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Toxicity of PARPi

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COI

Advisory Committee	AstraZeneca Pharmaceuticals LP, Lilly, Merck, Novartis, Pfizer Inc
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Case presentation: Dr Domchek

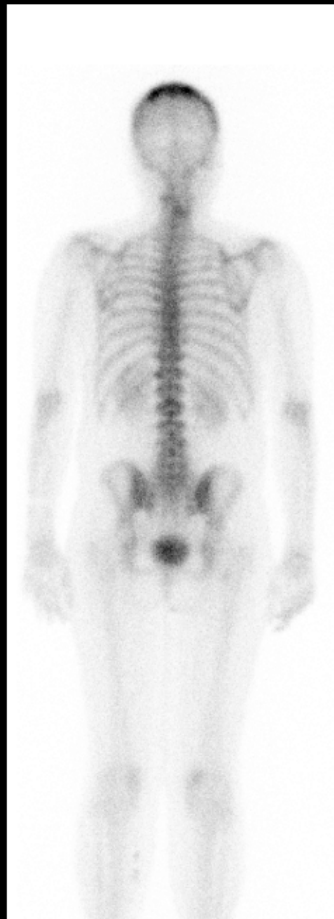
47-year-old woman diagnosed at age 45 with BRCA1 germline mutation

- 2007: Ovarian cancer treated with debulking surgery and 6 cycles of carboplatin and paclitaxel
- 2009: Developed recurrent disease and again received carboplatin and paclitaxel
- 2010: Relapsed within 6 months of treatment and started olaparib on a clinical trial; developed transfusion-dependent anemia and progressed after 7 months

Case presentation: Dr Gelmon

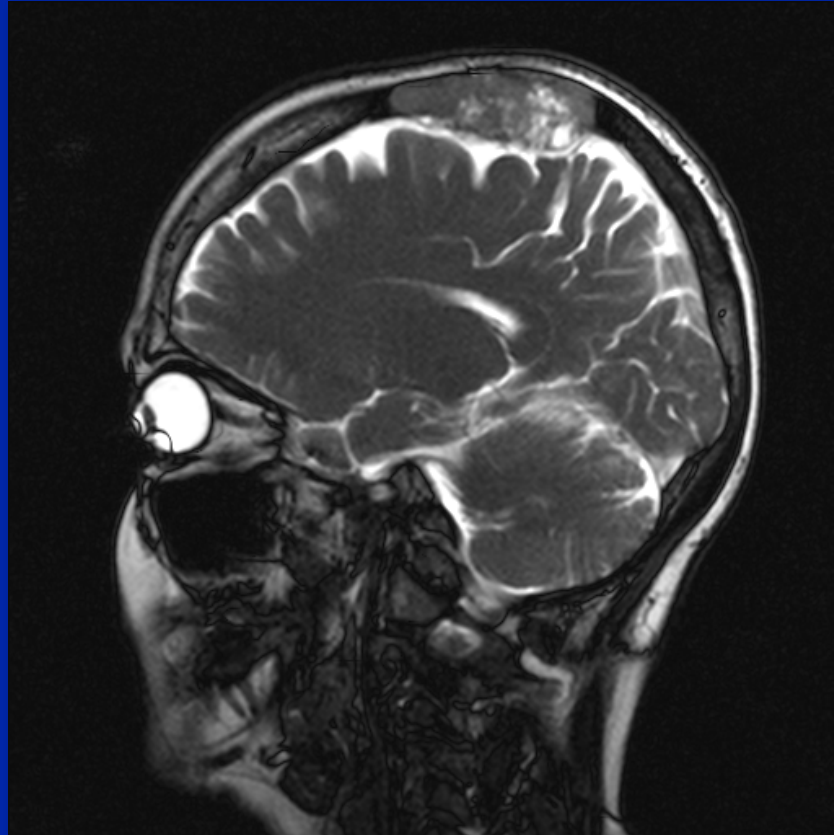
62-year-old woman with breast cancer and BRCA2 germline mutation

- 1991 (age 36): DCIS → R MRM
- 1996: Stage III ER-positive, HER2-negative BC → surgery → CMF → radiation and tamoxifen
- 2012: Metastatic breast cancer in bone
- 2012-2015: Hormonal therapy
- 2015-2016: Capecitabine with good response
- 2016-2017: Cisplatin/gemcitabine – ototoxicity with tinnitus
- 2017: Olaparib with dose modification (nausea) – partial response

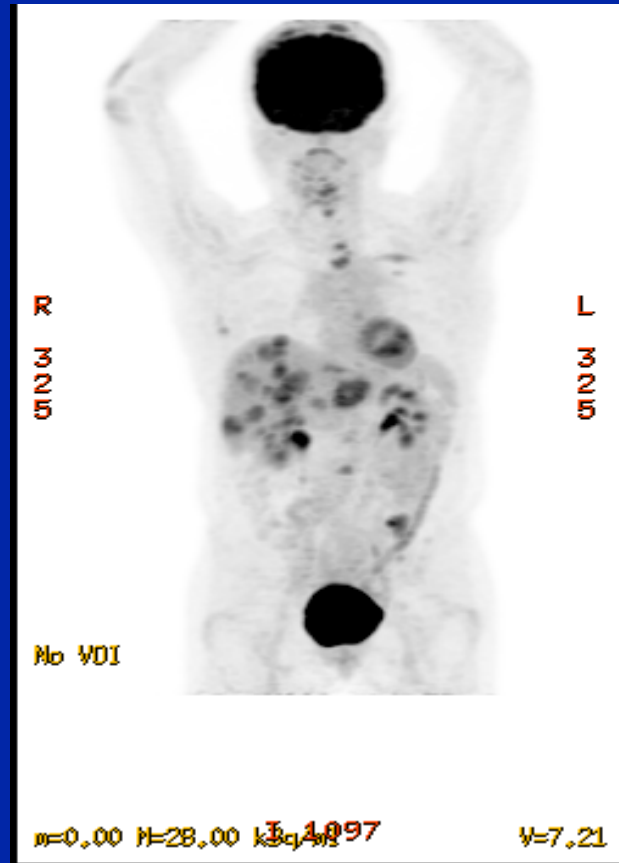
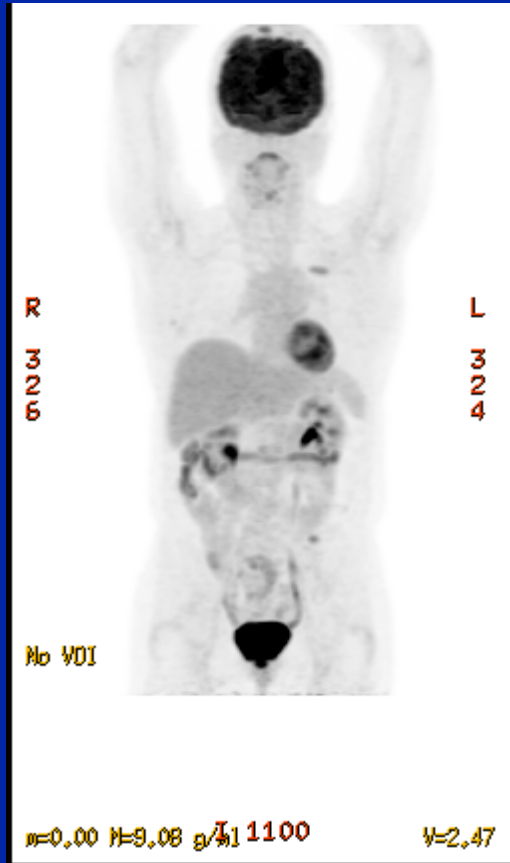


Bone scan at the time of diagnosis of recurrence with skull mets and subtle other bone lesions

MRI 2012: Skull Bone Metastases



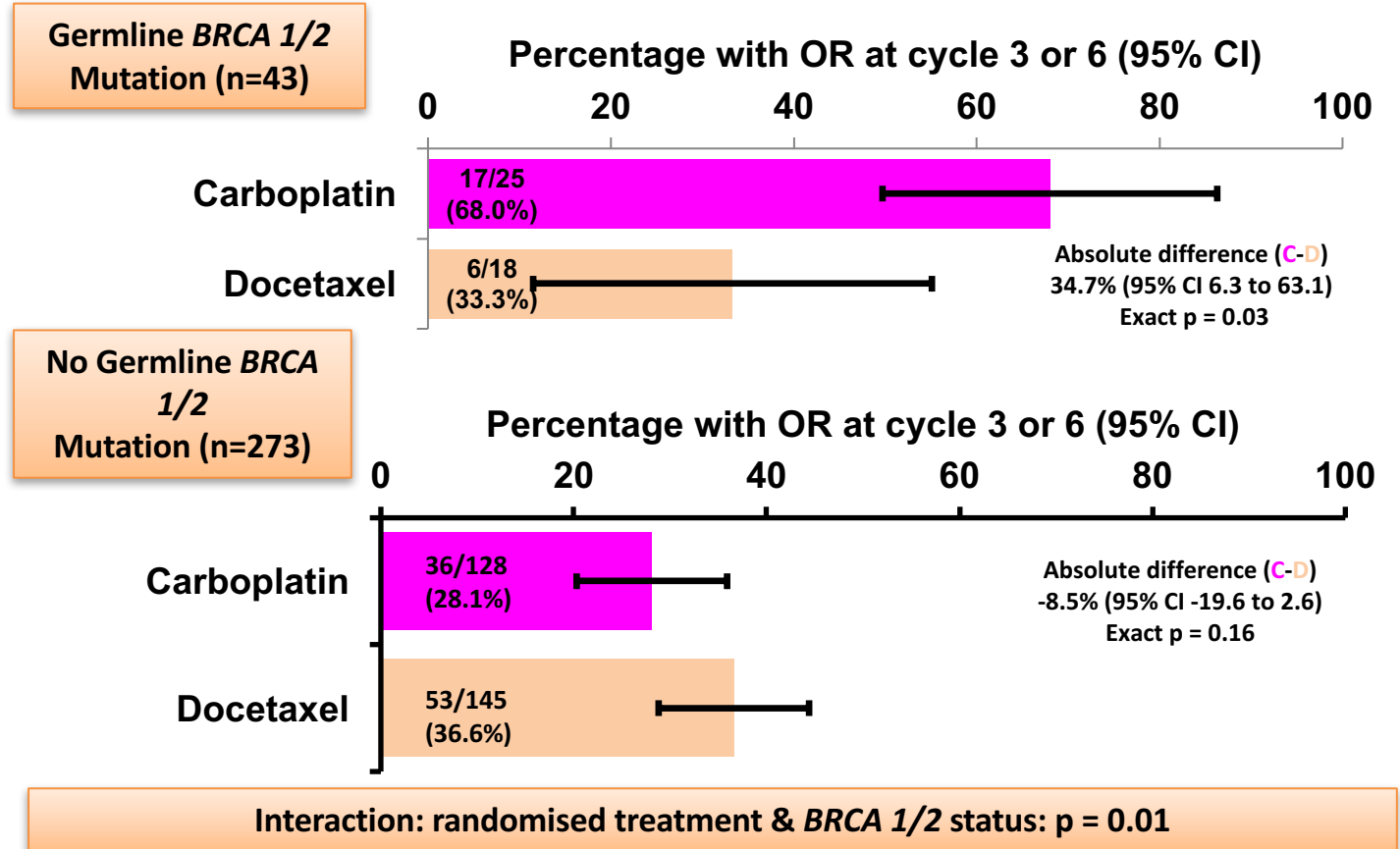
PET scans in March 2017 after response to cisplatin/gemcitabine and in summer of 2017 with progression pre-olaparib



Why are we concerned about the toxicity of PARPi?

- With advanced breast cancer, quality of life is paramount – thus, avoiding toxicity is key
- ALL treatments have some toxicity, so the decision tree must include benefit, degree of toxicity, quality of life, patient-related outcomes and also compliance/patient convenience
- Questions of sequencing of treatments must be considered, with toxicity being a key factor

TNT: Objective response – *BRCA* 1/2 status



TNT: Objective response – *BRCA* 1/2 status

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But the toxicity of both carboplatin and docetaxel needs to be considered

Long term treatment is difficult

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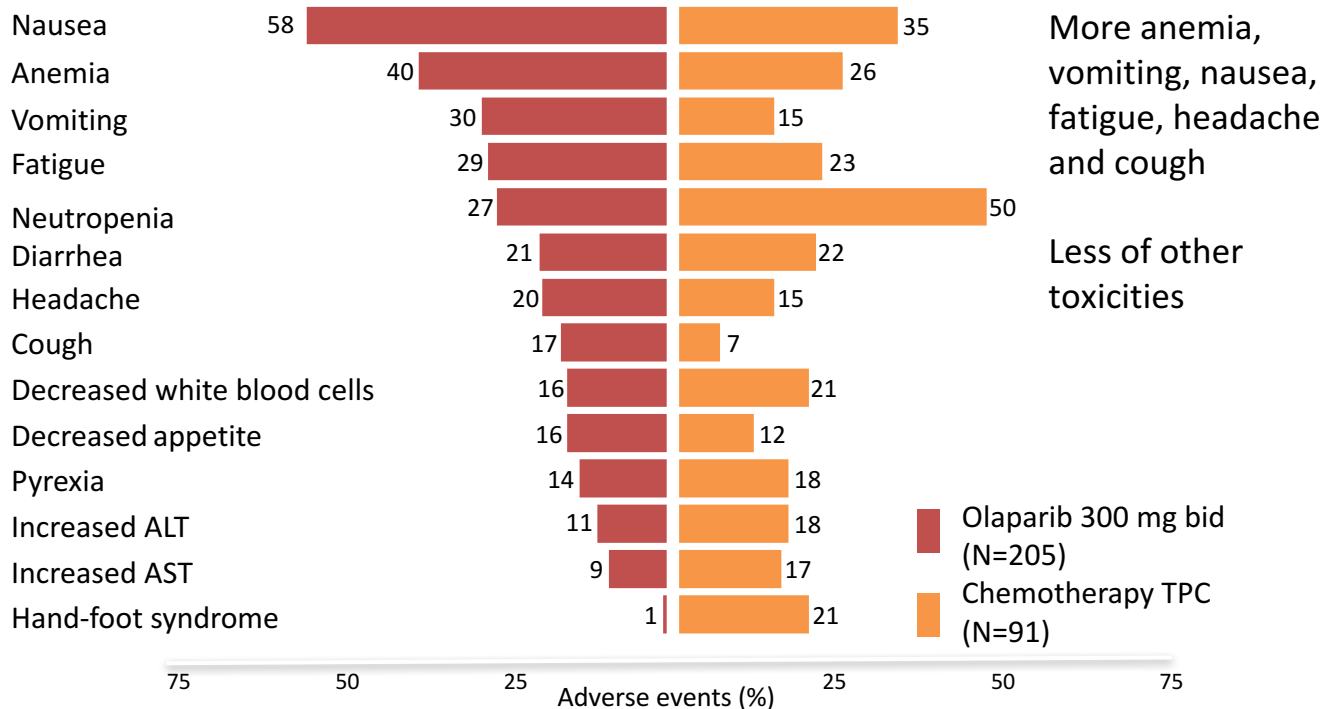
Ongoing toxicity

Need for intravenous infusions and ancillary medications

Frequent visits to the chemotherapy unit

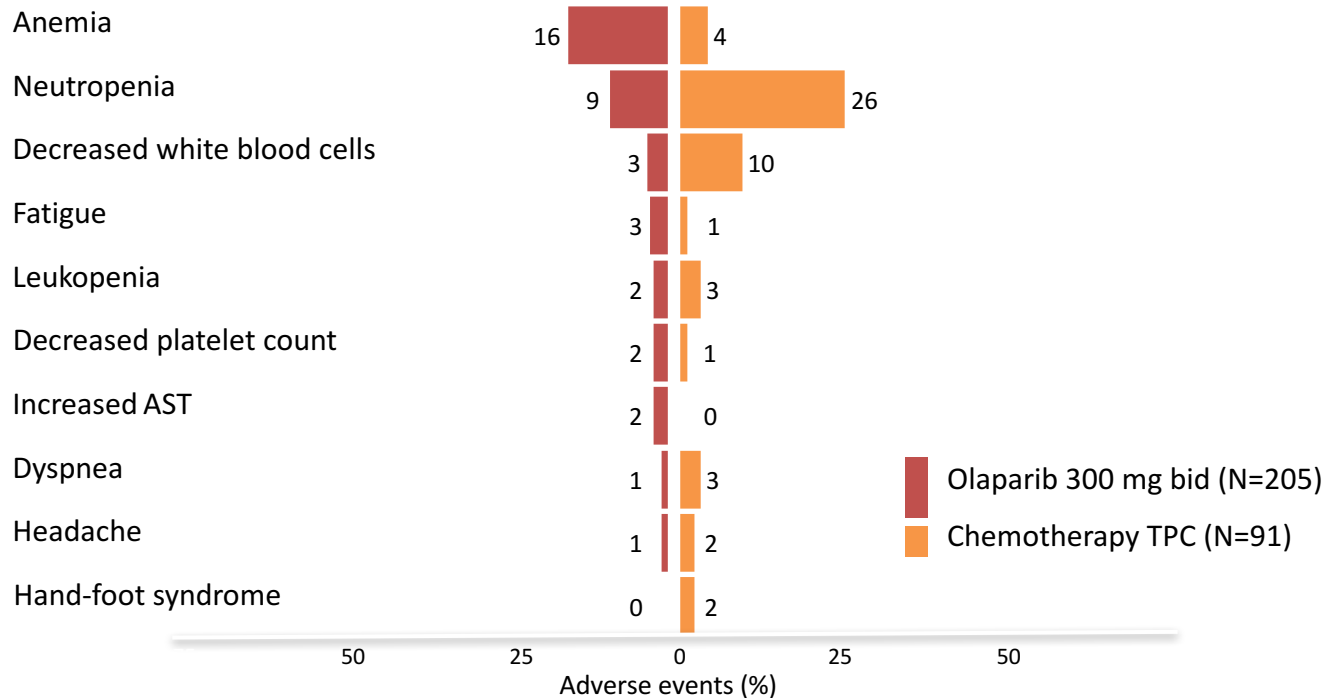
Interaction: randomised treatment & *BRCA* 1/2 status: $p = 0.01$

OLYMPIAD: Adverse events (any grade) in $\geq 15\%$ of patients



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

OLYMPIAD: Grade ≥ 3 adverse events in $\geq 2\%$ 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

Olaparib versus chemo TPC (OLYMPIAD trial)

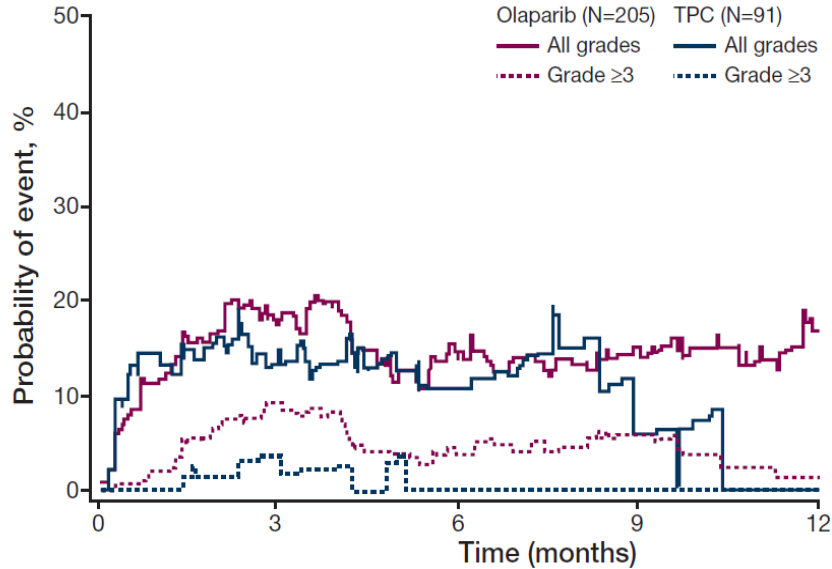
Summary of adverse events, all causality

n patients (%)	Olaparib 300 mg bid (N=205)	Chemotherapy TPC (N=91)
Grade 1–2	124 (60.5)	42 (46.2)
Grade ≥3	75 (36.6)	46 (50.5)
Death	1 (0.5)	1 (1.1)
Drug discontinuations	10 (4.9)	7 (7.7)
Dose reductions	52 (25.4)	28 (30.8)
Dose interruptions/delay	72 (35.1)	25 (27.5)

OLYMPIAD: Time curve of adverse events: anemia (olaparib)

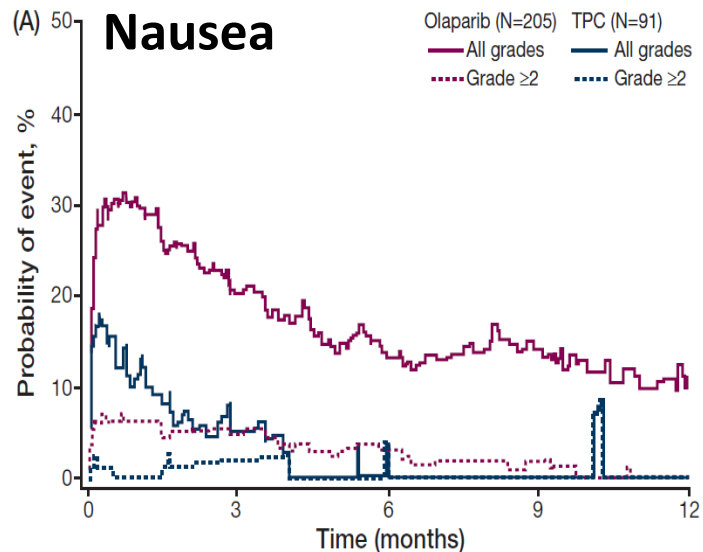
Prevalence of all and grade ≥ 3 anemia during the OlympiAD study

Anemia

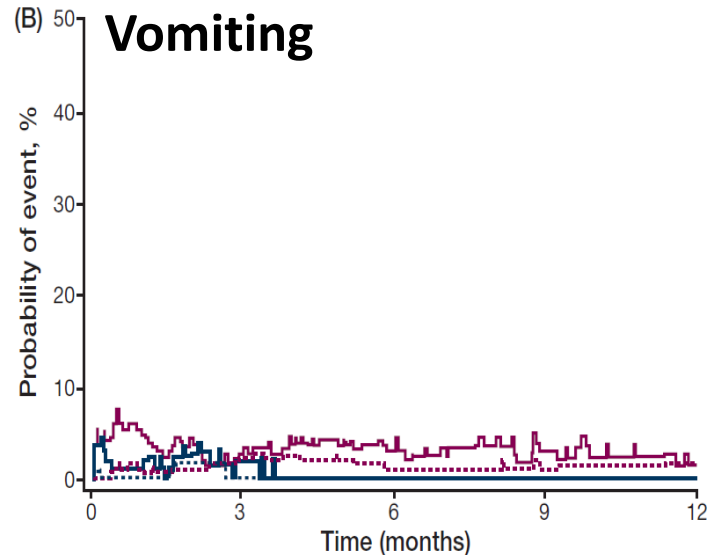


n at months	0	3	6	9	12
Olaparib	205	185	137	106	72
TPC	91	61	28	17	10

OLYMPIAD: Time curve of adverse events: nausea and vomiting (olaparib)



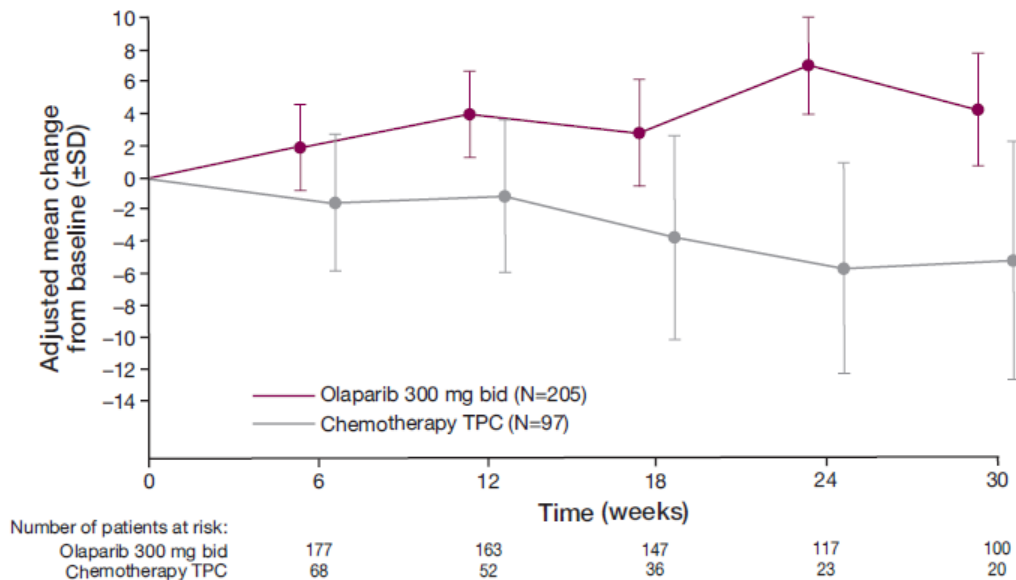
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QoL in the OLYMPIAD trial

Figure 2. Adjusted mean (\pm SD) change from baseline in global health status/QoL score across time points in patients in the olaparib and chemotherapy TPC arms



A higher score represents better overall health-related quality of life

Adjusted mean (\pm standard error) change from baseline in global health status/QoL score across all visits of 3.9 (\pm 1.2) versus -3.6 (\pm 2.2; **difference 7.5; 95% CI 2.48–12.44; p=0.0035**)

Robson et al, ESMO 2017, Abstract 4542, Poster No. 290P

Talazoparib in BRCA1/2 mutation carriers: ABRAZO trial

Safety – Hematologic

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, % (No.)	68.8 (33)	52.1 (25)	6.3 (3)	74.3 (26)	48.6 (17)	11.4 (4)
Anemia	50.0 (24)	33.3 (16)	0	54.3 (19)	37.1 (13)	0
Thrombocytopenia	37.5 (18)	16.7 (8)	4.2 (2)	25.7 (9)	11.4 (4)	5.7 (2)
Neutropenia	20.8 (10)	12.5 (6)	0	34.3 (12)	17.1 (6)	0
Leukopenia	14.6 (7)	2.1 (1)	0	17.1 (6)	5.7 (2)	0
Platelet count decreased	14.6 (7)	6.3 (3)	2.1 (1)	14 (5)	2.9 (1)	5.7 (2)

Transfusions: 1 patient with platelet transfusion, 23 patients (28%) with packed red blood cells.

Hemorrhage: 1 grade 3 hemorrhage (transient epistaxis).

Neutropenic sepsis in 1 patient; 2 patients required growth factor support.

No acute myeloid leukemia or myelodysplastic syndrome.

Talazoparib in BRCA1/2 mutation carriers: ABRAZO trial

Safety – Nonhematologic

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, % (No.)	97.9 (47)	22.9 (11)	4.2 (2)	97.1 (34)	28.6 (10)	2.9 (1)
Fatigue	60.4 (29)	6.3 (3)	0	22.9 (8)	0	0
Nausea	41.7 (20)	4.2 (2)	0	42.9 (15)	0	0
Diarrhea	35.4 (17)	2.1 (1)	0	28.6 (10)	0	0
Decreased appetite	22.9 (11)	2.1 (1)	0	25.7 (9)	0	0
Dyspnea	22.9 (11)	2.1 (1)	2.1 (1)	25.7 (9)	5.7 (2)	0
Alopecia (grade 1)	22.9 (11)	0	0	20.0 (7)	0	0
Back pain	22.9 (11)	0	0	20.0 (7)	0	0
Vomiting	20.8 (10)	0	0	20.0 (7)	0	0
Pleural effusion	8.3 (4)	6.3 (3)	0	11.4 (4)	5.7 (2)	0

No grade 5 TEAEs were observed; no clinically significant cardiovascular toxicity.
All TEAEs in ≥ 20% of patients and grade 3+ TEAEs in ≥ 5% of patients.

BROCADE2 study: VELIPARIB + C/P

Veliparib does not add significant toxicity to C/P

	Placebo + C/P (n=96)	Veliparib + C/P (n=93)
Grade 3/4 AE	80 (83.3)	73 (78.5)

Common hematologic grade 3/4 AEs, n (%)

Anemia	17 (17.7)	16 (17.2)
Febrile neutropenia	3 (3.1)	8 (8.6)
Leukopenia	11 (11.5)	15 (16.1)
Neutropenia	53 (55.2)	52 (55.9)
Thrombocytopenia	25 (26.0)	29 (31.2)

Common non-hematologic grade 3/4 AEs,
N (%)

Diarrhea	7 (7.3)	4 (4.3)
Drug hypersensitivity	0	5 (5.4)*
Fatigue	8 (8.3)	5 (5.4)
Peripheral neuropathy	5 (5.2)	7 (7.5)

* Statistically significant

Long term safety of PARPi: hematological malignancies

Long term incidence of AML, MDS, CMML in germline mutant carriers in phase III studies

Trial	Context	Treatment arm	Placebo arm
SOLO2	<ul style="list-style-type: none">Maintenance olaparib vs placebo, ovarian cancerGermline BRCA1/2 mutation	2% (med FU 22.2 months, med treatment duration 19.1 months)	4% (med FU 22.1 months, med treatment duration 5.5 months)
NOVA	<ul style="list-style-type: none">Maintenance niraparib vs placebo, ovarian cancerBoth sporadic and germline BRCA1/2 mutation	1,4% (med FU 16.9 months)	1,1% (med FU 16.9 months)
OLYMPIAD	<ul style="list-style-type: none">Olaparib vs placebo, breast cancerGermline BRCA1/2 mutation	0% (med FU 14.5 months)	0% (med FU 14.1 months)

FU: follow-up; med: median; AML: acute myeloblastic leukaemia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukaemia

CHALLENGE – WHERE do PARPi fit in the Decision Tree for ABC

- TNBC
- Other options for treatment are chemo
- PARPi may be better tolerated than IV chemo
- ? Compared to newer targeted therapies?
- Combo – Toxicity may increase with PARPi + IO?
Or PARPi + other
- LUMINAL BRCA+
- Better option than IV chemo but no data yet for sequencing
- ? CDK4/6 + ET vs PARPi which is the better 1st line ?
- ? PARPi + ET?
- Sequential single agent therapy?
- Duration of response

Summary

- Advanced breast cancer treatment – GOAL – prolong good quality of life
- PARPi appear to be very similar in toxicities, less toxicity seen in veliparib studies but less benefit
- Data from ovarian studies on toxicity is very similar
- Nausea/vomiting most common in first month of olaparib and can be managed by antiemetics or lower dose
- Anemia common but generally mild to moderate
- Other toxicities low grade and manageable
- PARPi compares well to other treatments for advanced breast cancer in terms of maintaining quality of life