Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced germline BRCA2 mutant prostate cancer

Therapeutic exploitation of the synthetic lethality between poly (ADP-ribose) polymerase (PARP) and BRCA1/2 is highly promising [1]. Trials have focused on ovarian and breast cancers with limited data available for BRCA1/2 mutant prostate cancer (PCa). Emerging data suggest that homologous recombination (HR) defects are common in PCa, potentially conferring a BRCA1ess phenotype [2]. PARP is also implicated in ERG transcription and androgen receptor (AR) signaling, key drivers in PCa. PARP inhibition results in antitumor activity in ERG rearranged cancer models and suppresses AR target gene expression and tumor proliferation [3, 4].

Four patients with advanced PCa and germline BRCA2 mutations were treated on three phase I studies- olaparib bioavailability (NCT00777582), olaparib dose-escalation and MK-4827 (NCT00749502) [1]. Methodology, clinical, pathological and molecular data are detailed in Table 1 and Supplementary Data S1 to S3. The median age at diagnosis was 58 years (range: 47–65); The Gleason score ranged between 6 and 9. All patients had bone metastases at diagnosis and subsequently developed visceral and/or soft tissue disease. An increased incidence of visceral metastasis was reported in BRCA1/2 mutant ovarian cancer but not previously described in PCa. The median duration to castration-resistance was 18 months (range 10–28). PSA and radiological responses lasting 34 and 26 months were noted in two patients treated with olaparib with a further patient having disease stabilization for 10 months. One patient exhibited primary resistance to MK-4827.

Molecular analyses focused on key events in prostate carcinogenesis. ERG rearrangements and positive ERG immunostaining were observed in all cases. All patients exhibited either heterozygous or homozygous PTEN allelic loss with the corresponding negative PTEN immunostaining. Massively parallel DNA sequence analysis carried out on tumor tissue obtained from a BRCA2 c.6174delT allele carrier progressing after 34 months of olaparib treatment did not identify secondary BRCA2 mutations (PMID: 18264088) as a putative resistance mechanism (Supplementary Data S1, S3 and Figure 3, available at Annals of Oncology online).

To our knowledge, this report is the largest account of BRCA2 mutant carriers with PCa treated with PARP inhibitors (PARPis) to date. The higher frequency of ERG rearrangements (four out of four cases) compared with the expected rate of 50%–60% in sporadic PCa supports the hypotheses that these gene rearrangements are accelerated in the presence of underlying HR defects [5]. One patient with an ERG rearrangement had a 44-month response to abiraterone and subsequently responded to olaparib. The increased incidence of ERG rearrangements in BRCA2 mutant carriers coupled with our previous data showing ETS rearrangements predict for improved response to abiraterone implies that targeting AR signaling may also be beneficial for these patients (PMID: 19339269).

PARPis are the first molecular stratified treatment for BRCA1/2 mutation carrier PCa patients and has promising antitumor activity. Importantly, the HR/PARP synthetic lethal paradigm may be more broadly relevant in PCa with germline or somatic inactivating mutations in HR DNA repair genes such as CHEK2, BRIP1/FANCJ, NBS1 BRCA1 and ATM, collectively reported to occur in 20%–25% of PCas [2].

Future studies of PARPis in sporadic PCa will need to address critical issues, including identifying predictive biomarkers of HR defects, incorporating biomarkers of efficacy beyond PSA and investigating mechanisms of resistance.

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Table 1: Summary of patient demographics, clinicopathological parameters, responses and molecular profiling studies in prostate cancer patients with BRCA2 mutations treated on a poly (ADP-ribose) polymerase inhibitor (PARPi)

| Pt Characteristics at diagnosis (age, stage, histology, Gleason score, PSA) | Prior treatments, duration, and response | PARP inhibitor treatment (response, PFS, toxicity, reason for progression) | Subsequent therapies and follow-up | BRCA 2 mutations | PTEN IHC | PTEN FISH | ETS rearrangements | ERG IHC |
|---|---|---|---|---|---|---|---|---|---|
| 1 58 years, T3N0M1 (bone), adenocarcinoma, Gleason 4 + 3, PSA 4.7 | Androgen blockade (LHRH, Bicalutamide): PFS: 27.6 months, PSA nadir 0.59 | Olaparib: 200 mg capsules bd; PSA fall from 1.8 to 0.27 µg/l (−85%); No soft tissue disease; 34 months on treatment; Toxicity: anemia; Treatment ceased: due to locally progressive disease in the prostate requiring TURP and radiotherapy | Second line therapy: Carboplatin AUC6: PD after two cycles; Third line therapy: docetaxel (8 cycles) with good clinical and PSA response; PSA nadir <0.04; Patient alive 8 years after diagnosis of metastatic PCa | BRCA2 6172delT mutation | Cytoplasmic and nuclear staining: negative | PTEN+/- | ERG rearranged (Edel) ETV1 not rearranged | Positive |
| 2 47 years, T1cN1M0 adenocarcinoma, Gleason 3+3, PSA 5.9 | Radical radiotherapy: to the prostate, recurrence after 3 years; Androgen blockade (LHRH, bicalutamide): PFS: 24 months | Olaparib: 200 mg capsules bd; 11 months on treatment; Best response: SD; PSA fall from 3.1 to 2.7 µg/l (−12%) | RT to inguinal lymph nodes; Patient developed visceral disease (liver); Patient alive 11.6 years after diagnosis of metastatic PCa | BRCA2 c.4876_4877delAA mutation | Cytoplasmic and nuclear staining: negative | PTEN+/- & PTEN+/- | ERG rearranged (Edel and 2 +Edel) ETV1 not rearranged | Positive |
| 3 54.6 years, T3N0M1 (bone), adenocarcinoma, Gleason 4-4, PSA 75.8 | Androgen blockade (LHRH, bicalutamide): PFS: 18 months, PSA nadir 0.81; Docetaxel + figitumumab; PFS: 10 months; PSA: fall 70% (Docetaxel stopped after 8 cycles due to neuropathy); E72389 for 3 months, PD in bone; Abiraterone, PFS: 44 months, PSA fall 97%; PD: soft tissue and PSA | Olaparib: 300 mg tablet bd; RECIST: PR; PSA fall from 63 to 3.8 µg/l (−94%); On treatment: 26 months, ongoing; Toxicity: myelotoxicity, dose reduced by 33%; Treatment ongoing after 26 months | Patient alive 9.1 years after diagnosis of metastatic PCa | BRCA2 3386T>G mutation | Cytoplasmic and nuclear staining: negative | PTEN+/- & PTEN+/- | ERG rearranged (2 +Edel) ETV1 not rearranged | Positive |

continued...
The recommended dose of olaparib capsules is 400 mg bd. Olaparib tablets are currently under evaluation and the optimal dose remains to be decided.

Pt, patient; LHRH, luteinizing hormone-releasing hormone; PR, partial response; PTEN, phosphatase and Tensin homolog; IHC, immunohistochemistry; PFS, progression-free survival; RT, radiotherapy; AUC6, area under curve 6; bd, twice daily; od, once daily; TURP, transurethral resection of the prostate; m, month; y, year; PD, progressive disease; CTCs, circulating tumor cells.

disclosure
JdB reports receiving fee from AstraZeneca and Merck for a consultant and advisory role and grant funding from AstraZeneca and Merck for clinical research; SK reports receiving fee from AstraZeneca and Merck for a consultant and advisory role; AA and CJL report that they may benefit financially from the development of PARPis through patents held jointly with KuDOS–AstraZeneca through the Institute of Cancer Research ‘rewards to inventors’ scheme; TAY reports receiving fee from Merck for a consultant and advisory role and grant funding from Merck; SKS reports receiving grant funding from AstraZeneca for clinical research. There are no other potential conflicts of interest relevant to this manuscript.

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Neuroprotectant agents against oxaliplatin induced neurotoxicity: lackings, facts and future prospective

The recent meta-analysis by Wen et al. [1] aiming to ascertain if Ca/Mg infusion is a valid neuroprotectant against acute and cumulative/chronic oxaliplatin (OXA) neurotoxicity concludes that it might decrease its incidence, without altering the efficacy of chemotherapy. However, this observation is arguable beyond the biases already properly pointed out by the authors.

In fact, a key issue that might reduce strength of their conclusions was not acknowledged: the lack of a gold standard in Chemotherapy-Induced Peripheral Neurotoxicity (CIPN) assessment and, consequently, uncertainty in CIPN incidence and prevalence. This might compromise validity of the protocols designed so far and might introduce an uncontrolled