Serial blood-based analysis of AR-V7 in men with advanced prostate cancer

M. Nakazawa1, C. Lu1, Y. Chen1, C. J. Paller2, M. A. Carducci2, M. A. Eisenberger2, J. Luo1* & E. S. Antonarakis2
Departments of 1Urology; 2Oncology, Johns Hopkins University School of Medicine, Baltimore, USA

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Background: We previously showed that pretreatment detection of androgen receptor splice variant-7 (AR-V7) in circulating tumor cells (CTCs) from men with castration-resistant prostate cancer is associated with resistance to abiraterone and enzalutamide, but not to taxane chemotherapies. Here, we conducted serial measurements of AR-V7 and evaluated patterns of longitudinal AR-V7 dynamics over the course of multiple sequential therapies.

Patients and methods: Metastatic prostate cancer patients treated at Johns Hopkins with AR-directed therapies or taxane chemotherapies underwent serial liquid biopsies for CTC-based AR-V7 analysis at baseline, during therapy, and at progression. We used a CTC enrichment platform followed by multiplexed reverse-transcription polymerase chain reaction analysis to detect full-length androgen receptor and AR-V7 transcripts. Patients selected for inclusion in this report were those who provided ≥4 CTC samples, at least one of which was AR-V7 positive, over the course of ≥2 consecutive therapies.

Results: We identified 14 patients who received a total of 37 therapies and contributed 70 CTC samples for AR-V7 analysis during a median follow-up period of 11 months. Three patients remained AR-V7 positive during the entire course of therapy. The remainder underwent transitions in AR-V7 status: there were eight instances of ‘conversions’ from AR-V7-negative to -positive status (during treatment with first-line androgen deprivation therapy, abiraterone, enzalutamide, and docetaxel), and six instances of ‘reversions’ from AR-V7-positive to -negative status (during treatment with docetaxel and cabazitaxel).

Conclusions: AR-V7 is a dynamic marker, and transitions in AR-V7 status may reflect selective pressures on the tumor exerted by therapeutic interventions. While ‘conversions’ to AR-V7-positive status were observed with both AR-directed therapies and taxane chemotherapies, ‘reversions’ to AR-V7-negative status only occurred during taxane therapies. Serial blood-based AR-V7 testing is feasible in routine clinical practice, and may provide insights into temporal changes in tumor evolution.

Key words: AR-V7, splice variant, androgen receptor, circulating tumor cell, prostate cancer

introduction
Prostate cancer is the most common noncutaneous malignancy in the United States and is the second leading cause of cancer deaths among males, claiming ~30,000 lives each year [1]. While prognosis is favorable for early-stage disease, most men with castration-resistant prostate cancer (CRPC) eventually die from their illness. CRPC often remains androgen-dependent and AR-driven. Several mechanisms of castration resistance have been identified, many of which contribute to sustained AR signaling: production of adrenal and intratumoral androgens [2–4], AR amplification or overexpression [5, 6], AR activation through alternative pathways [7, 8], nontraditional ligand synthesis pathways [9, 10], and activating AR mutations allowing promiscuous signaling [11, 12].

Adding to this complexity, AR splice variants (AR-Vs) also play a significant role in therapeutic resistance. AR-Vs are truncated forms of the AR lacking portions of the ligand-binding domain, resulting in constitutively active functions [13, 14]. Androgen receptor splice variant-7 (AR-V7) is one such variant, capable of being activated without ligand binding [15, 16]. This quality, along with its relative abundance, increased expression in CRPC tissues, and its ability to encode a detectable protein product, is suggestive of its clinical significance [16–18]. Indeed, several preclinical studies have demonstrated that AR-V7 confers resistance to novel AR-directed therapies, abiraterone and enzalutamide [19, 20]. Recently, our group has shown that AR-V7 is associated with clinical resistance to these two agents; patients...
with detectable AR-V7 in circulating tumor cells (CTCs) had inferior prostate-specific antigen (PSA) responses as well as worse progression-free and overall survival compared with their AR-V7-negative counterparts [21]. However, AR-V7 does not appear to be a predominant mechanism of resistance to taxane chemotherapies (docetaxel and cabazitaxel) [22].

In this study, we assessed the feasibility of performing serial blood-based AR-V7 sampling across the contemporary treatment landscape of metastatic prostate cancer, and to better understand AR-V7 marker dynamics that may be subject to influences by the different therapies. We describe temporal changes in CTC tumor marker dynamics in men undergoing sequential therapies using AR-targeting agents and taxane chemotherapies with a focus on AR-V7 status. Given the large number of agents now FDA-approved for CRPC, serial AR-V7 analysis might yield important insights into optimal sequencing strategies which are currently unknown [23]. This is particularly relevant in an era of increasing cross-resistance between abiraterone and enzalutamide [24–25], as well as cross-resistance between AR-targeting therapies and taxane chemotherapies [26–27]. Sequential sampling of CTCs for AR-V7 analysis could therefore provide conceptual insights on tumor evolution in response to multiple treatments in a noninvasive manner.

**methods**

**patients**

**study population.** We prospectively enrolled men with metastatic prostate cancer beginning standard-of-care therapy with AR-targeting agents [androgen deprivation therapy (ADT) (luteinizing hormone releasing hormone agonists/antagonists ± first-generation antiandrogen), enzalutamide, and abiraterone] or taxane chemotherapies (docetaxel and cabazitaxel) under an institutional review board-approved protocol allowing sequential collection of liquid biopsies. Both hormone-sensitive and castration-resistant patients were eligible. Peripheral blood samples for CTC-specific AR-V7 analysis were collected at up to three time-points for each therapy received. Specifically, samples were collected before therapy initiation, during the course of therapy, and at the time of clinical/radiographic progression. Subjects were excluded if they planned to receive concurrent immunotherapies, radiopharmaceutical drugs, or other investigational agents; there were no restrictions on prior anticancer therapies. Patients provided written informed consent before each therapy.

**study design and assessments.** We aimed to prospectively evaluate the dynamics of AR-V7 status in response to AR-directed and taxane therapies administered in sequential fashion across the treatment continuum. Only men who provided ≥4 CTC samples across the course of ≥2 consecutive therapies were included in the present analysis (see selection criteria, supplementary Figure S1, available at *Annals of Oncology* online). Patients had PSA evaluations every 1–2 months and underwent imaging with a computed tomography and bone scan every 3–4 months; treatment was continued until disease progression or unmanageable toxicity. For simplistic purposes, patients were defined as ‘responders’ if they exhibited a ≥50% PSA decline at any time on therapy, maintained for ≥4 weeks.

**materials**

**analysis of CTCs for AR-V7.** We used a modified version of the AdnaTest platform for CTC analysis, as previously described [21]. Briefly, CTCs were enriched from peripheral blood using the ProstateCancerSelect kit.

mRNA expression analysis was conducted using the ProstateCancerDetect kit, along with multiplexed reverse-transcription polymerase chain reaction analyses using custom primers to detect full-length AR (AR-FL) mRNA and AR-V7 mRNA. The relative abundance of AR-V7 was reported as a ratio of AR-V7 to AR-FL transcripts [21].

**results**

**patient characteristics**

From December 2012 to March 2015, we enrolled 225 men with metastatic prostate cancer beginning therapy with AR-targeting agents or taxane chemotherapies at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center. After applying our selection criteria (supplementary Figure S1, available at *Annals of Oncology* online), we identified a total of 25 men who had consented to CTC collections over the course of ≥2 consecutive treatments and provided ≥4 total CTC samples, of which 14 patients had ≥1 sample positive for AR-V7. The characteristics of the remaining 11 patients, whose CTCs remained AR-V7 negative throughout the treatments assessed, are summarized in supplementary Table S1, available at *Annals of Oncology* online. A proportion of these patients have been analyzed as part of our previous studies [21, 22], but only in the context of one single therapy at a time. Supplementary Table S2 summarizes the baseline characteristics of all patients.

The present analysis focuses on the 14 CTC-positive patients at baseline with at least one AR-V7-positive CTC sample during follow-up. Table 1 shows baseline characteristics (at the time of study entry) for these patients, who had variable disease burden and prior treatment exposures. Two men, patients 8 and 9, were hormone-sensitive, whereas 12 men were castration-resistant at the time of study entry. Common sites of metastatic disease included bones and lymph nodes. At the first CTC collection, six patients (43%) had detectable AR-V7. In total, 37 therapies were administered [mean 2.6 (range 2–4) therapies per subject], and 70 CTC AR-V7 tests carried out [mean 4.9 (range 4–8) tests per subject], during a median follow-up of 11 [range 6–18] months. The type and duration of each therapy, the PSA response status, and the serial blood-based AR-V7 measurement results are summarized in Figure 1.

**AR-V7 conversions and reversions**

Given our selection criteria, all 14 patients had at least one instance of detectable AR-V7 during their follow-up. Three patients (7, 10, and 12) were AR-V7 positive during the entire follow-up period. Of the remaining 11 patients, 5 underwent ‘conversions’ from AR-V7 negative to AR-V7 positive during the course of therapy, 1 underwent a ‘reversion’ from AR-V7 positive back to AR-V7 negative, and 5 men experienced both a conversion and a reversion at different points along their treatment trajectory. Two patients (patients 5 and 6) experienced conversions off therapy (during which time they only received ADT). These transitions in AR-V7 status are summarized according to treatment type in Table 2.

We observed eight instances of ‘conversions’ in AR-V7 status (i.e. negative to positive transitions) during the course of 15 treatments (53.5%) (Table 2, A), and six ‘reversions’ (i.e. positive to negative transitions) during the course of 22 treatments...
Table 1. Characteristics of the 14 selected patients at the time of baseline CTC sampling

<table>
<thead>
<tr>
<th>Age</th>
<th>Years since Dx</th>
<th>Gleason score</th>
<th>Metastatic sites</th>
<th>Previous treatments</th>
<th>PSA (ng/ml)</th>
<th>ALK (U/l)</th>
<th>ECOG PS</th>
<th>AR-V7 status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>1.2</td>
<td>9</td>
<td>Bone, LN, liver</td>
<td>L, B</td>
<td>7.5</td>
<td>112</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>2.4</td>
<td>10</td>
<td>Bone</td>
<td>L, B, D</td>
<td>2.2</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>4.9</td>
<td>9</td>
<td>Bone, LN, liver</td>
<td>L, B, S</td>
<td>25.3</td>
<td>315</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>9.1</td>
<td>9</td>
<td>LN</td>
<td>L, B, N, K, A</td>
<td>22.2</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>8.0</td>
<td>10</td>
<td>Bone</td>
<td>L, B, N, K, E</td>
<td>23.3</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>5.0</td>
<td>9</td>
<td>Bone, LN</td>
<td>L, B</td>
<td>63.5</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>0.8</td>
<td>10</td>
<td>Bone, LN</td>
<td>L, B, A</td>
<td>53.4</td>
<td>486</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>0.1</td>
<td>9</td>
<td>Bone, LN</td>
<td>None</td>
<td>314</td>
<td>270</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>0.6</td>
<td>9</td>
<td>Bone, LN</td>
<td>None</td>
<td>365</td>
<td>142</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>1.1</td>
<td>9</td>
<td>Bone</td>
<td>L, B</td>
<td>157</td>
<td>189</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>2.1</td>
<td>10</td>
<td>Bone, LN, liver, lung, adrenals</td>
<td>L, B, A</td>
<td>75.0</td>
<td>101</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>58</td>
<td>3.4</td>
<td>9</td>
<td>Bone, LN</td>
<td>L, B</td>
<td>58.7</td>
<td>838</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>68</td>
<td>5.0</td>
<td>9</td>
<td>Bone</td>
<td>L, B, A</td>
<td>50.7</td>
<td>112</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>82</td>
<td>1.1</td>
<td>Unknown</td>
<td>Bone</td>
<td>L, B, A</td>
<td>895</td>
<td>464</td>
<td>1</td>
</tr>
</tbody>
</table>

L, LHRH agonist/antagonist; B, bicalutamide; N, nilutamide; K, ketoconazole; A, abiraterone; E, enzalutamide; D, docetaxel; S, sipuleucel-T; ECOG PS, Eastern Cooperative Oncology Group performance status.

Figure 1. Swimmer plot indicating treatments that patients received, along with timing (and AR-V7 status) of CTC sampling, and whether or not PSA responses occurred during each therapy. Shaded boxes indicate failure to achieve PSA response; unshaded boxes indicate achievement of 50% PSA reduction on therapy. Percentage values indicate best PSA response. Daggers indicate deceased patient. Thirteen of 14 patients have previously been included in our prior publications, but only in the context of a single therapy.
Conversions and reversions in AR-V7 status during treatment with AR-directed therapies and taxane chemotherapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remained AR-V7 negative</th>
<th>‘Conversions’ to AR-V7 positive</th>
<th>'Reversions' to AR-V7 negative</th>
<th>Unknown*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line ADT (n = 2)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abiraterone (n = 4)</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enzalutamide (n = 4)</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel (n = 3)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cabazitaxel (n = 2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (n = 15)</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(A) Number of baseline AR-V7-negative individuals that either remained AR-V7 negative or converted to AR-V7 positive during treatment.

(B) Number of baseline AR-V7-positive individuals that either remained AR-V7 positive or reverted back to AR-V7 negative during treatment.

*Patient had no sample collected at progression, or progression has not yet occurred.

In the 14 total instances of AR-V7 conversions (n = 8) or reversions (n = 6), we examined the ratio of AR-V7 to AR-FL transcript to quantify relative changes in AR-V7 expression across time (Figure 2). Among patients who experienced conversions or reversions in AR-V7 status during the second sample collected, AR-V7/AR-FL ratios increased further in the third sample in men with conversions (patients 4 and 9) and decreased further before disappearing in the patient who reverted back to negative (patient 4).

**Discussion**

This is a descriptive study examining temporal changes in AR-V7 status among men undergoing sequential AR-directed therapies and/or taxane chemotherapies for metastatic prostate cancer. While it is possible to remain AR-V7 negative throughout multiple lines of therapy, we were especially interested in those patients who displayed AR-V7 positivity at least once during their follow-up, and thus selected 14 patients based on this additional criterion. We have focused specifically on AR-V7 analysis because of its relative abundance and its established significance in mediating therapy resistance in CRPC. While there are multiple context-specific mechanisms of treatment resistance in CRPC, the emergence of AR-V7 is likely to be important in the setting of AR-directed therapies, where we have previously established the association between blood-based AR-V7 detection and resistance to abiraterone and enzalutamide [21], but not to taxane chemotherapies [22]. In the current study, we demonstrate again that all patients receiving AR-directed therapies with a baseline-positive AR-V7 sample did not exhibit a PSA response; conversely, PSA responses were observed among AR-V7-positive patients receiving taxane agents. We further confirm that AR-V7 is an abundant AR variant (sometimes reaching levels of >50% relative to AR-FL), and AR-V7 appears to always coexist with AR-FL in prostate cancer patients. In addition to these confirmatory findings, this study established the feasibility of serial noninvasive CTC sampling for AR-V7 analysis in routine clinical practice. Indeed, 8 of 14 patients provided ≥5 samples during the course of their therapies.

We also show that AR-V7 is a dynamic marker. In this study, we observed eight instances of conversions from AR-V7-negative to -positive status, and six instances of reversions from AR-V7 positive to negative. Notably, five of eight conversions that occurred were with AR-directed therapies (ADT, abiraterone, enzalutamide), while all six instances of reversions occurred during docetaxel or cabazitaxel treatment. Although AR-V7 conversions can certainly occur during taxane therapy (patients 11, 13, 14—all of whom received docetaxel), reversions have never been observed with AR-targeting drugs. Although similar instances of conversions and reversions occurred in our previous studies examining the role of AR-V7 in predicting resistance to abiraterone/enzalutamide [21] and taxanes [22], the current analysis represents the first study on dynamic changes of AR-V7 over the course of sequential therapies, further demonstrating potentially differential effects of the therapies on detection of AR-V7 in blood.

Conversions from AR-V7-negative to -positive status could reflect adaptive AR-V7 induction as well as selective pressure following potent inhibition of canonical AR signaling by abiraterone and enzalutamide. Reversions from AR-V7-positive to -negative status may reflect the relaxation of inhibition on the AR-signaling axis (rather than a direct effect of taxane treatment per se), relieving the selective pressure for AR-V7 expression, thereby decreasing detectable AR-V7. Additionally, the cytotoxic properties of taxanes may also decrease the number of
CTCs in blood beyond our detection limit for AR-V7. Of note, 14 of the 70 sampling time-points assessed were negative for CTCs, and many of these CTC-negative samples corresponded to samples taken during clinical responses to therapy. Considering the results from quantitative analysis of AR-V7 and AR-FL copy numbers (Figure 2), we observe that a subset of patients experiencing reversions (patients 1, 2, and 6) had undetectable AR-V7 and AR-FL during treatment and at progression, reflecting the depletion of CTCs. We note that a limitation of this study is that the AdnaTest platform does not permit CTC enumeration, and thus we are unable to assess the AR-V7 positive-to-negative transitions in light of quantitative changes in CTC number.

The clinical significance of these changes in AR-V7 status remains unknown. There is a theoretical possibility that taxanes

Figure 2. Quantification of AR-V7/AR-FL ratios in patients with conversions and reversions in AR-V7 status with AR-directed therapies or taxane chemotherapies. (A) Patients undergoing conversions from AR-V7-negative to -positive status during treatment with AR-directed therapies (ADT, abiraterone, and enzalutamide) as well as docetaxel chemotherapy. Percentage values indicate ratio of AR-V7 to AR-FL transcripts. Note that positive AR-FL values may not appear due to Log conversion of AR-FL transcript copy numbers. (B) Patients undergoing reversions from AR-V7-positive to -negative status during treatment with taxane chemotherapy (docetaxel or cabazitaxel). Percentage values indicate ratio of AR-V7 to AR-FL transcripts. Note that positive AR-FL values may not appear due to Log conversion of AR-FL transcript copy numbers.
may sensitize AR-V7-positive patients to subsequent AR-directed therapies if the AR-V7 status reverts from positive to negative during taxane therapy. This scenario is exemplified by patient 3, who subsequently exhibited a favorable response to abiraterone lasting 7 months. Another example is patient 2, who converted to AR-V7 positive upon progression on enzalutamide, but subsequently reverted to AR-V7 negative during cabazitaxel therapy; he was then re-treated with abiraterone which resulted in a transient PSA reduction of 37%, as shown in supplementary Figure S2B, available at Annals of Oncology online (note: the second abiraterone treatment is not included in Figure 1 because he did not re-enroll in the study during abiraterone re-treatment).

Interestingly, although the threshold of 50% PSA reduction was not reached, this patient achieved a greater PSA reduction during his second course of abiraterone treatment (compared with the first), which lasted 3 months before further progression occurred. If this anecdotal trend is substantiated by larger patient numbers, taxane treatment could be entertained following progression on abiraterone/enzalutamide for AR-V7-positive individuals who may then become re-sensitized to further AR-directed therapies. However, not all AR-V7-positive patients undergoing taxane treatment revert to negative, and some AR-V7-negative patients even experience conversions to positive status with taxanes. Furthermore, AR-V7 reversions did not necessarily correlate with PSA responses to taxane treatments.

All abiraterone/enzalutamide-treated patients who were AR-V7 positive at baseline remained positive at follow-up; AR-V7 detection thus appears to persist during therapy with AR-targeting agents. Coupled with observations from our previous study [21], we have yet to report an instance where reversions from AR-V7 positive to negative occurred during treatment with an AR-targeting agent, supporting the hypothesis that potent AR-signaling inhibition may promote the induction and maintenance of the AR-V7-positive phenotype.

The present analysis should be interpreted with caution. Our cohort represents a population with very advanced prostate cancer, and is not reflective of the general CRPC population. While our overall CTC collection protocol also enrolled patients with lower risk features, the inclusion criteria for the current analysis [i.e. ≥4 CTC samples (≥1 AR-V7 positive) across ≥2 therapies] invariably selected for patients with more lethal disease (and is therefore biased), as evidenced by higher Gleason scores and higher PSA at baseline (supplementary Table S2, available at Annals of Oncology online). In addition, the criteria for the current analysis selected for patients regularly monitored at our institution who agreed to longitudinal follow-up and periodic blood donations. Although the clinical utility of AR-V7 testing might be greatest in high-risk patient populations, further elucidation of subpopulations that may benefit from AR-V7 analysis will require additional studies.

**conclusion**

This descriptive analysis suggests that AR-V7 can be reliably detected from peripheral blood CTCs, providing a noninvasive means of serially probing AR-V7 in advanced prostate cancer patients. Importantly, we show that AR-V7 is a dynamic marker: patients may exhibit transitions in AR-V7 status as a result of different treatments. Conversions from AR-V7 negative to positive most often occur in patients undergoing AR-directed therapies, whereas reversions from AR-V7 positive to negative seem to occur only with taxane chemotherapies. Sequential CTC sampling could provide insights into disease evolution, and follow-up studies will shed further light on the clinical significance of these AR-V7 transitions.

**acknowledgements**

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**disclosure**

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**references**

Treatment outcome and patterns of relapse following adjuvant carboplatin for stage I testicular seminomatous germ-cell tumour: results from a 17-year UK experience

C. Chau1,2,3, R. Cathomas4, M. Wheeler3, D. Klingbiel5, M. Fehr6, J. Bennett7, H. Markham8, C. Lee1,3, S. J. Crabb1,3 & T. Geldart*1

1Cancer Sciences Unit, University of Southampton Faculty of Medicine, Southampton; 2NIHR Wellcome Trust Clinical Research Facility, University of Southampton, Southampton; 3Department of Medical Oncology, University Hospital Southampton NHS Foundation Trust, Southampton, UK; 4Department of Medical Oncology, Kantonsspital Graubünden, Chur; 5Swiss Group for Clinical Cancer Research Coordinating Center, Bern; 6Department of Medical Oncology, Kantonsspital St Gallen, Switzerland; 7Dorset Cancer Centre, Poole Hospital NHS Foundation Trust, Poole; 8Department of Histopathology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

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Background: Following inguinal orchidectomy, management options for patients with stage I seminoma include initial surveillance or treatment with adjuvant radiotherapy or chemotherapy. The anticipated relapse rate for patients followed by surveillance alone is ~15%, with adjuvant treatment this risk is reduced to ~4%–5% at 5 years. After carboplatin treatment, follow-up strategies vary and there are no validated, predictive markers of relapse.

Patients and methods: We conducted a retrospective analysis of all patients presenting with stage I seminoma who received a single cycle of adjuvant carboplatin in South Central England between 1996 and 2013. We report on outcome and the results of univariate and multivariate analysis evaluating possible risk factors for post carboplatin relapse.