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Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial.

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Disclosures

- A.O. and J.d.B. have served as advisors to Astra-Zeneca.

- The Institute of Cancer Research is a joint applicant for the patent entitled ‘DNA damage repair inhibitors for treatment of cancer’ which includes the granted application US8143241.

Background

1. Synthetic lethality between PARP inhibition and DNA repair aberrations including BRCA1 and BRCA2 loss.
2. Clinical trials reported antitumour activity with PARPi in BRCA mutation carriers including CRPC.
3. PARPi have antitumour activity in *BRCAness* cancers.
4. Sporadic CRPC can have DNA repair defects with preliminary evidence for antitumor activity with PARPi

1) Farmer et al, Nature 2005; 2) Fong et al, NEJM 2009; 3) Edwards et al, Nature 2008 ; Fong et al, JCO 2010, 4) Grasso et al, Nature 2012; Sandhu et al, Lancet Oncology 2013

Trial design

- **Investigator-initiated phase II trial.**
  - NCT-01682772; CR-UK/11/029.
- **Adaptive design** for biomarker-driven selection based on response rate, multi-stage.
  - Test set (all comers) and validation set (biomarker driven)
- Open label, Olaparib (tabs) 400mg BID.

STUDY OBJECTIVES

- To evaluate antitumour activity of olaparib in mCRPC.
- To identify molecular signatures for PARP inhibitor antitumour activity.

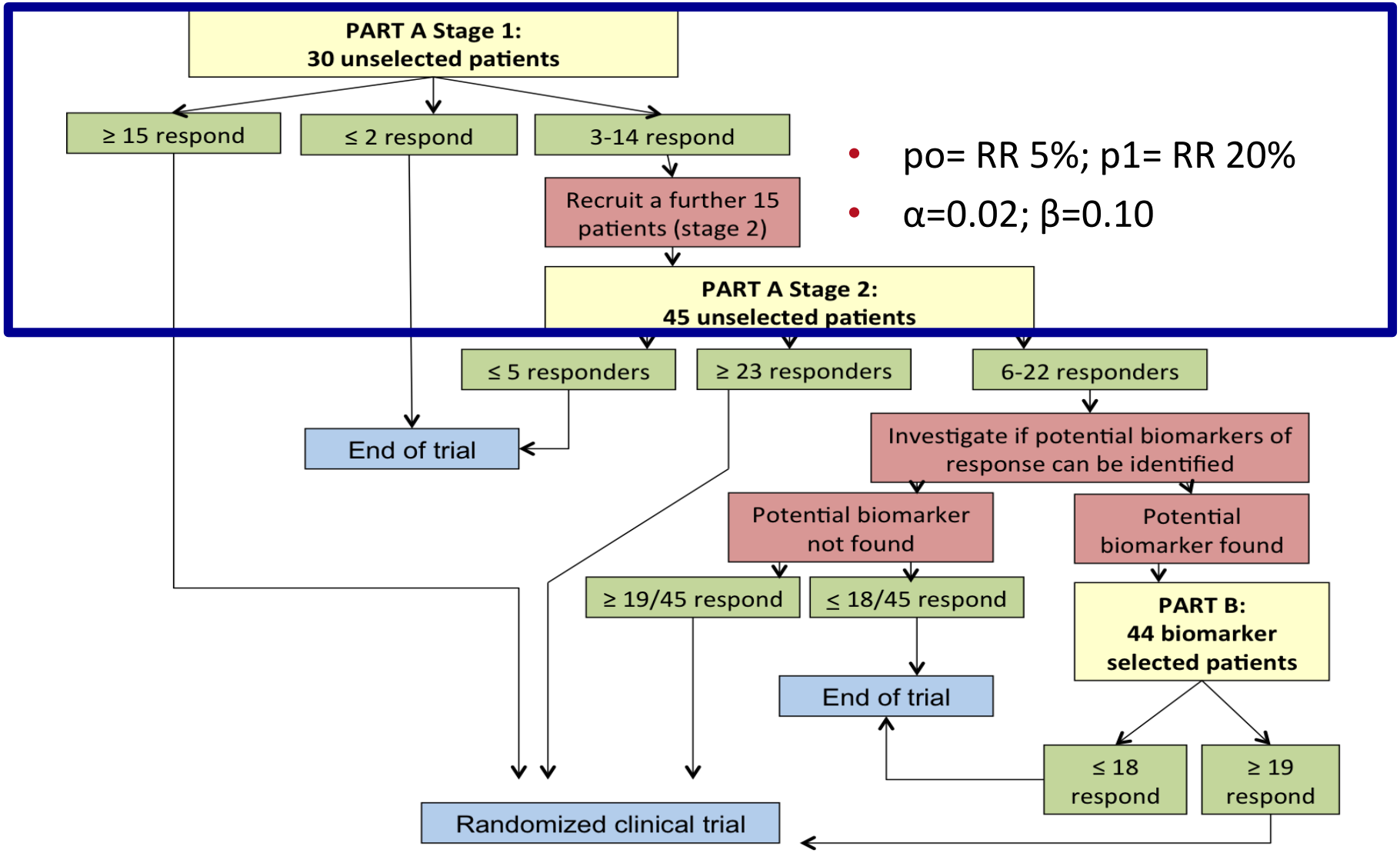
Trial design

- **Primary endpoint: RESPONSE RATE**
  - **Response as per RECIST 1.1**
  - **PSA decline ≥50% (PCWG-2)**
  - **CTC conversion (≥5 to <5/7.5ml)**

    Confirmed by a second assessment ≥4 weeks later

- Secondary endpoints: PFS, rPFS, OS, time to PSA progression (PCWG-2), time to radiological progression, rate of CTC conversion, duration of responses, safety-tolerability.
- Exploratory endpoints:
  - Study of **diffusion-weighted MRI** as response biomarker
  - QOL studies (pain improvement)

Trial design



Biomarker studies

- Mandated pre-and post-treatment tumour biopsies.
- Including studies of DNA repair aberrations:
  - Whole exome and transcriptome in pre-dose samples.
  - Study of circulating tumour DNA in plasma.
- PD studies (markers of DNA damage) in tumour tissues.

Trial population

- Metastatic CRPC after 1-2 lines of taxane chemotherapy.
- Documented progressive disease by RECIST or PSA (PCWG2).
- ECOG Performance Status 0-2.
- Appropriate organ-function: Hb >10g/l, Neut>1.5x10^9/l, Plt>100x10^9/l, Bilir<1.5x ULN, AST/ALT<2.5x uLN (x5 liver mets), Creatinine<1.5x ULN.
- No prior PARPi, platinum, cyclophosphamide or mitoxantrone.
- **CTC count of ≥5 cells/7.5mls blood at screening.**

Baseline characteristics

Patients screened	51
Patients dosed	31
Evaluable for response	30

Median age (range)	67.5 y (40-79)
ECOG-PS 0-1	24 (80%)
ECOG-PS 2	6 (20%)
Bone M1	**29 (96.6%)**
Visceral M1	**9 (30%)** **Lung: 1 (3.3%)** **Liver: 8 (26.6%)**

Prior lines of treatment	n (%)
Docetaxel	**30 (100%)**
Cabazitaxel	**17 (56.7%)**
Abiraterone	**29 (96.7%)**
Enzalutamide	5 (16.7%)
Palliative radiotherapy	16 (53.3%)

Baseline blood test results	Median (IQR)
Haemoglobin (g/L)	106 (102-113)
LDH (U/L)	235 (178-484)
Alkaline Phosphatase (U/L)	**168 (84-374)**
PSA (ng/ml)	405.5 (141-1095)
CTC count/7.5ml blood	**42.5 (16-110)**

Treatment emerging AEs

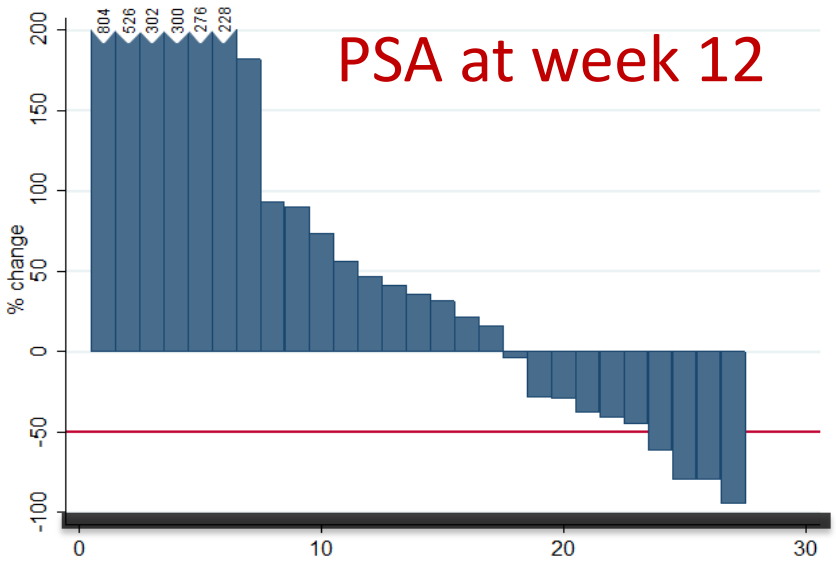
Event	All grades	Grade 3-4
Anaemia	25 (83.3%)	**6 (20%)**
Fatigue	20 (66.7%)	3 (10%)
Pain	11 (36.7%)	1 (3.3%)
Nausea	**11 (36.7%)**	-
Dyspnoea	8 (26.7%)	1 (3.3%)
Anorexia	7 (23.3%)	-
Cough	7 (23.3%)	-
Leg oedemas	7 (23.3%)	-
Diarrhoea	7 (23.3%)	-
Constipation	6 (20%)	-
Vomiting	**5 (16.7%)**	-
Thrombocytopenia	5 (16.7%)	**2 (6.7%)**

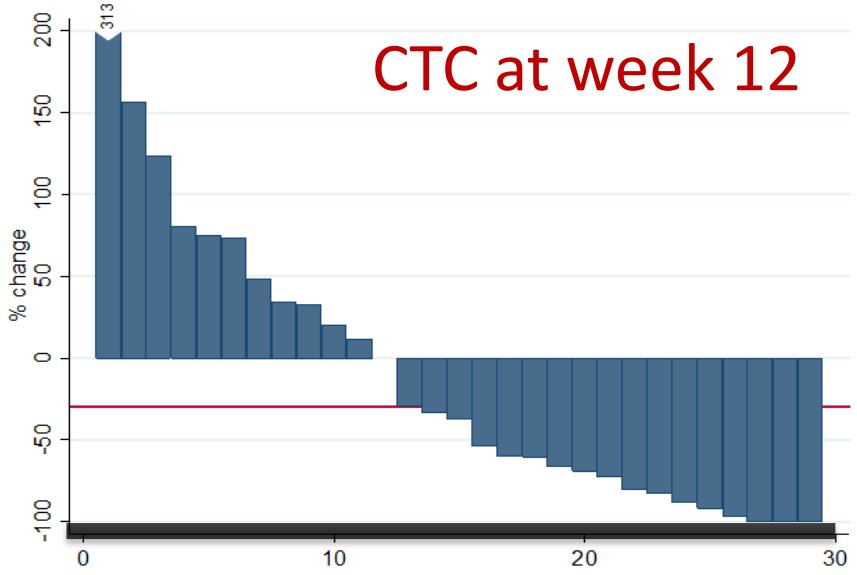
7 pts (23%) required a **dose reduction** (300mg BID, tablet) mainly due to anaemia (5).

Primary endpoint assessment

- 10 responses among the first 30 patients.
- RR 33% (95% C.I. 17.3%-52.8%)

	Median time on treatment	Range
RESPONDERS	7.8 months	2.8*-14.4
NON RESPONDERS	2.7 months	0.2- 5.6





** Patient still receiving treatment, follow-up cut-off Aug 2014.*

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Results: primary endpoint RR

Responder	Max PSA decline	Measurable disease CT?	Best RECIST response (if measurable)	CTC conversion	Baseline CTC count (x/7.5ml)	Max CTC decline	Time on treatment (weeks)
1	No decline	YES	PD	YES	6	83%	12
2	**47%**	NO		YES	**38**	**95%**	**62**
3	**95%**	YES	**PR**	YES	**8**	**100%**	24
4	**59%**	YES	SD	YES	**22**	**100%**	**36+**
5	**80%**	NO		UNCONF	**87**	**100%**	**42+**
6	**80%**	YES	**PR**	YES	**18**	**100%**	**36**
7	**29%**	YES	SD	YES	**105**	**97%**	17
8	**83%**	NO		YES	**102**	**100%**	**39**
9	**51%**	NO		YES	**24**	**100%**	**32+**
10	No decline	YES	SD	YES	38	100%	12+

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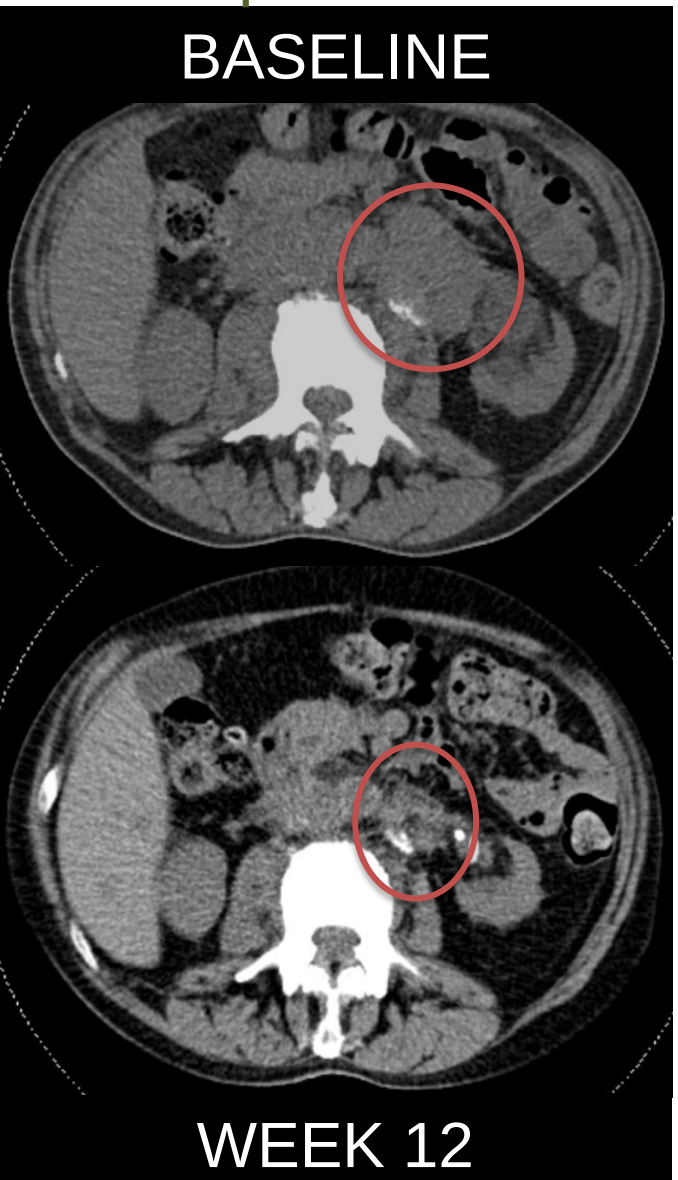
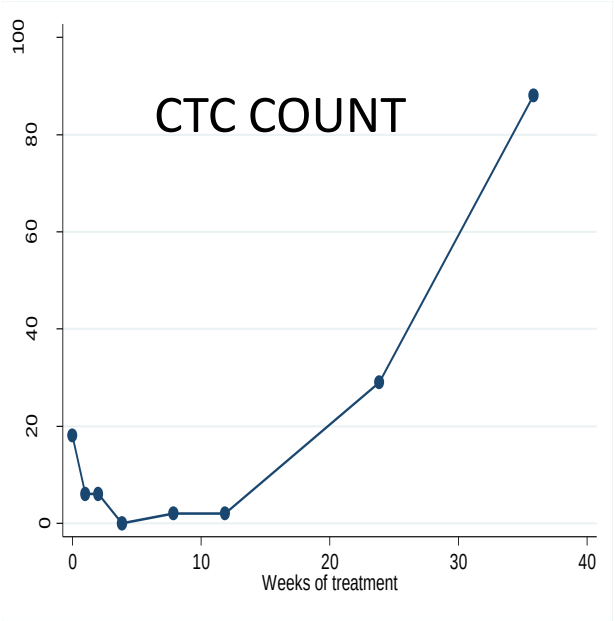
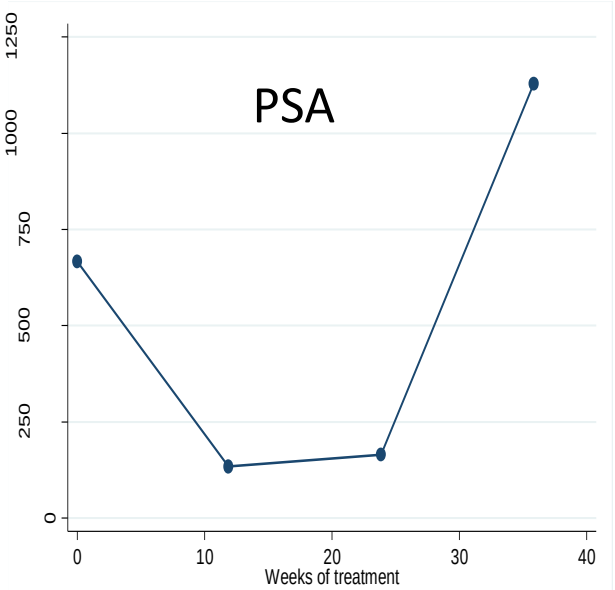
Olaparib induces responses in mCRPC

Example case 1





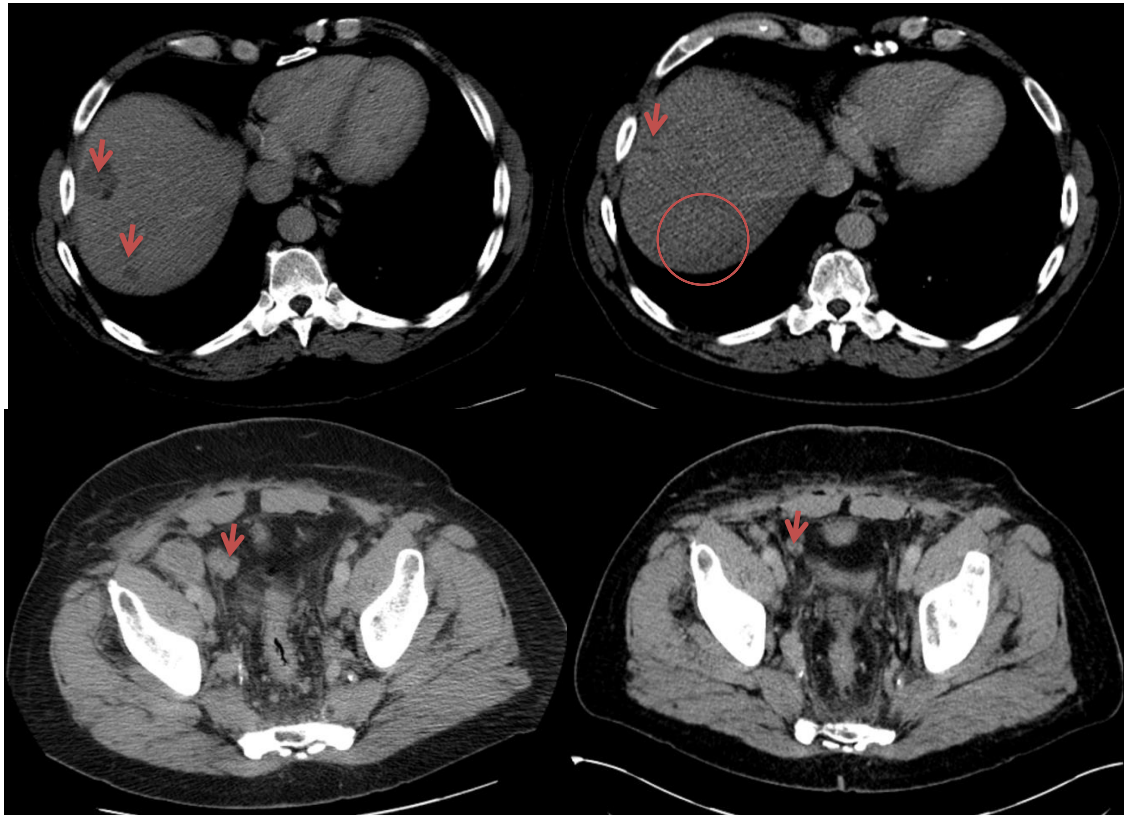


- Durable radiological PR, with progression after 9 months.
- Previously unreported germline BRCA2 mutation + loss of 2nd copy in tumor (no family history of cancer)

Example case 2

Patient with somatic DNA repair defects respond to Olaparib

BASELINE WEEK 12



- Somatic DNA analysis:
  - One copy loss BRCA2
  - Fs substitution in the other BRCA2 allele.
- Germline DNA: conserved both copies of BRCA2.

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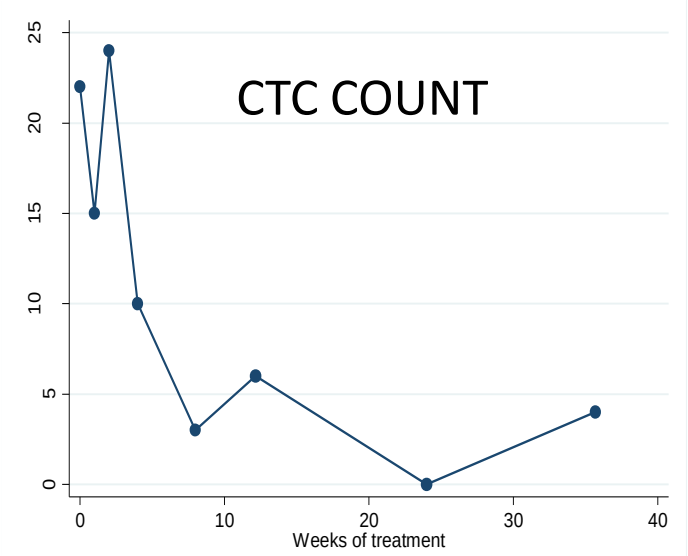
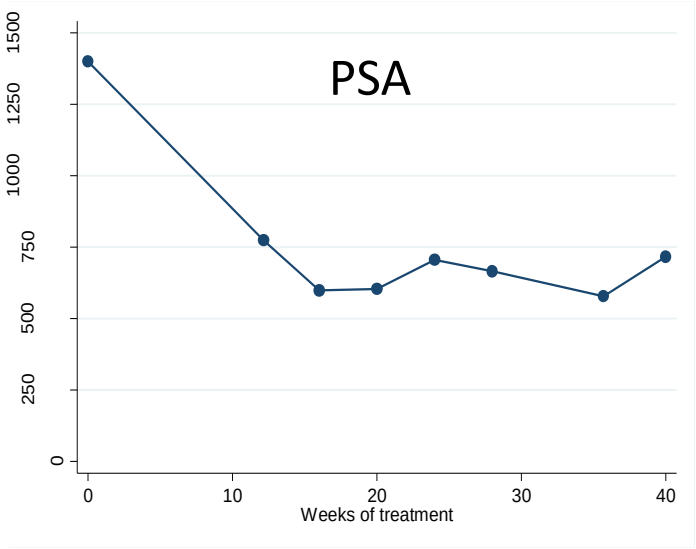
Patient with somatic DNA repair defects respond to Olaparib

Example case 3

- Prolonged response in a patient post docetaxel, cabazitaxel, abiraterone and enzalutamide.
- The patient is still responding after 10+ months. Has stopped opioids and his mobility has improved.
- Germline FS del ATM + LOH in tumor.
- Transcriptome analysis: very low ATM expression in tumor.



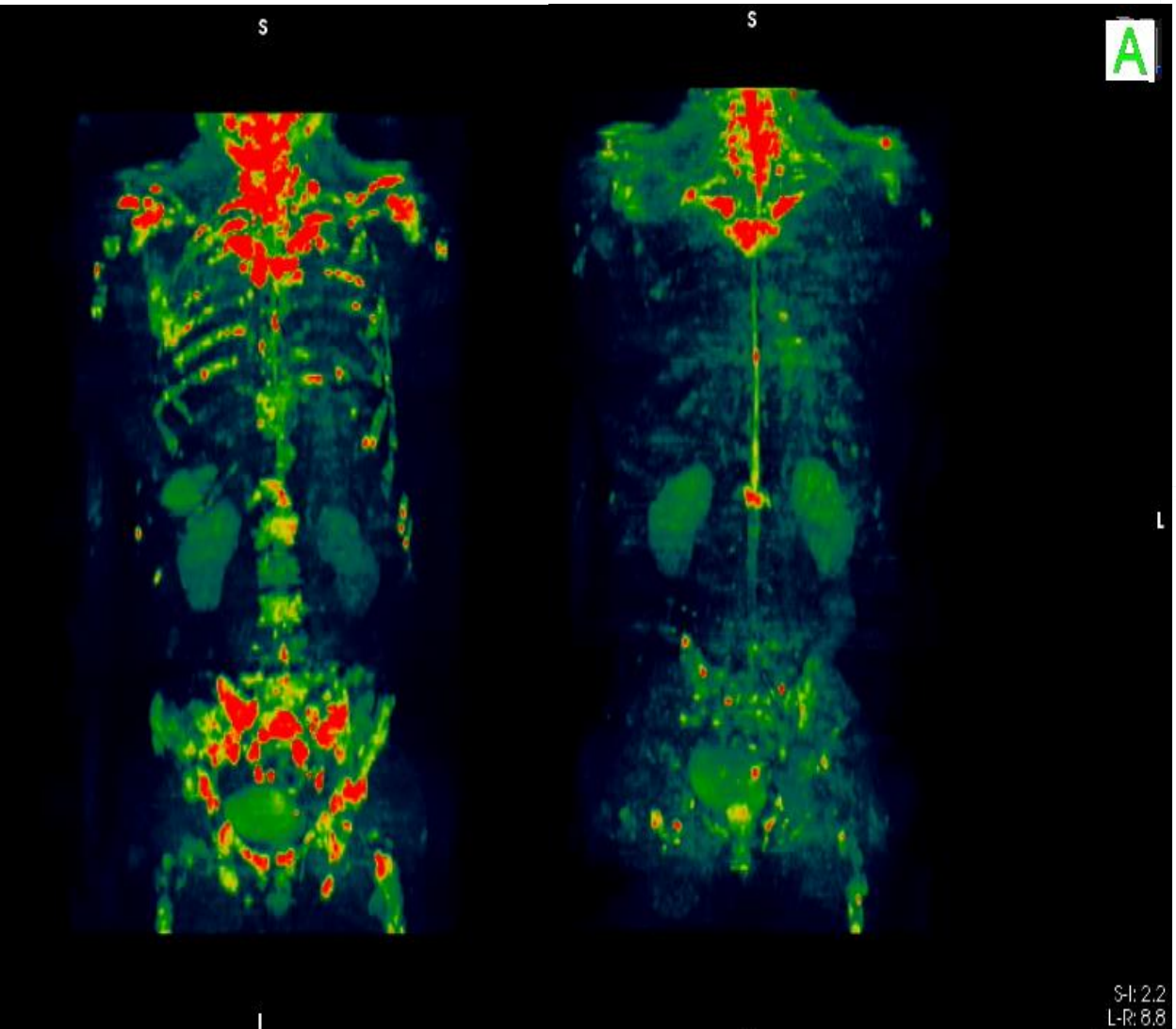


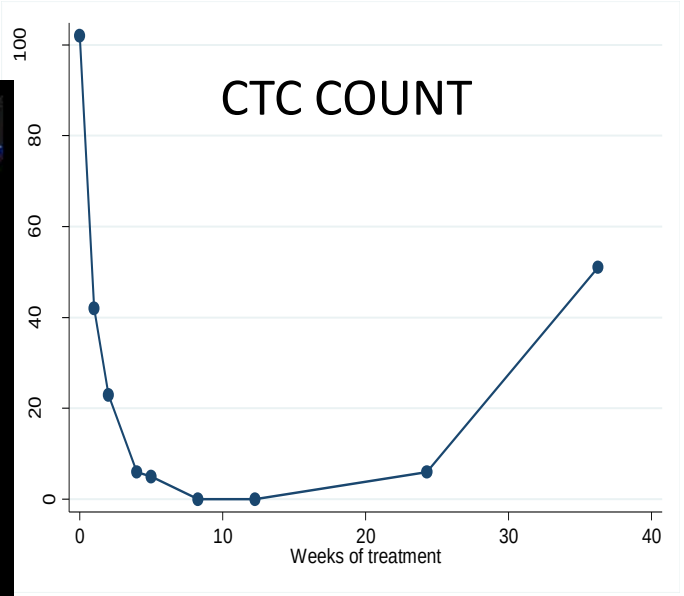
Radiological assessment of response in patients with bone-only disease

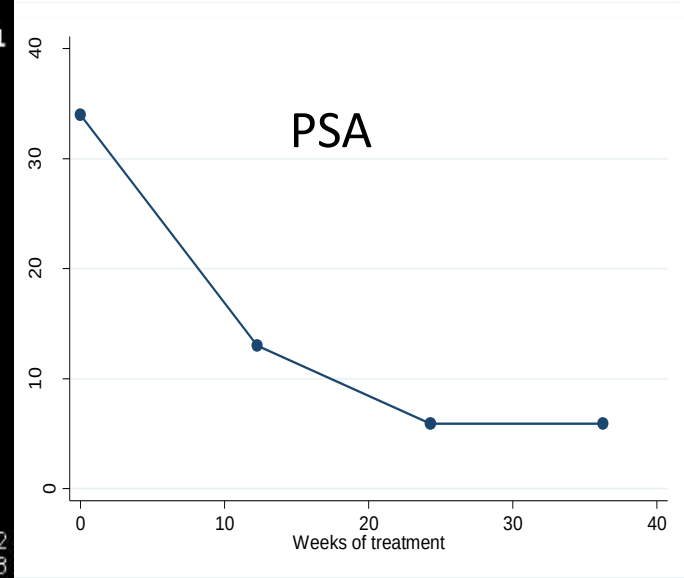
Example case 4

BASELINE

WEEK 24



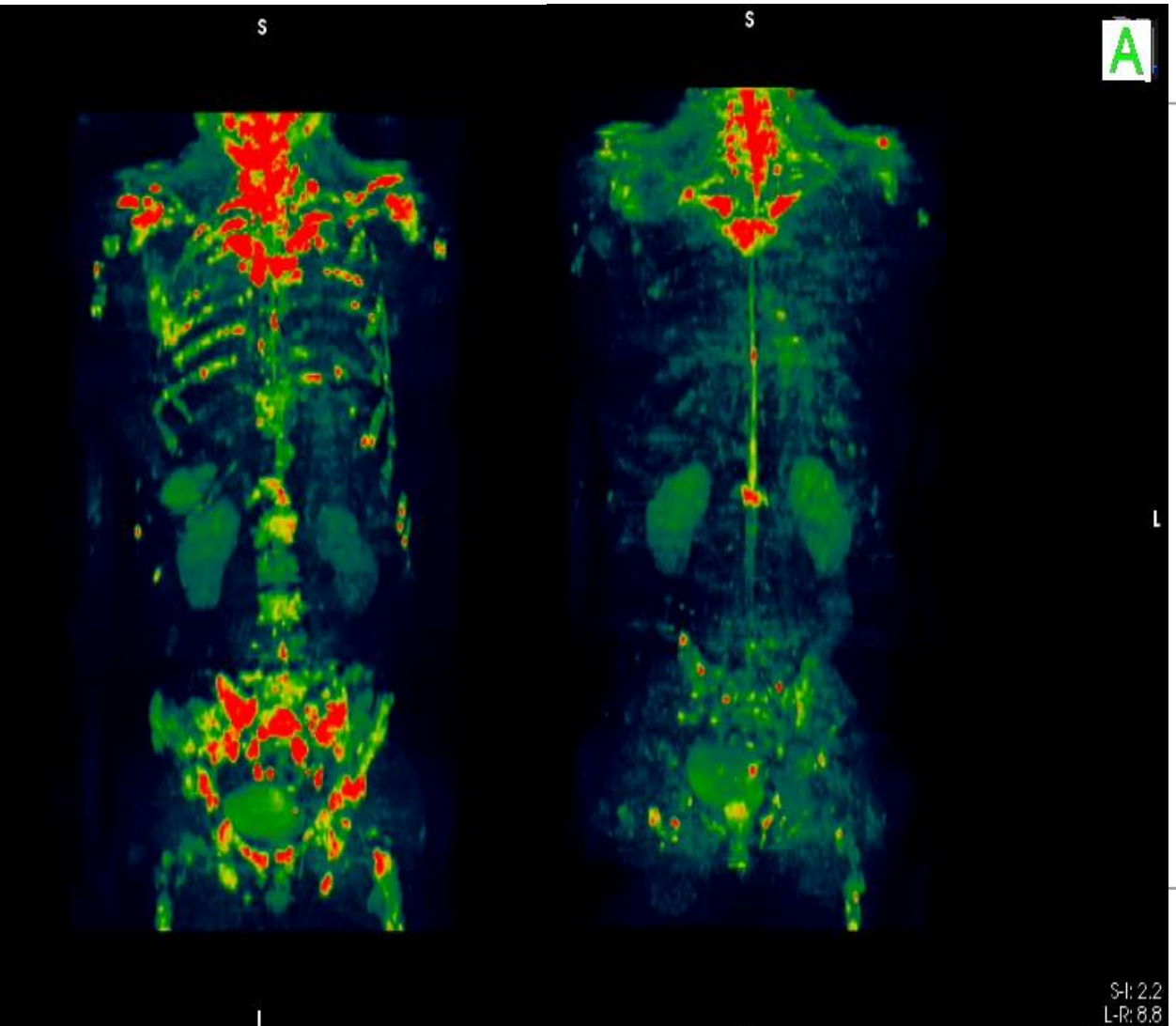


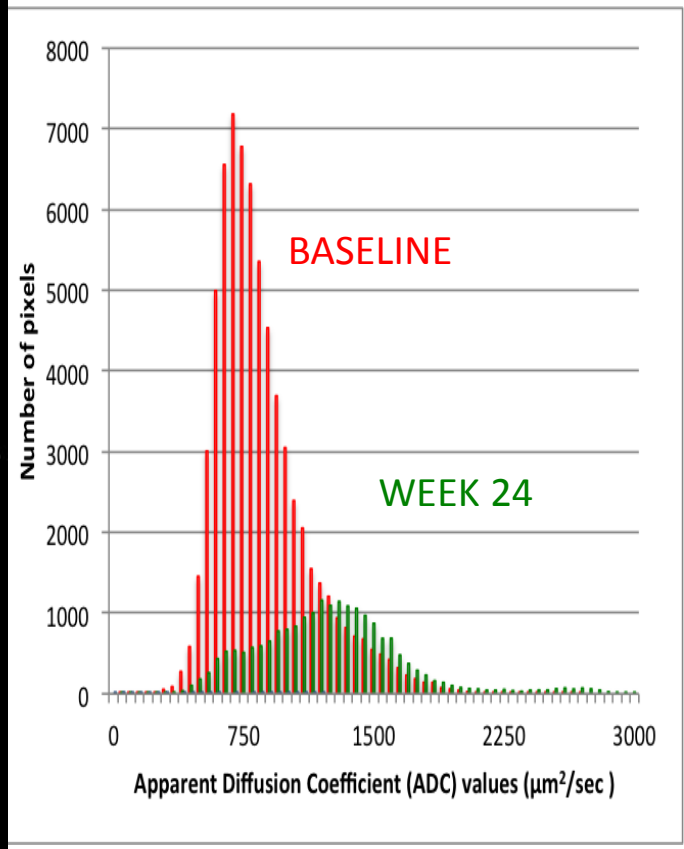


Radiological assessment of response in patients with bone-only disease

Example case 4

BASELINE WEEK 24



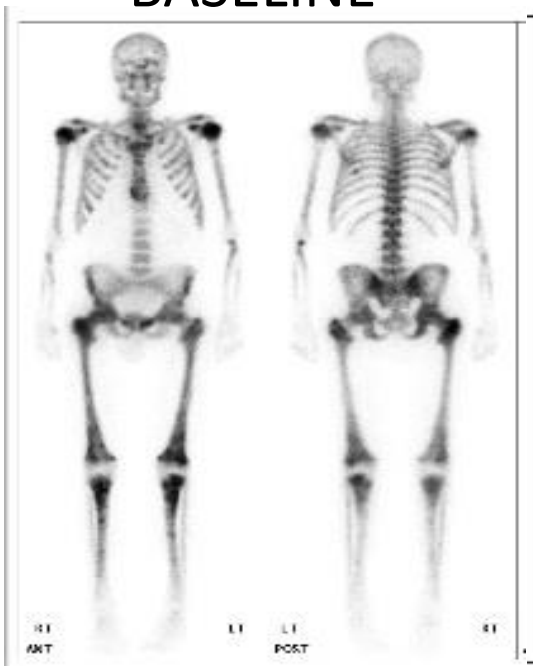


Durable responses to Olaparib

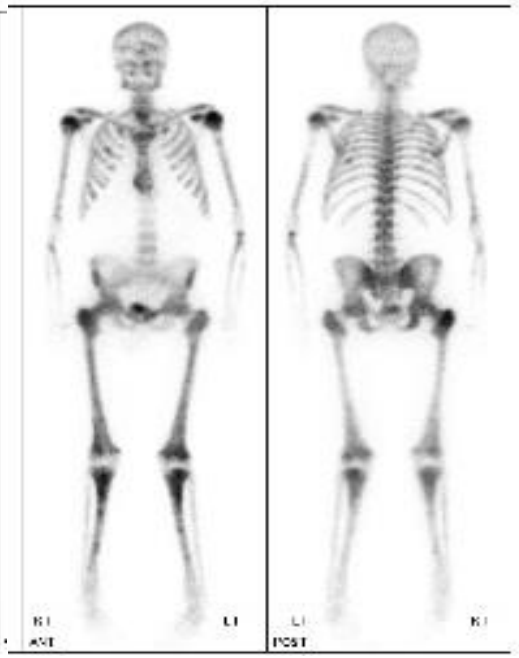
Example case 5

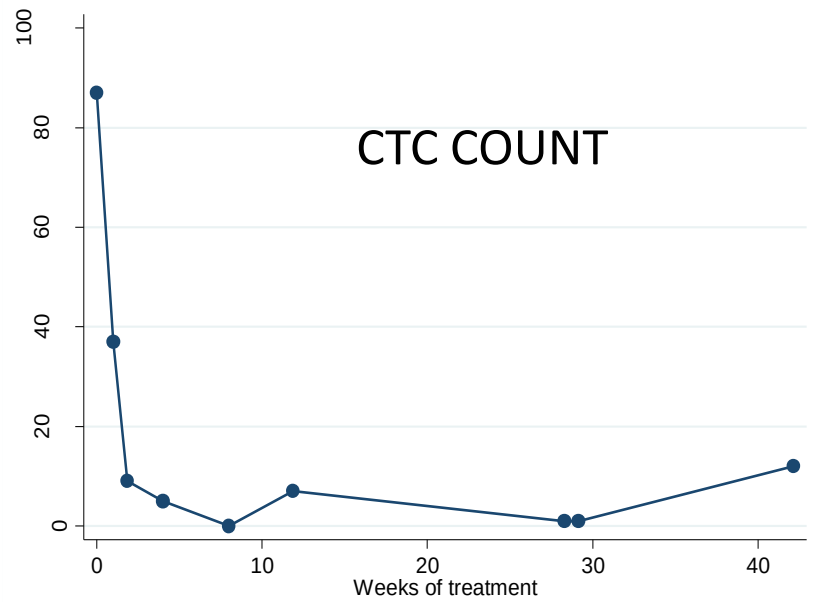
- Maintained response in a patient dose-reduced to 300mg BID (tablet).

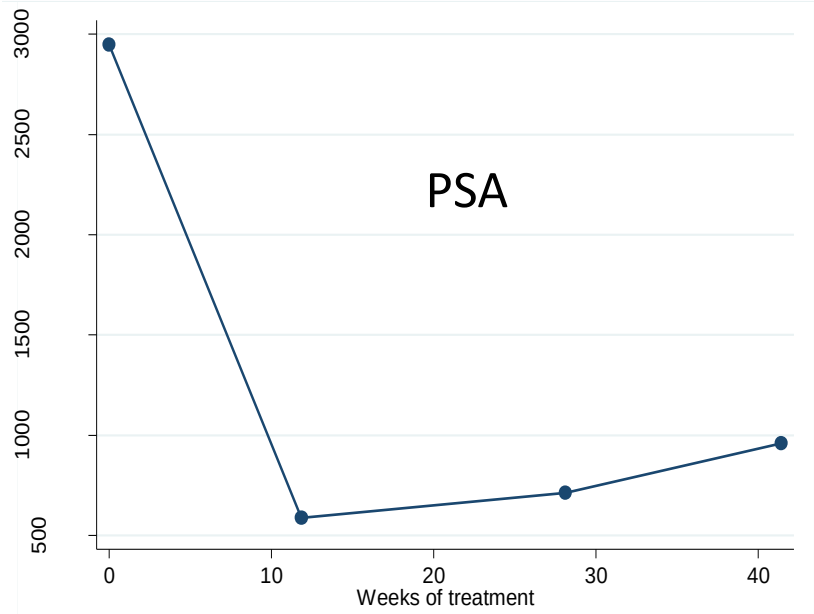
BASELINE

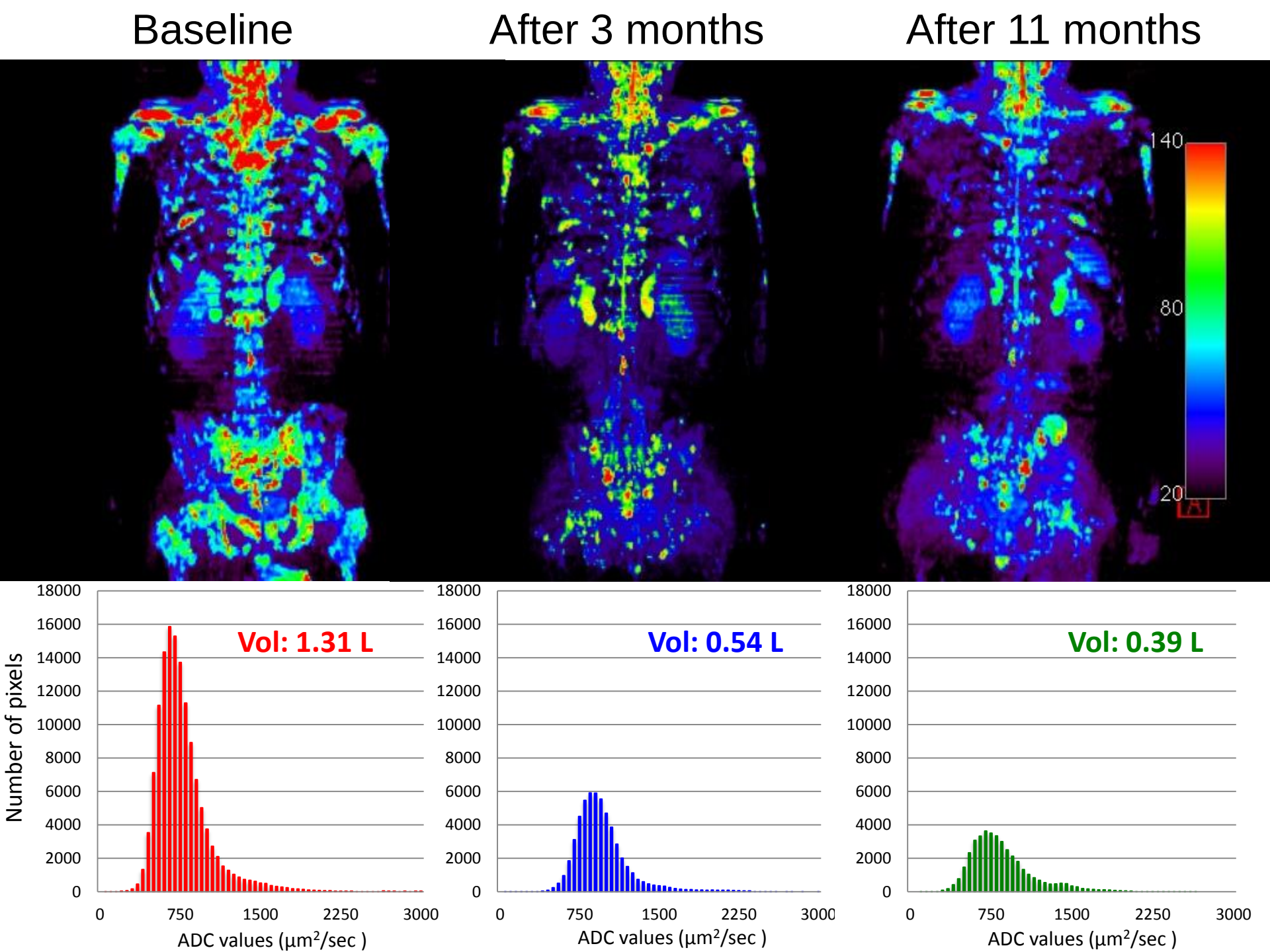


WEEK 12








Baseline
After 3 months
After 11 months
140
80
20
Vol: 1.31 L
Vol: 0.54 L
Vol: 0.39 L
Number of pixels
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
750
1500
2250
3000
ADC values (µm²/sec)

Conclusions

- **PARP inhibition with olaparib has antitumour activity in heavily pretreated, sporadic, unselected, CRPC.**
- Olaparib is well tolerated. Toxicities, mainly anaemia, was managed with dose interruptions and reductions.
- Loss of function of DNA repair genes, such as BRCA2 and ATM was identified in responding patients.

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