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)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Molecular characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt Characteristics at diagnosis (age, stage, histology, Gleason score, PSA)</td>
<td>BRCA2 mutations</td>
</tr>
<tr>
<td>Prior treatments, duration, and response</td>
<td>PARP inhibitor treatment (response, PFS, toxicity, reason for progression)</td>
</tr>
<tr>
<td>1 58 years, T3N0M1 (bone), adenocarcinoma, Gleason 4+3, PSA 4.7</td>
<td>Androgen blockade (LHRH, Bicalutamide): PFS: 27.6 months, PSA nadir 0.59</td>
</tr>
<tr>
<td>2 47 years, T1cN1M0 adenocarcinoma, Gleason 3+3, PSA 5.9</td>
<td>Radical radiotherapy: to the prostate, recurrence after 3 years; Androgen blockade (LHRH, bicalutamide): PFS: 24 months</td>
</tr>
<tr>
<td>3 54.6 years, T3N0M1 (bone), adenocarcinoma, Gleason 4+4, PSA 75.8</td>
<td>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</td>
</tr>
</tbody>
</table>

| 3386T> G mutation | Cytoplasmic and nuclear staining: negative | PTEN−/− & PTEN−/+ | ERG rearranged (Edel and 2 + Edel) ETV1 not rearranged | Positive |

Continued
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references


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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