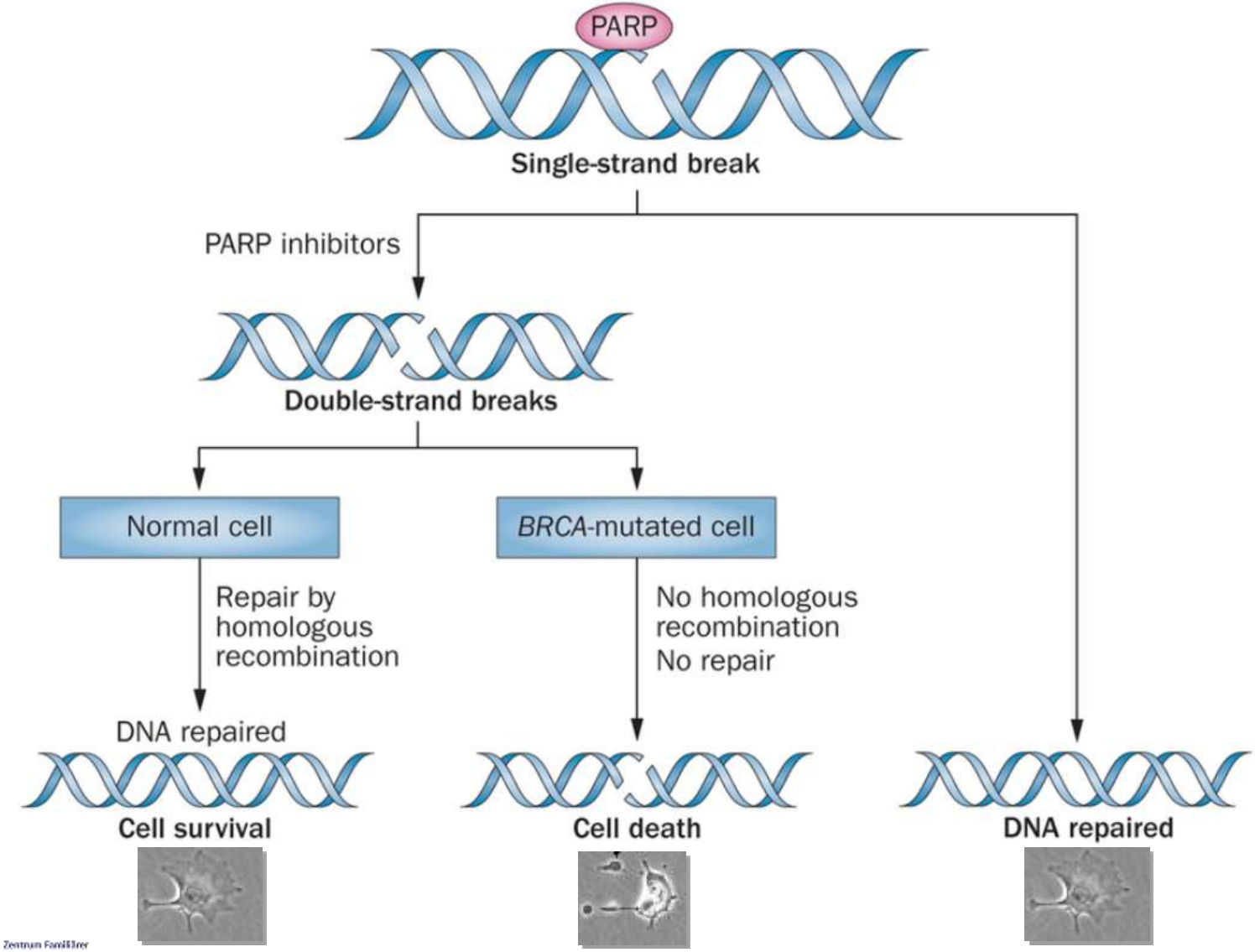
PARP-Inhibitoren – Wirkmechanismus



Livraghi L et al. BMC Med. 2015

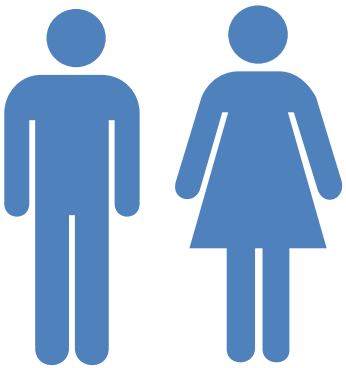
PARP-Inhibitoren- Wirkmechanismus

Das Prinzip der synthetischen Lethalität



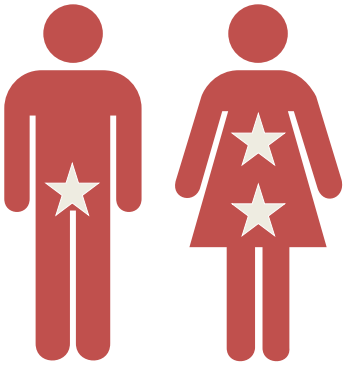
[Sonnenblick A et al. Nat Rev Clin Oncol 2015]

Bei *BRCA*-Mutationen handelt es sich entweder um Keimbahnmutationen oder um somatische Mutationen[1–3]



***BRCA*-Keimbahnmutationen**
Geerbte Mutationen, in allen Körperzellen

***BRCA*-Keimbahnmutationen** können in **Blutproben** nachgewiesen werden



Somatische *BRCA*-Mutationen
Erworbene Mutationen, nur in Tumorzellen

Somatische *BRCA*-Mutationen können in **Tumorproben** nachgewiesen werden

[1. National Cancer Institute. Erhältlich unter: http://www.cancer.gov/dictionary?cdrid=46384. Letzter Zugriff: Januar 2018]
[2. National Cancer Institute. Erhältlich unter: http://www.cancer.gov/dictionary?CdrID=46586. Letzter Zugriff: Januar 2018]
[3. Vergote I et al. Eur J Cancer 2016]

Durchschnittliche Prävalenz von *BRCA*-Mutationen beim Mamma- und Ovarialkarzinom[1–7]

Entität		Prävalenz von *BRCA*-Keimbahn-Mutationen	Prävalenz somatischer *BRCA*-Mutationen
Ovarialkarzinom	Bei Erstdiagnose	~ 22,7 %	~ 4,4 %
	Im Rezidiv	~ 23,3 %	~ 4,4 %
Fortgeschrittenes Mammakarzinom	Triple-negativ (HR-negativ/HER2-negativ)	~ 13 %	~ 5-6 %
	HR-positiv/HER2-negativ	~ 5 %	~ 1-2 %

[1. Harter P et al. J Clin Oncol 2016]
[2. Hahnen E et al. J Clin Oncol 2016]
[3. AstraZeneca data on file]
[4. The Cancer Genome Atlas Network. Nature 2012]
[5. Billar J et al. Ann Surg Oncol 2010]
[6. Harter P et al. PLoS ONE 12(10): e0186043]
[7. Winter C et al. Ann Oncol 2016]

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DEUTSCHES KONSORTIUM Familiärer Brust- und Eierstockkrebs

PARP-Inhibitoren

- OlympiAD

Zulassungsstudie Olaparib

PARPi vs. CTH beim met. und gBRCAm MaCa

OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- 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

Olaparib
300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

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[Robson ME. ASCO 2017]

PARPi vs. CTH beim met. und gBRCAm MaCa

Patient characteristics

	Olaparib 300 mg bd (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 PR+	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)

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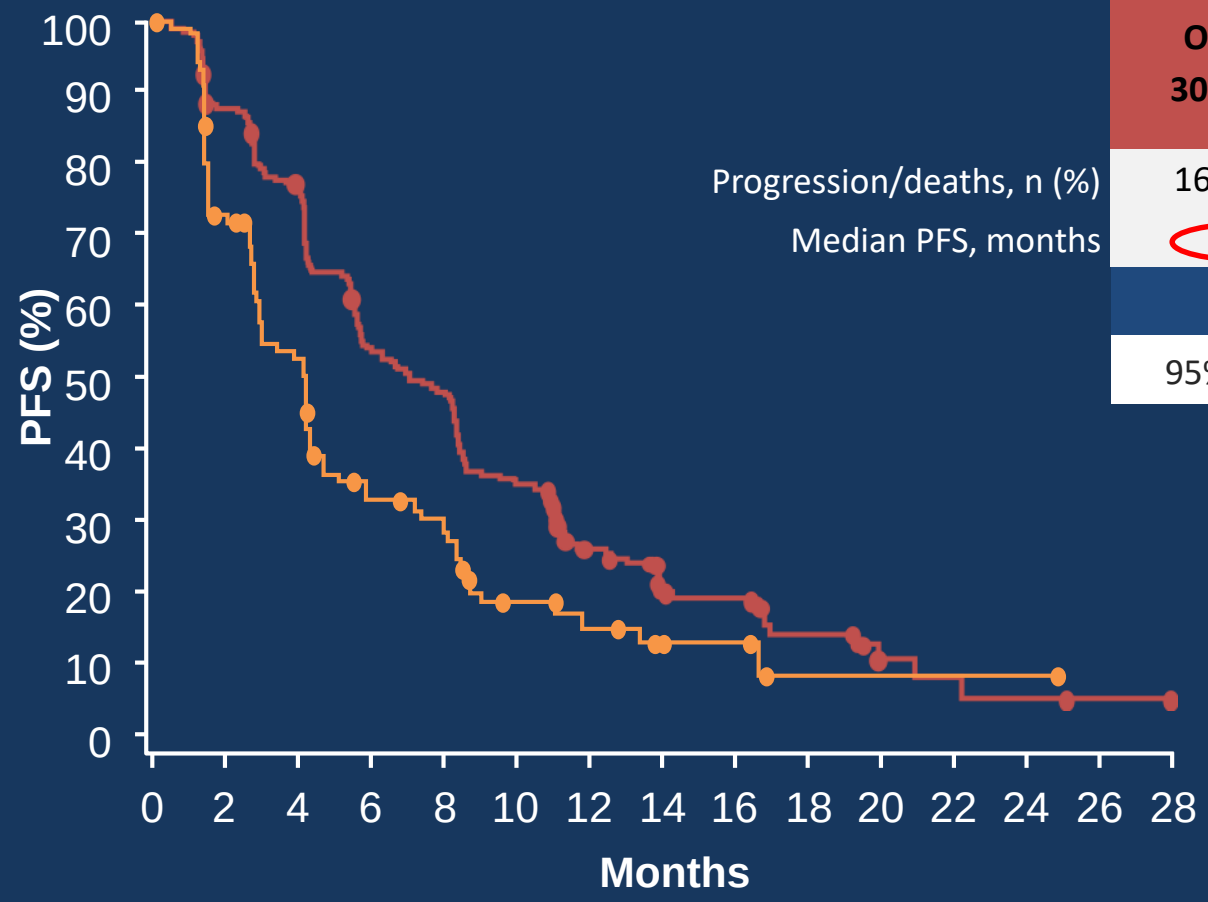
[Robson ME. ASCO 2017]

Primärer Endpunkt: **Progressionsfreies Überleben** by BICR



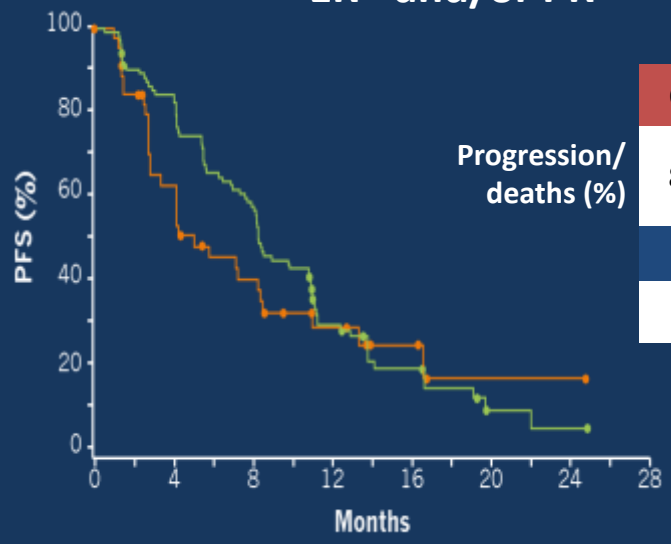
	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR 0.58	
	95% CI 0.43 to 0.80; *P*=0.0009	

At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

[Robson ME. ASCO 2017]

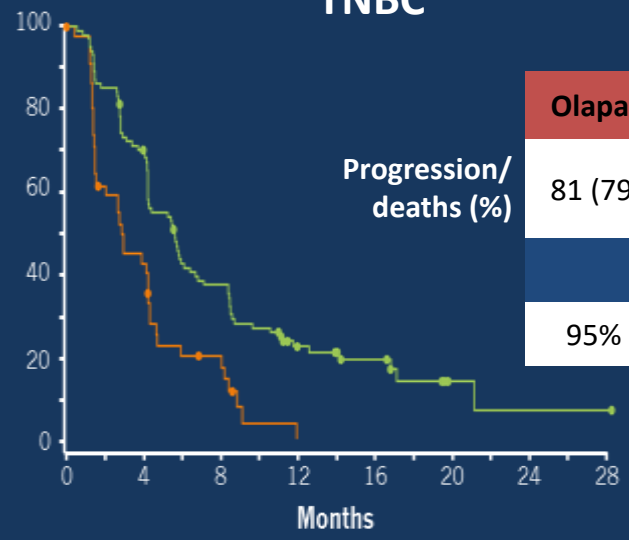
Subgruppenanalyse: PFS by BICR

ER+ and/or PR+



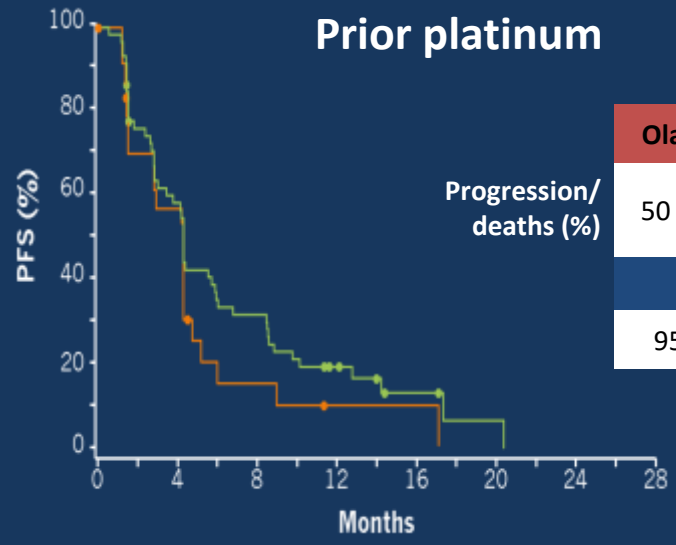
	Olaparib	TPC
Progression/ deaths (%)	82 (79.6)	31 (63.3)
HR 0.82		
95% CI 0.55 to 1.26		

TNBC



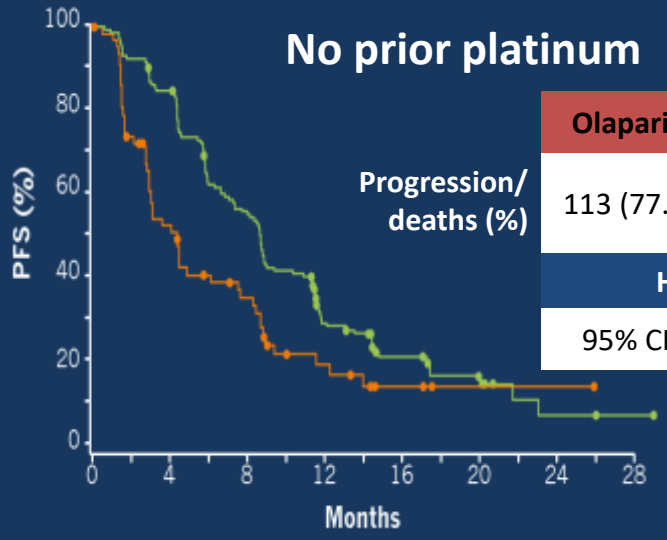
	Olaparib	TPC
Progression/ deaths (%)	81 (79.4)	40 (83.3)
HR 0.43		
95% CI 0.29 to 0.63		

Prior platinum



	Olaparib	TPC
Progression/ deaths (%)	50 (83.3)	21 (80.8)
HR 0.67		
95% CI 0.41 to 1.14		

No prior platinum



	Olaparib	TPC
Progression/ deaths (%)	113 (77.9)	50 (70.4)
HR 0.60		
95% CI 0.43 to 0.84		

[Robson ME. ASCO 2017]

Subgruppenanalyse: PFS by BICR

Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
Hormone-receptor status			
Hormone-receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55–1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29–0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41–1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43–0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43–0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30–1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43–0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41–1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37–0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45–1.07)
Age			
<65 yr	154/194 (79.4)	67/93 (72.0)	0.66 (0.49–0.88)
≥65 yr	9/11 (81.8)	4/4 (100.0)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34–0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48–1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22–0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48–0.95)
Other	54/71 (76.1)	24/34 (70.6)	0.51 (0.32–0.85)

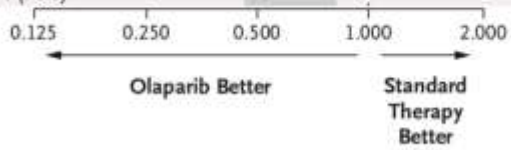
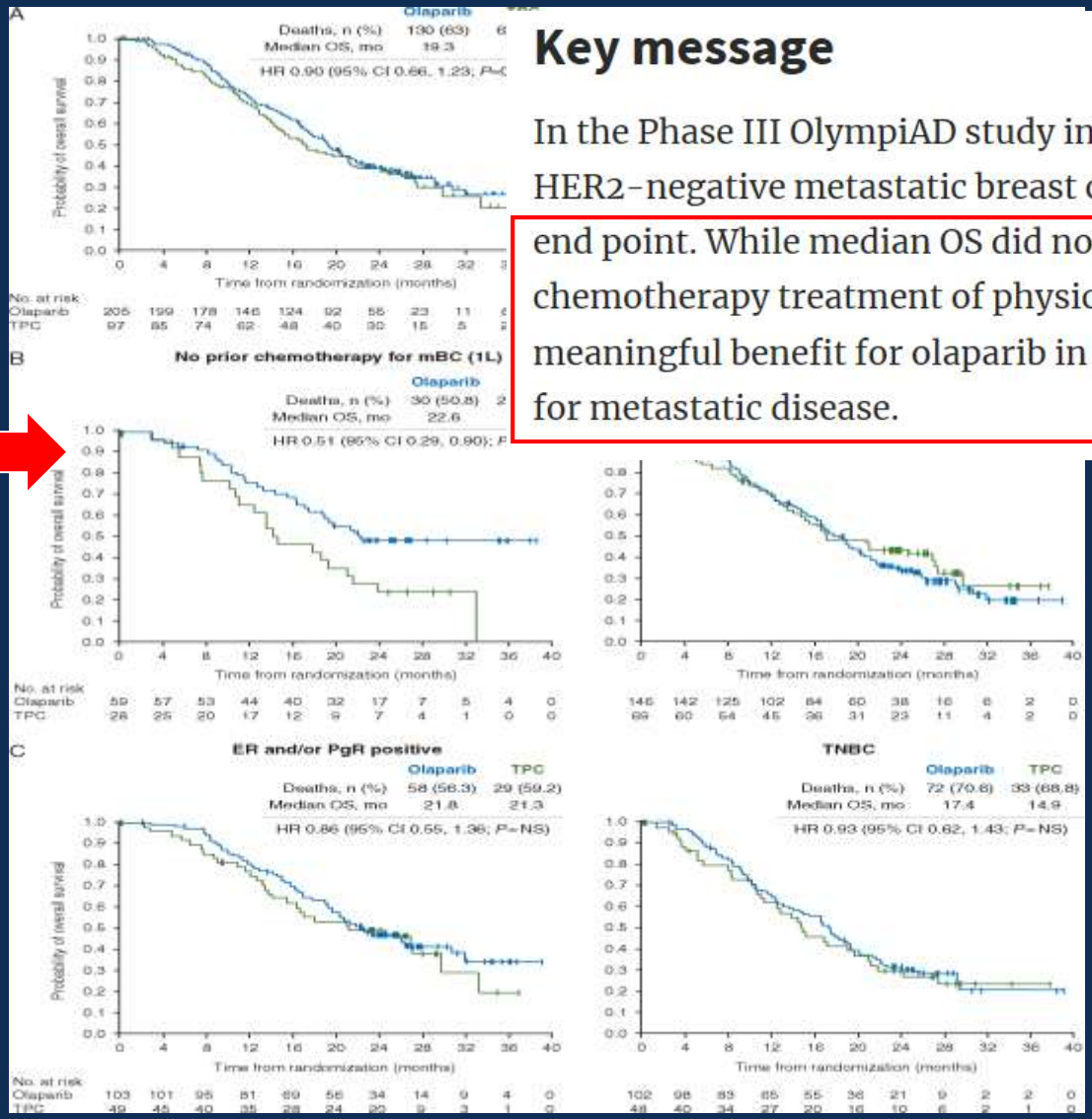


Figure 3. Subgroup Analysis of Progression-free Survival.

[Robson ME et al. NEJM 2017]

OlympiAD: Kaplan-Meier Kurven für das **overall survival** (64% data maturity)



Key message

In the Phase III OlympiAD study in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer, overall survival (OS) was a secondary end point. While median OS did not differ significantly for olaparib and chemotherapy treatment of physician's choice, there was a potential meaningful benefit for olaparib in patients who had not received chemotherapy for metastatic disease.

[Robson ME et al. Ann Oncol 2019]

Subgruppenanalyse für das Overall Survival

Annals of Oncology

Subgroup	Olaparib	TPC	HR (95% CI)
	No of patients with events/total no (%)		
All patients	130/205 (63%)	62/97 (64%)	0.90 (0.66, 1.23)
Received previous chemotherapy for metastatic breast cancer			
Yes (2nd-/3rd-line)	100/146 (69%)	41/69 (59%)	1.13 (0.79, 1.64)
No (1st-line)	30/59 (51%)	21/28 (75%)	0.51 (0.29, 0.90)
Receptor status			
ER and/or PgR positive	58/103 (56%)	29/49 (59%)	0.86 (0.55, 1.36)
ER and PgR negative	72/102 (71%)	33/48 (69%)	0.93 (0.62, 1.43)
Prior platinum for BC			
Yes	42/60 (70%)	19/26 (73%)	0.83 (0.49, 1.45)
No	88/145 (61%)	43/71 (61%)	0.91 (0.64, 1.33)
Measurable vs non measurable disease			
Measurable	112/165 (68%)	50/72 (69%)	0.85 (0.61, 1.19)
Non-measurable	18/40 (45%)	12/25 (48%)	0.90 (0.44, 1.91)
Progressive disease at randomization			
Yes	102/159 (64%)	48/73 (66%)	0.85 (0.61, 1.20)
No	28/46 (61%)	14/24 (58%)	1.08 (0.58, 2.11)
BRCA mutation type			
BRCA1	78/114 (68%)	37/50 (74%)	0.83 (0.57, 1.25)
BRCA2	47/84 (56%)	25/45 (56%)	0.90 (0.56, 1.48)
Age, years			
<65	126/194 (65%)	59/93 (63%)	0.95 (0.70, 1.31)
≥65	4/11 (36%)	3/4 (75%)	NC
Age, years			
< median 44	64/99 (65%)	28/39 (72%)	0.92 (0.60, 1.46)
≥ median 44	66/106 (62%)	34/58 (59%)	0.87 (0.58, 1.34)
Region			
Asia	33/59 (56%)	16/28 (57%)	0.96 (0.54, 1.79)
Europe	63/97 (65%)	29/45 (64%)	0.97 (0.63, 1.53)
North and South America	34/49 (69%)	17/24 (71%)	0.66 (0.38, 1.21)
Race			
White	89/134 (66%)	41/63 (65%)	0.90 (0.63, 1.32)
Other	41/71 (58%)	21/34 (62%)	0.89 (0.53, 1.53)

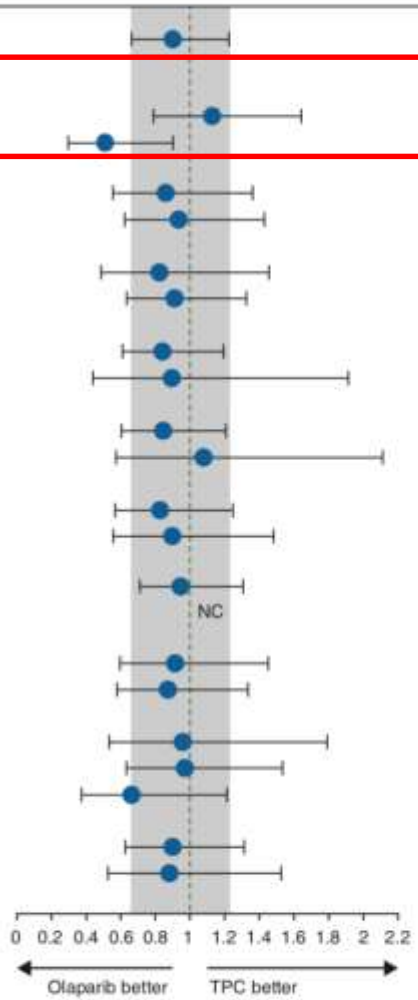
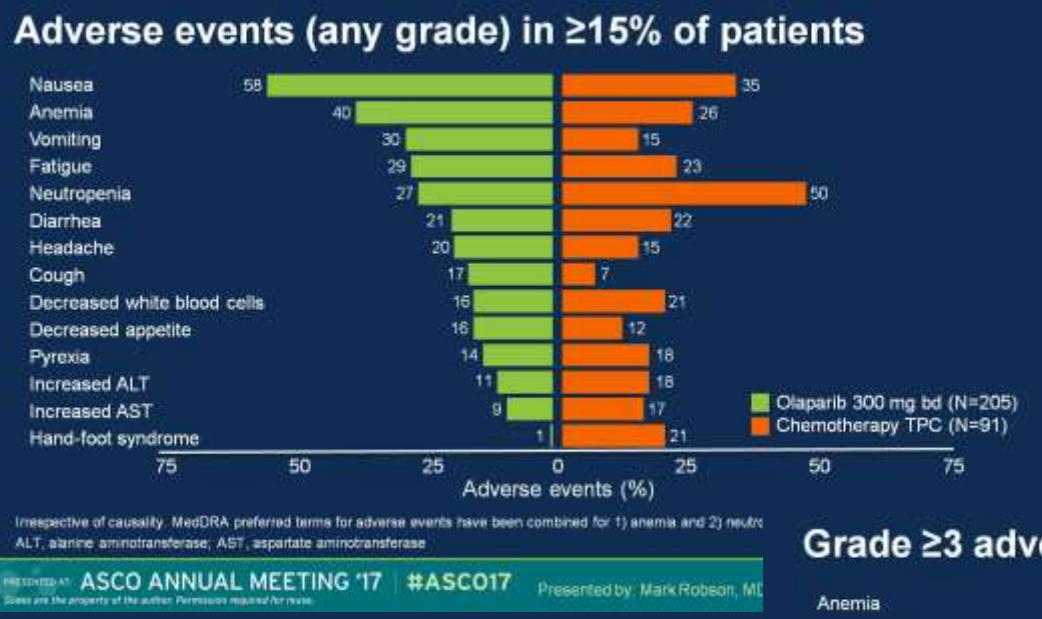
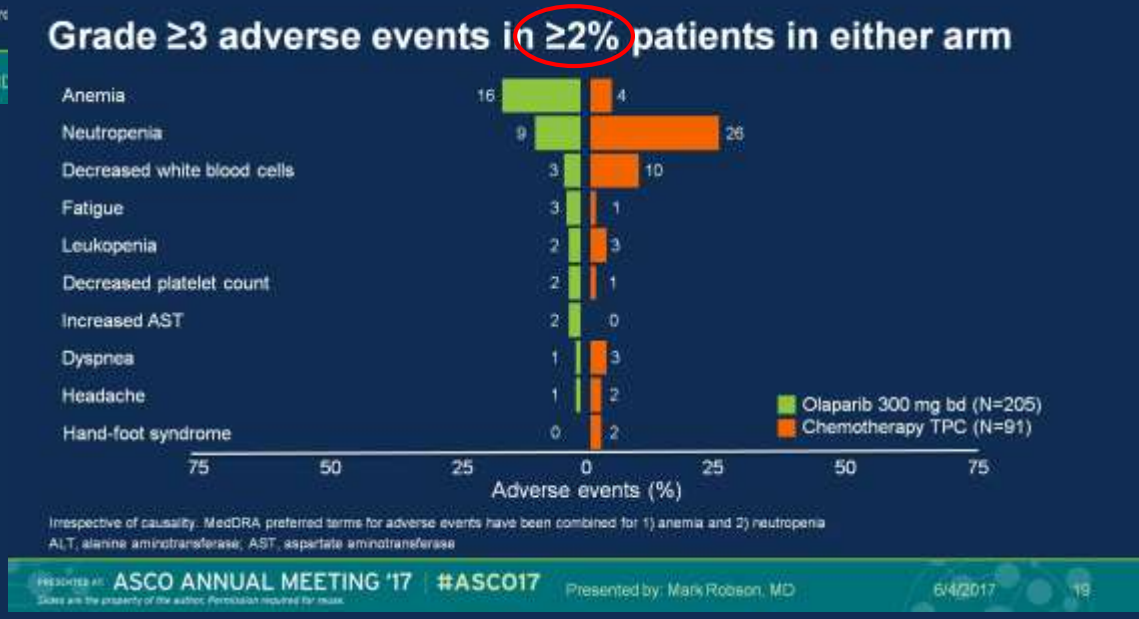


Figure 2. Forest plots of final OS overall population and all subgroup analyses. BC, breast cancer; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; NC, not calculated; PgR, progesterone receptor; TPC, treatment of physician's choice.

[Robson ME et al. Ann Oncol 2019]

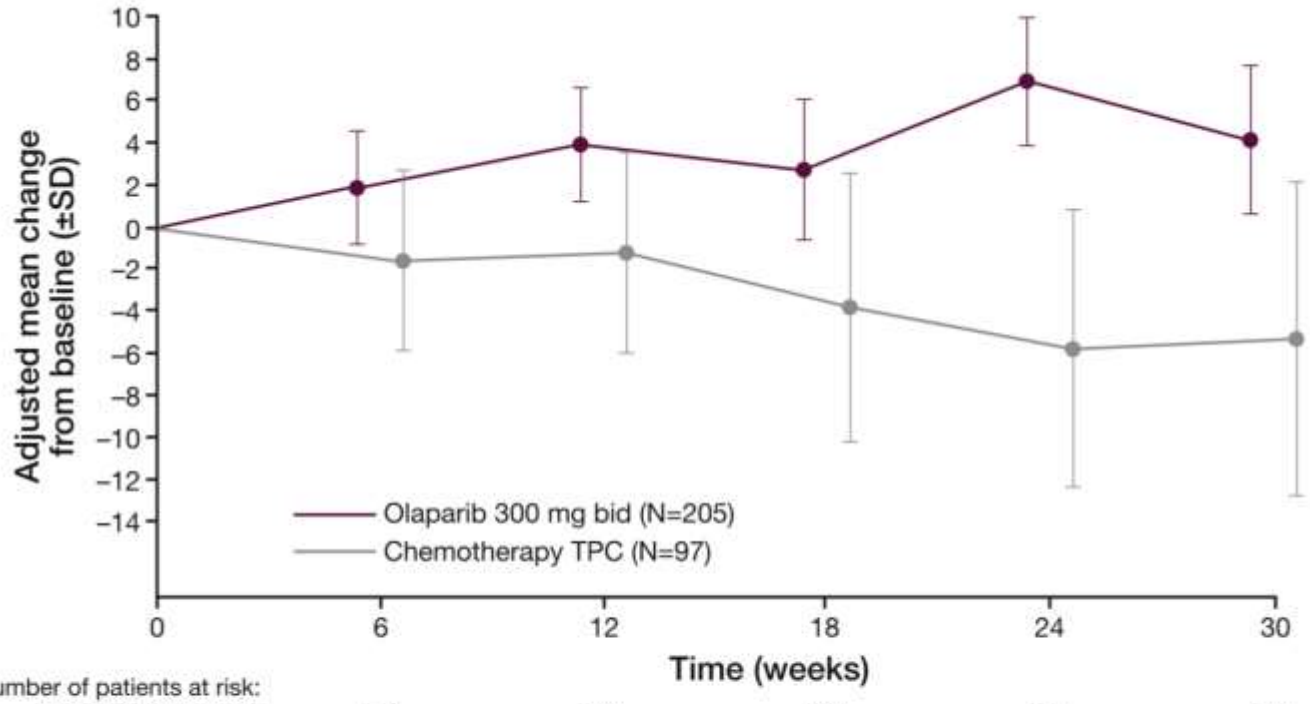
Adverse events





[Robson ME. ASCO 2017]

EORTC QLQ-C30 global health status/quality of life score

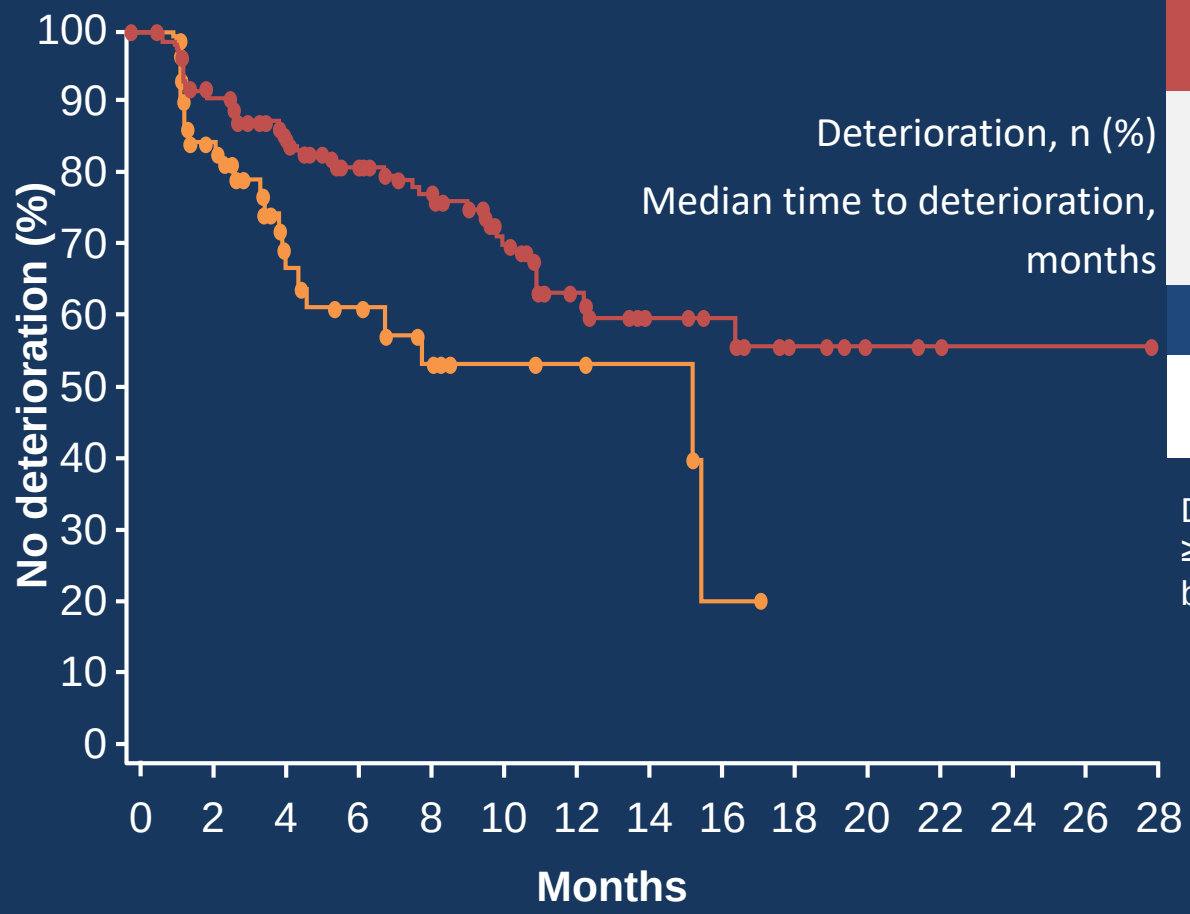


Number of patients at risk:					
Olaparib 300 mg bid	177	163	147	117	100
Chemotherapy TPC	68	52	36	23	20

Fig. 2. Adjusted mean (SD) change from baseline in EORTC QLQ-C30 global health status/quality of life score across time points in patients in the olaparib and TPC arms. bid, twice daily; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module; SD, standard deviation; TPC, treatment of physician's choice. A higher score represents better overall health-related quality of life. Note that data are restricted to visits with at least 20 patients in each treatment arm.

[Robson ME et al. Eur J Cancer 2019]

Time to deterioration of global HRQoL scores



	Olaparib 300 mg bd	Chemotherapy TPC
Deterioration, n (%)	49 (24)	25 (27)
Median time to deterioration, months	NC	15.3
	HR 0.44	
	95% CI 0.25 to 0.77 *P*=0.0043	

Deterioration is defined as ≥10 point decrease from baseline

At risk, n															
Olaparib 300 mg bd	201	164	134	93	77	56	40	20	15	7	4	2	1	1	0
Chemotherapy TPC	93	54	30	19	13	8	7	4	1	0	0	0	0	0	0

[Robson ME. ASCO 2017]

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PARP-Inhibitoren

- EMBRACA

Zulassungsstudie Talazoparib

PARPi vs. CTH beim met. und gBRCAm MaCa
EMBRACA-Studie

San Antonio Breast Cancer Symposium, December 5-9, 2017

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 ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

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

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

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

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)

[Litton JK. SABCS 2017]

Patientenkollektiv

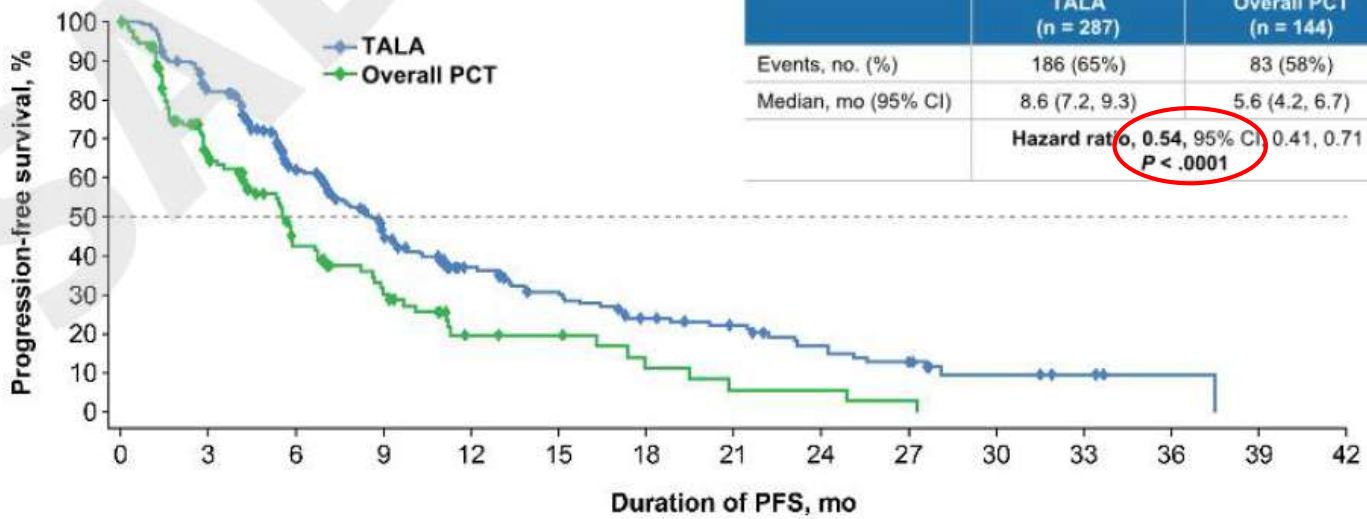
Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Talazoparib Group (N=287)	Standard-Therapy Group (N=144)
Age — yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age <50 yr — no. (%)	182 (63.4)	67 (46.5)
Female sex — %	98.6	97.9
ECOG performance status score — %†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breast cancer stage — no. (%)‡		
Locally advanced	15 (5.2)	9 (6.2)
Metastatic	271 (94.4)	135 (93.8)
Measurable disease assessed by investigator — no. (%)	219 (76.3)	114 (79.2)
History of CNS metastases — no. (%)	43 (15.0)	20 (13.9)
Visceral disease — no. (%)	200 (69.7)	103 (71.5)
Hormone-receptor status — no. (%)		
Triple-negative	130 (45.3)	60 (41.7)
Hormone-receptor–positive	157 (54.7)	84 (58.3)
BRCA status — no. (%)§		
BRCA1-positive	133 (46.3)	63 (43.8)
BRCA2-positive	154 (53.7)	81 (56.2)
<12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)	108 (37.6)	42 (29.2)
Previous adjuvant or neoadjuvant therapy — no. (%)	238 (82.9)	121 (84.0)
No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previous platinum therapy — no. (%)	46 (16.0)	30 (20.8)
Previous cytotoxic regimens for advanced breast cancer — no. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
3	12 (4.2)	8 (5.6)

[Litton JK et al. NEJM 2018]

PARPi vs. Chemotherapie beim met. und gBRCAm Ma-Ca EMBRACA-Studie

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**	

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)	86 (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)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

12

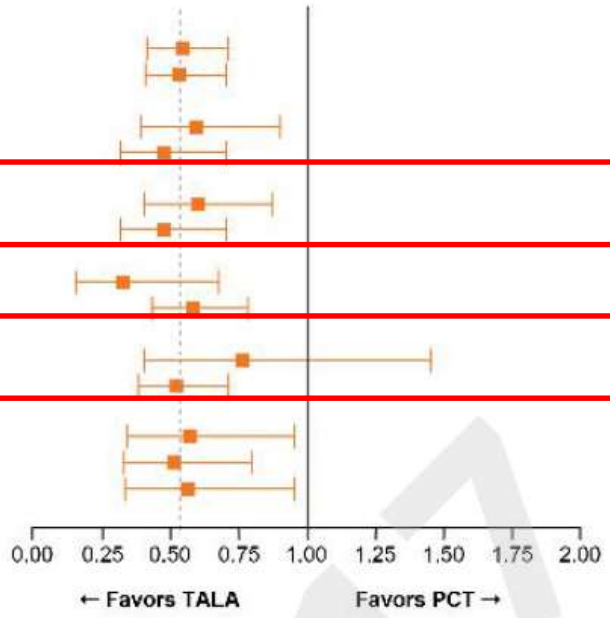
[Litton JK. SABCS 2017]

PARPi vs. CTH beim met. und gBRCAm MaCa
EMBRACA-Studie

San Antonio Breast Cancer Symposium, December 5-9, 2017

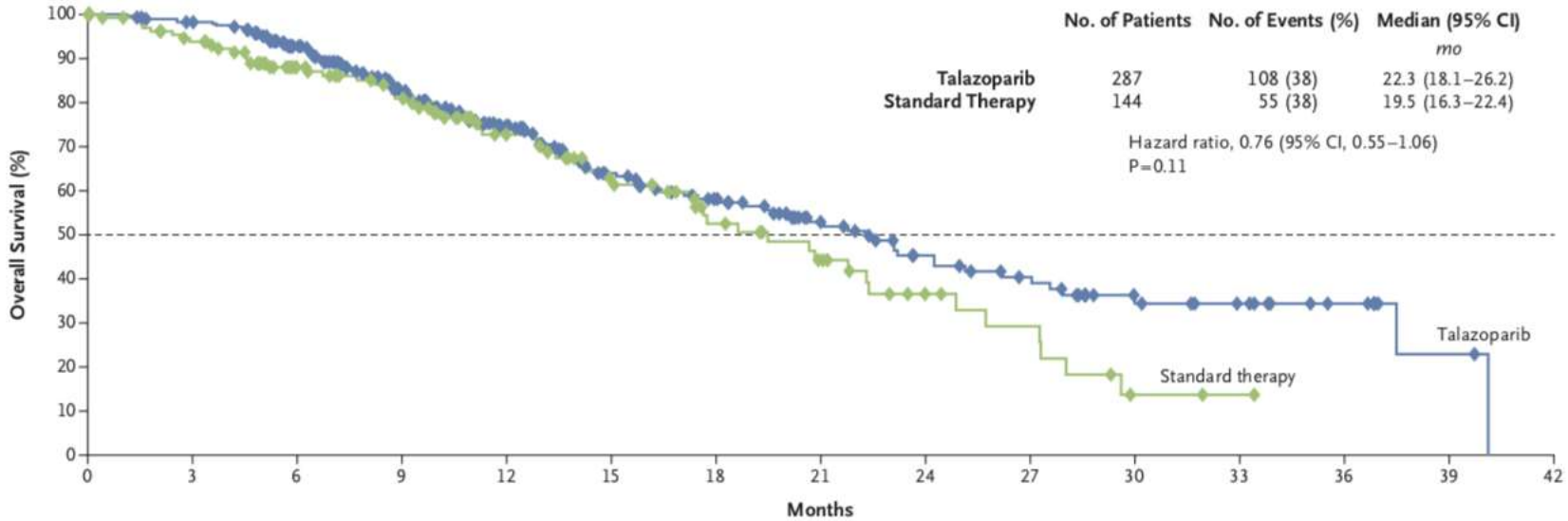
PFS: Subgroup Analysis

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA status by 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		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	241 (55.9)	0.47 (0.32-0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15-0.68)
No	368 (85.4)	0.58 (0.43-0.78)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
0	165 (38.3)	0.57 (0.34-0.95)
1	161 (37.4)	0.51 (0.33-0.80)
≥ 2	105 (24.4)	0.56 (0.34-0.95)



[Litton JK et al. NEJM 2018]

Overall Survival



No. at Risk (events/cumulative events)

Talazoparib	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
Standard therapy	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Figure 2. **Interim Analysis of Overall Survival.**

[Litton JK et al. NEJM 2018]

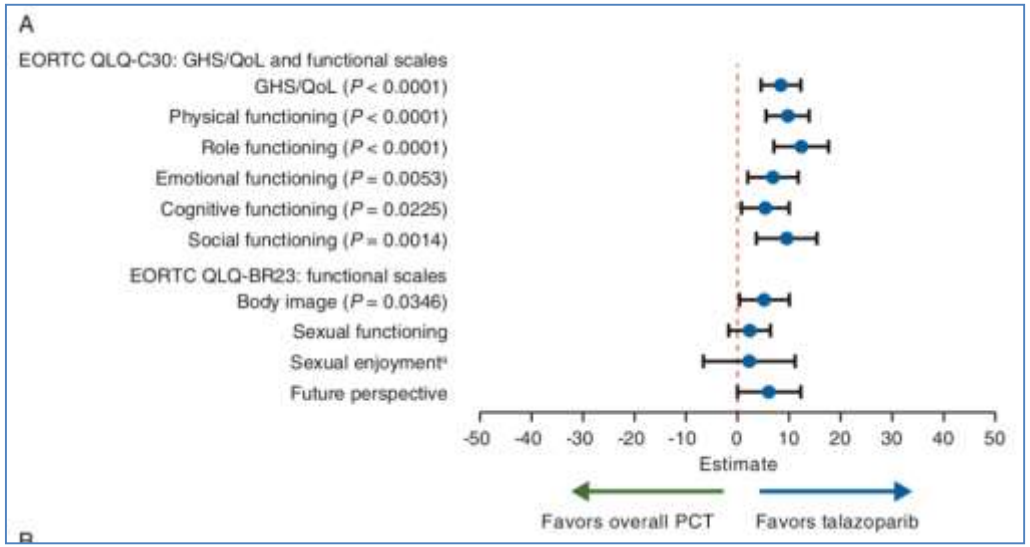
Adverse Events

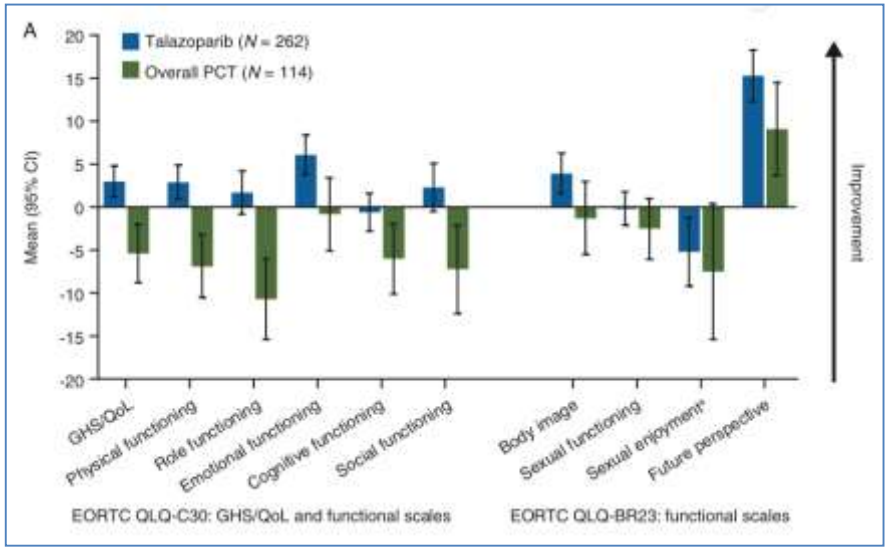
Table 3. Summary of Adverse Events.*

Adverse Event	Talazoparib Group (N=286)	Standard-Therapy Group (N=126)
	number of patients (percent)	
Any adverse event	282 (98.6)	123 (97.6)
Serious adverse event†	91 (31.8)	37 (29.4)
Serious and drug-related adverse event	26 (9.1)	11 (8.7)
Grade 3 or 4 serious adverse event	73 (25.5)	32 (25.4)
Adverse event resulting in permanent drug discontinuation	17 (5.9)	11 (8.7)

[Litton JK et al. NEJM 2018]

Quality of Life





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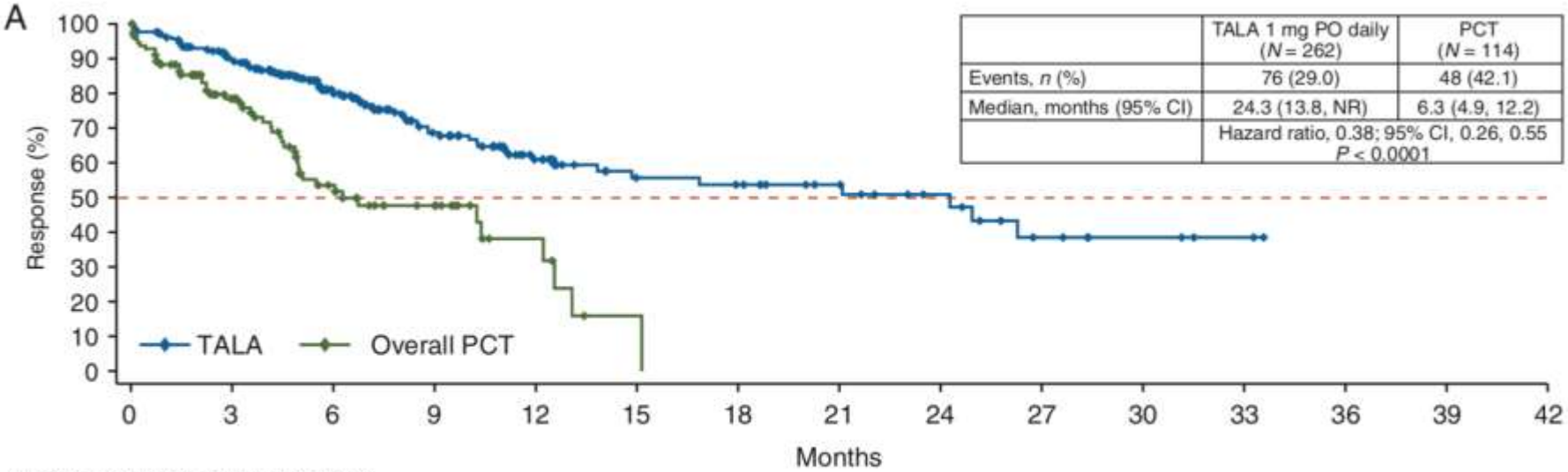
[Ettl J et al. Ann Oncol 2018]

Time to deterioration



	TALA 1 mg PO daily (N = 262)	PCT (N = 114)
Events, n (%)	76 (29.0)	48 (42.1)
Median, months (95% CI)	24.3 (13.8, NR)	6.3 (4.9, 12.2)
	Hazard ratio, 0.38; 95% CI, 0.26, 0.55 $P < 0.0001$	

Number at risk (events/cumulative events)

TALA	262 (0/0)	212 (26/26)	139 (18/44)	78 (17/61)	44 (7/68)	28 (3/71)	26 (1/72)	20 (0/72)	14 (1/73)	7 (3/76)	4 (0/76)	2 (0/76)	0 (0/76)	0 (0/76)	0 (0/76)
PCT	114 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

[Ettl J et al. Ann Oncol 2018]

PARP-Inhibitoren im Vergleich

	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR 0.58	

95% CI 0.43 to 0.80; *P*=0.0009

	No. of Patients	No. of Events (%)	Median (95% CI) mo
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard Therapy	144	83 (58)	5.6 (4.2–6.7)

Hazard ratio for progression or death, 0.54 (95% CI, 0.41–0.71)
P<0.001

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PARP-Inhibitoren

- PARPi Zulassung

OlympiAD

FDA U.S. FOOD & DRUG ADMINISTRATI

FDA approves c
mutated metast

f SHARE | TWEET | in LINKED

On January 12, 2018, the Food an
(Lynparza, AstraZeneca Pharmace
treatment of patients with deleteric
negative metastatic breast cancer
adjuvant, or metastatic setting.

This is the first FDA-approved trea
Patients with hormone receptor (H
therapy or be considered inapprop
on an FDA-approved companion c

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Lynparza
olaparib

On 28 February 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Lynparza. The marketing authorisation holder for this medicinal product is AstraZeneca AB.

The CHMP adopted a new indication for Lynparza tablets as follows:

> "Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (see section 5.1).
>
> Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy."

EMBRACA

U.S. FOOD & DRUG ADMINISTRATION

FDA approves t
negative locally
cancer

SHARE TWEET LINKEDIN

On October 16, 2018, the Food and
(ADP-ribose) polymerase (PARP) in
mutated (gBRCAm), HER2-negative
therapy based on an FDA-approved

Approval was based on EMBRACA
gBRCAm HER2-negative locally adv
choice of chemotherapy (capecitabi
known deleterious or suspected dele
cytotoxic chemotherapy regimens fo
received treatment with an anthracy
and/or metastatic treatment setting.

The primary efficacy outcome was p
Solid Tumors (RECIST) 1.1, as asse
and 5.6 months in the talazoparib ar

The prescribing information includes
leukemia, myelosuppression, and e
fatigue, anemia, nausea, neutropeni
appetite.

EUROPEAN MEDICINES AGENCY

Talzenna
talazoparib

On 26 April 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Talzenna, intended for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2-negative locally advanced or metastatic breast cancer. The applicant for this medicinal product is Pfizer Europe MA EEIG.

Talzenna will be available as hard capsules (0.25 and 1 mg). The active substance of Talzenna is talazoparib, an inhibitor of PARP enzymes, PARP1 and PARP2, which play a role in DNA repair (ATC code: L01XX60). The inhibition of PARP catalytic activity as well as PARP trapping, whereby a PARP enzyme bound to a PARP inhibitor does not readily dissociate from a DNA lesion, result in DNA damage and tumour cell death.

The benefits with Talzenna are its ability to improve patients' progression-free survival compared with chemotherapy. The most common side effects are fatigue, anaemia, nausea, neutropenia, thrombocytopenia, and headache.

The full indication is:

"Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy."

PARP-Inhibitoren

	Olaparib	Talazoparib
Trade name	Lynparza™	Talzenna®
Administration	oral	oral
Dose	2 x 300mg tablets/day	1 x 1mg tablets/day
FDA	Approval 01/2018	Approval 10/18
EMA	Approval 04/2019	Approval 06/2019
Requirements	FDA: gBRCAm met Her2 neg breast cancer after chemotherapy with anthrac/taxane (neoadj, adj or met situation) or HR+ after endocrine therapy	FDA: gBRCAm met Her2 neg breast cancer after chemotherapy with anthrac/taxane (neoadj, adj or met situation) or HR+ after endocrine therapy
Type of treatment	Treatment, mono	Treatment, mono
Approval/Submission based on	OlympiAD	EMBRCA

Nebenwirkungsspektrum aus der OC Therapie mit PARP Inhibitoren

	Olaparib		Niraparib	Rucaparib
	Study19[1]	SOLO2 [2]	NOVA[3]	ARIEL3 [4]
≥ Grade 3 AE	43.4%	36.9%	74%	56%
Dosisreduktionen	25.7%	25.1%	67%	55%
AE mit Therapieabbruch	5.9%	10.8%	15%	13,4%
TEAEs of interest (Grade 3/4)				
Anämie	5.9%	19.5%	25.3%	18,8%
Neutropenie	3.7%	5.1%	19.6%	6,7%
Thrombocytopenie	0.7%	1.0%	33.8%	5,1%
Übelkeit	2.2%	2.6%	3.0%	3,7%
Erbrechen	2.2%	2.6%	1.9%	4,0%
Diarrhö	2.2%	1.0%	0.3%	0,5%
Erhöhte Leberenzyme (AST/ALT)	0.5%	0	1-2%	10,5%
Hypertension	0.7%	0	8.2%	
MDS/AML	1.5%	2.1%	1.4%	<1%

[1] Gourley, C. *et al.* Clinically significant long-term maintenance treatment with olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *J Clin Oncol 35* (poster related to suppl; abstr 5533) (2017).

[2] Pujade-Lauraine et al, Lancet Oncol 2017;18(9): S.1274-1284

[3] Mirza MR et al., NEJM 2016, Oct 8

[5] Coleman, R. et al, Lancet Oncol 2017;

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PARP-Inhibitoren

- Zusammenfassung

Zusammenfassung

- **PARP-Inhibitoren sind wirksam beim HER2-negativem, lokal fortgeschrittenen bzw. metastasierten MaCa mit Keimbahnmutation in *BRCA1/2***
- **Wirksamkeit der PARP-Inhibitoren beim MaCa ohne Keimbahnmutation in *BRCA1/2* ist unklar**
- **Für das MaCa liegen bisher keine Daten zur Effektivität bei alleiniger somatischer *BRCA*-Mutation vor**
- **Der prädiktive Effekt eines HRD Tests ist nicht bewiesen**

Vielen Dank für Ihre Aufmerksamkeit!