Therapeutic windows and opportunity cost cast upon prostate cancer's fatal shore

The last 3 years have seen a myriad of new therapies for advanced castration-resistant prostate cancer (CRPC), including immunotherapy, novel chemotherapy, two hormonal agents and bone calcium matrix targeted radionuclide. For patients and clinicians involved in making decisions on treatment in these settings, each therapy is welcome but presents a challenge of which patient it is best used in, when and in what sequence. Generally, new cancer agents are developed in an artificial vacuum, where the new treatment is considered in a phase III construct that is defined ahead of time with an agreed end point to facilitate regulatory approval funding. This paradigm fundamentally ignores the fact that standard therapy may change over the course of a clinical trial and alter assumptions made in designing the trial. In the setting of CRPC, this was not a challenge, because only docetaxel (Taxotere) demonstrated a required overall survival advantage, and newer agents were orientated relative to it: 'pre' or 'post' docetaxel. Most agents were moved into phase III trials after docetaxel because it was considered a lower risk; a trial run before docetaxel might have a poorer chance of demonstrating an overall survival benefit because sequential treatment with chemotherapy would dilute any difference between the study arms.

In the context of the development of two new classes of hormonal agents directed at the androgen receptor signaling pathway in prostate cancer, androgen biosynthesis hydrolase inhibitors and second-generation androgen receptor antagonists, the prototypical drugs were each tested in phase III trials before and after chemotherapy with a requirement that patients had not received the other novel agent. The post docetaxel trials, the Cougar 301 trial for the androgen biosynthesis hydrolase inhibitor, abiraterone acetate, and AFFIRM trial for the second generation androgen receptor antagonist, enzalutamide, accrued first and were followed by pre-docetaxel trials called Cougar 302 and PREVAIL respectively [1–3]. The question about optimal sequence of each of these drugs relative to the other has been of considerable interest but is currently dictated by regulatory approval of abiraterone acetate in the pre and post docetaxel setting and enzalutamide only in the post-docetaxel. On that basis, if patients are to receive both agents then they are likely to get abiraterone first and then possibly docetaxel followed by enzalutamide. This issue of whether one mechanism of inhibiting the androgen receptor axis followed by the other may be additive, neutral or negative for the second agent has not been addressed, until now.

Two articles in this edition of Annals report on the efficacy and safety of abiraterone and enzalutamide. The key endpoints of these study cohorts and the abiraterone treated patients from the Cougar 301 study are summarized in Table 1. Loriot and et al. report a shorter duration of eff and less serum PSA kinetic change in 38 patients given abiraterone and prednisone after docetaxel and enzalutamide [4]. The enzalutamide was given as part of the AFFIRM trial [3] and patients who were randomly assigned to placebo in that trial and treated with abiraterone with no prior enzalutamide had longer and better responses to abiraterone than those that received enzalutamide on the trial. In the North American study, patients previously treated with enzalutamide had short median PFS and less robust PSA responses than experienced by patients given abiraterone after prior docetaxel in the Cougar 301 trial [1, 5]. Patients in this cohort at the commencement of abiraterone were more likely to be on opioid analgesia and had higher serum alkaline phosphatase and lactate dehydrogenase levels than when they commenced enzalutamide therapy. These factors are indicative of increased disease burden and morbidity when the patients commenced the second agent. Neither the duration of response nor the depth of PSA response to prior enzalutamide correlated with subsequent response to abiraterone. There were recorded responses to abiraterone in patients with early resistance to enzalutamide. There is no suggestion of excess toxicity or safety concerns from abiraterone in these groups of enzalutamide-treated patients. It is not possible for us to construct a definitive comparison of enzalutamide exposed and non-exposed patients with the data from these cohorts. In addition, the rigor of patient selection does not come close to that of a formal clinical trial and the endpoints, which are largely PSA based, would be considered only surrogate markers of potential benefit in our clinical trials. Despite this, these are the best data we have and bear analysis simply because they may help inform clinical decisions in the absence of level 1 evidence. The duration of response and proportion falling to a PSA <50% of baseline are very similar for patients given abiraterone after the placebo arm of AFFIRM and abiraterone given in Cougar 301, while the duration of response and PSA declines are less in the patients who received prior enzalutamide.

Increase in the duration of response and rates of PSA decline with sequential therapies targeting the AR pathway suggest that the second end point was not achieved.
some degree of acquired resistance despite different mechanisms of action for the two drugs. While it appears to be safe to treat patients sequentially with these novel hormonal agents and some patients have surrogacy of response as indicated by PSA kinetics, the overall benefit of the sequence is in question. The data beg several questions: is there any optimal sequence of enzalutamide and abiraterone to produce the best outcome? Do prostate cancer cells manifest enzymatic-mediated resistance, become AR-null or demonstrate other more general oncogenic or epigenetic changes that could be assessed as biomarkers to optimize treatment?

The emergence of AR-null populations is a potential mechanism of resistance to secondary hormonal manipulations. Within the AR-null group, the small-cell SCPC or neuroendocrine prostate carcinoma morphological variant has long been recognized as a distinct entity that predicts for a poor response to androgen deprivation therapies [6] and a high but short-lived response to chemotherapy [7, 8]. Although ‘primary’ (present at initial diagnosis) SCPC is rare [9] autopsy series published in the last decade [10, 11] show ‘secondary’ (emerged during the progression of an initial prostate adenocarcinoma diagnosis) SCPC in 10%–20% of men dying of CRPC. Recent studies have shown that SCPC (similarly to small-cell carcinomas from other anatomic origins) are characterized by loss of RB1 and AR expression but display frequent AURKA and UBE2C expression [18, 19]. Interestingly, a subset were positive for AR but negative for RB1 and were associated with low serum levels of PSA and PAP, suggesting that even in the presence of AR expression, AR-signaling may be impaired. Early work using circulating tumor cells (CTCs) in patients treated with abiraterone suggests that oncogenes such as MYC in tandem with changes in the AR amplicon may be important heralds of resistance [20]. Whether AR-independent prostate cancers developing in response to more potent AR-pathway inhibition also share this biology remains to be tested.

The modest response to abiraterone in patients previously treated with enzalutamide may be mediated by mechanisms of cross-resistance such as increased steroidogenesis and activation of ligand-independent AR variants, the latter possibly induced by PI3K/AKT signaling. Indeed, a growing volume of work has demonstrated that cancer cell populations are quite heterogeneous, and that therapy resistance and tumorigenicity reside disproportionately in relatively small subpopulations of cells that may ultimately mediate disease progression [21, 22]. Interestingly, recent studies have shown that resistance need not necessarily emerge from pre-existing resistant cells; rather, cancer cells lacking drug resistant aggressive properties could acquire this phenotype under selective pressure [23, 24]. In studies at the University of Southern California, highly tumorigenic drug-resistant cancer cells arose spontaneously by direct conversion from cancer cells lacking these traits [25], findings that were also observed by others [26]. In related work, we found that the PI3K/Akt pathway (upstream) partnered with β-catenin and CBP (downstream) to mediate this phenotypic plasticity. It is likely that additional mechanisms are involved; for example, in prostate cancer tumors and cell lines, we and others found that telomerase expression and activity were disproportionately elevated in drug-resistant subpopulations [27, 28], and that introducing telomerase into prostate cancer cells could augment and expand this phenotype [unpublished data]. Such mediators of phenotypic plasticity, while still being elucidated, may ultimately provide the mechanistic underpinnings for the rapid emergence of the cross-resistant disease clinically observed in the current studies.

Emergence of cross-resistance underscores the need for determining the optimal sequencing of novel agents, and the critical importance of developing new predictive biomarkers to select patients who will benefit from a second-line therapy. In

Table 1. Data from recent cohorts of mCRPC patients treated with novel hormonal agents after docetaxel.

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<tbody>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>16</td>
<td>30</td>
<td>797</td>
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<tr>
<td>Prior docetaxel</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, median 10 cycles</td>
<td>Yes</td>
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<tr>
<td>Prior enzalutamide</td>
<td>Yes (active agent on AFFIRM)</td>
<td>No (placebo on AFFIRM)</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Median PFS (months) (95% CI)</td>
<td>2.7 (2.3–4.1)</td>
<td>6.5 (3.7–19.7)</td>
<td>3.6 (2.6–4.9)</td>
<td>5.6 (10.2–NR)</td>
</tr>
<tr>
<td>Median OS (months) (95% CI)</td>
<td>7.2 (5.0–NR)</td>
<td>11.4 (7.3–NR)</td>
<td>11.8 (6.8–16.7)</td>
<td>14.8</td>
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<tr>
<td>PSA response</td>
<td></td>
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<td></td>
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<tr>
<td>&gt;30%</td>
<td>18%</td>
<td>36%</td>
<td>11%</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>8%</td>
<td>29%</td>
<td>3%</td>
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*Time to PSA progression.
the prostate cancer arena, the sub-optimal sensitivity and specificity of PSA have significantly diminished its use in the advanced disease setting [29, 30], and a variety of newer potential biomarkers are undergoing clinical validation, including EPCA-2, AMACR, GSTP1-methylation, TMPRSS2-ETS and DD3 [31]. To date, most of these markers have been assayed from primary tumor tissue, an approach with limited utility in the setting of advanced metastatic disease: primary tumors sampling is unlikely to reflect dynamic phenotypic plasticity driven by sequential therapies for advanced metastatic disease, such as that observed in the current papers. To address this need, analysis of CTCs has gathered momentum as a tissue source that can be obtained repeatedly in real time for prognostic and predictive purposes after progression on various treatments [32–35]. Recently, several groups have made promising strides in the molecular characterization of CTCs for prostate cancer-specific phenotypes such as the TMPRSS2-ERG fusion product or androgen receptor mutations in metastatic disease [32, 36, 37]. Our own group also has explored this approach by focusing on CTC telomerase activity. Using a Parylene-C slot microfilter, we detected telomerase activity in live CTCs captured from the blood of men with metastatic prostate cancer [38], an approach which has been integrated into biomarker correlative studies in a SWOG phase III prostate cancer trial, where telomerase activity in CTCs was prognostic [39, 40]. These and other rapidly evolving technologies may ultimately enable individualized tailoring of treatments such as sequential hormonal therapies. One envisions CTC sampling before, during and after a given therapy, with analysis of captured cells by immunofluorescence, FISH or qPCR for biomarkers relevant to hormonal therapy resistance, such as the presence of particular AR variants or activation of resistance pathways like PI3K/AKT or MYC [20]. The use of such CTC-derived biomarkers, once validated, may significantly improve patient selection in the setting of sequential therapies.

While the challenge of prostate cancer resistance is being informed by eloquent science, and we can ponder whether the cancer confronting is AR null, telomerase overactive or MYC overriden, we are left with the art of patient management guided by our best clinical trial evidence. The studies in this edition of Annals of Oncology lead us to presuppose that abiraterone will be less active after enzalutamide, but not in every patient. Evidence for effectiveness of enzalutamide after abiraterone will likely come from reports on the enzalutamide expanded access program in which as many as 80% of patients were previously treated with abiraterone. The equation may be very complicated since some data suggest that docetaxel, a cornerstone of CRPC therapy, may be less efficacious if given after abiraterone [41]. Would docetaxel resistance be mediated by similar factors to hormonal agent resistance? As experience and evidence accumulates, we will be left pondering the opportunity cost of starting with one agent and keeping others until later. We are where breast cancer therapeutics was 20 years ago, when aromatase inhibitors challenged tamoxifen and chemotherapy became the standard for receptor-negative disease. Will prostate cancer be the same or different? Will the next decade’s progress help us select based on biology and biomarker rather than a predetermined sequence? Stay tuned for an increasingly fascinating ride.

disclosure
DIQ has participated in advisory boards for Algeta, Astellas, Bayer, Dendreon, Janssen, Medivation, Veridek, Teva, and OncoGenex, and given testimony for Teva and Medivation. The other authors have declared no conflicts of interest.

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