Supplementary Information

Table S1: Pivotal Clinical Trial inclusion/exclusion criteria as utilised for identification of potentially eligible patients using electronic record linkage

	Abiraterone		Enzalutamide	
	Post-chemotherapy	**Pre-chemotherapy**	**Post-chemotherapy**	**Pre-chemotherapy**
Screening time frame	14 days prior to 1st dose	14 days prior to 1st dose	28 days prior to 1st dose	28 days prior to 1st dose
Age	≥ 18 years	≥ 18 years	-	-
Previous prostate cancer treatment	1 or 2 previous chemo regimens, one of which was docetaxel	Surgical or chemical castration; if LHRH used, treatment initiation at least 4 weeks prior to 1st dose	1 or 2 previous chemo regimens, one of which was docetaxel; prev orchidectomy or ongoing treatment with GnRH analogues	No prior chemotherapy for prostate cancer; surgical or chemical castration
ECOG performance status	≤ 2	≤ 1	≤ 2	≤ 2
Serum testosterone	<2.0 nM	<2.0 nM	<1.2 nnml/L	<1.73 nnml/L
Haemoglobin	≥ 9 g/dl	≥ 10 g/dl	< 9 g/dL	< 9 g/dL
Platelet count	≥100,000/µl	≥100,000/µl	< 100,000/µL	< 100,000/µL
Serum albumin	≥ 3.0 g/dL	≥ 3.5 g/dL	< 30 g/L	< 30 g/L
Serum creatinine	< 1.5 * ULN	< 1.5 * ULN	> 177 µmol/L	> 177 µmol/L
Serum potassium	≥3.5 mmol/L	≥ 3.5 mmol/L	-	-
Serum bilirubin	≥ 1.5 * ULN *[1]*	< 1.5 * ULN *[1]*	> 2 * ULN	> 2.5 * ULN
AST	≥ 2.5 * ULN	< 2.5 * ULN	> 2 * ULN	> 2.5 * ULN
ALT	≥ 2.5 * ULN *[2]*	< 2.5 * ULN	> 2 * ULN	> 2.5 * ULN
Neutrophil count	-	-	< 1500/µL	< 1500/µL
Comorbidities	Viral hepatitis or chronic liver disease; myocardial infarction (MI) 6 months prior; unstable angina	Viral hepatitis or chronic liver disease; MI 6 months prior to screening; unstable angina	MI within 6 months, unstable angina within 3 months; hypotension or bradycardia; TIA within 12 months; prior stroke	MI within 6 months, unstable angina within 3 months; hypotension or bradycardia; TIA within 12 months; prior stroke
Other prior treatment	Prostatic intervention or chemo within 30 days of first dose	-	Chemo within 4 weeks of enrolment	-
Prior/concomitant medication	Prior treatment with abiraterone	Opioid within 4 weeks *[3]*; itraconazole within 4 week; flutamide within 4 weeks, bicalutamide or nilutamide within 6 weeks	Prior treatment with abiraterone or enzalutamide; finasteride, dutasteride, bicalutamide, flutamide, nilutamide, or estrogens within 4 weeks; aminophylline, theophylline, bupropion, dolasetron, droperiodol, gatafloxacin, moxifloxacin, lithium, pethidine, venlafaxine, amiodarone, disopyramide, procainamide, quinidine, sotalol, maprotiline, mirtazapine within 28 days	Prior treatment with abiraterone or enzalutamide; opioid within 4 weeks *[3]*; finasteride, dutasteride, flutamide, estrogens, or cyproterone within 4 weeks; bicalutamide or nilutamide within 6 weeks

[1] except in patients with Gilbert's disease – assumed patients don't have disease;
[2] except in patients with liver metastasis – assumed patients don't have these;

[3] for cancer pain – assumed this is the indication for prescribing.

Please note: All inclusion criteria needed to be fulfilled in order to be eligible for the trial; exclusion from trial occurred when at least one of the exclusion criteria applied (shaded cells).

Criteria Assumed and/or not able to be assessed within this analysis

Due to the nature of the data available for analysis, a range of criteria originally employed in the clinical trials could not be replicated using electronic record linkage. These criteria fell broadly into three categories: first, specifics with regards to disease definitions as the basis for trial inclusion; second, comorbidities present at baseline; and third, previous treatment. The latter two categories represent exclusion criteria.

1. All four trials had specific requirements regarding ***diagnosis and disease progression*** (e.g. confirmed adenocarcinoma without neuroendocrine differentiation or small cell histology; metastatic disease confirmed by bone scan, CT, or MRI; asymptomatic or mildly symptomatic disease based on BPF-SF questionnaire). In addition, most trials required an estimated life expectancy of at least 6 months. As SMR06 does not provide this level of detail and specialist pathology/imaging records were not available, the assumption was that all patients receiving abiraterone or enzalutamide would fulfil these criteria.

2. On top of the ***comorbidities*** identified through SMR00/SMR01 records, a range of additional conditions were listed in the study protocols which would have led to trial exclusion, e.g. other malignancies, brain metastases or bone lesions; uncontrolled hypertension, history of pituitary or adrenal dysfunction, or active epidural disease; gastrointestinal disorders potentially interfering with the absorption of the drug; and possibly a range of other concurrent diseases or co-morbidities, which were not further specified but instead subsumed as “serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection” (abiraterone) or “severe, concurrent disease, infection, or co-morbidity” (enzalutamide). In order to apply these criteria, additional details of how these comorbidities have been defined within the trials, as well as access to primary care records, would be required.

3. Previous ***treatment*** that would have led to trial exclusion included, e.g., major surgery; and radiotherapy or immunotherapy within a specified timeframe prior to treatment initiation. As with comorbidities, additional details with regards to the treatment options specified in the study protocols

would be required in order to apply these criteria; however, most of this information would not have been available in the records used for analysis (e.g. ARIA records appeared to be incomplete).

4. Furthermore, limitations of the available patient records with regards to some of the criteria utilised for identification of potentially eligible patients need to be kept in mind (e.g. the identification of liver disease, heart disease, and history of seizures was not based on the complete criteria as listed in the study protocols but used a subset due to data availability).

Table S2: Baseline Characteristics of trial eligible patients

	Abiraterone		Enzalutamide	
Characteristic	**Post-chemo**	**Pre-chemo**	**Post-chemo**	**Pre-chemo**
Number patients	43	21	41	16
Median age [years] (IQR)	73 (66.5 – 75.5)	73 (72 – 81)	72 (67 – 79)	80.5 (74.8 – 83.3)
Number patients ≥ 75 years (%)	12 (27.9)	10 (47.6)	14 (9.8)	12 (75.0)
Baseline ECOG performance status (%) †				
0 – 1	20 (46.5)	13 (61.9)	24 (58.5)	9 (56.3)
2 – 3	<5	0	<5	0
Gleason score at diagnosis (%) †				
≤ 7	10 (23.3)	8 (38.1)	<5	<5
≥ 8	21 (48.8)	10 (47.6)	30 (73.2)	<5
Number prior docetaxel cycles				
Median (IQR)	10 (6 – 10)	0	10 (7 – 10)	0
Range	2 – 13	0	1 – 10	0
Baseline PSA [µg/L]				
Median (IQR)	78.6 (20.1 – 227.6)	23.3 (8.6 – 92.9)	76.4 (49.9 – 227.2)	15.2 (9.1 – 47.0)
Range	5.0 – 1352.5	0.1 – 399.2	6.5 – 6308.0	4.9 – 505.4
Baseline haemoglobin [g/L]				
Median (IQR)	126 (115 – 132)	136.5 (124.8 – 141.2)	124 (115.5 – 132)	130.5 (120.8 – 136.5)
Range	90 – 154	113 – 151	95 – 145	110 – 139
Baseline alkaline phosphatase [IU/L]				
Median (IQR)	163.5 (106.8 – 306.8)	110 (82.8 – 126.3)	158.5 (107 – 246.5)	77 (60.5 – 98)
Range	53 – 1013	58 – 182	32 – 3140	57 – 320
Baseline albumin [g/L]				
Median (IQR)	36 (33.3 – 38)	37 (37 – 38)	35 (33 – 36)	35.5 (35 – 39)
Range	22 – 42	35 – 45	30 – 42	35 – 41

†-Percentages do not match up to 100% due to missing values

ECOG – Eastern Cooperative Oncology Group; IQR – interquartile range; PSA – prostate-specific antigen

Table S3: Baseline Characteristics of trial ineligible patients

	Abiraterone		Enzalutamide	
Characteristic	**Post-chemo**	**Pre-chemo**	**Post-chemo**	**Pre-chemo**
Number patients	39	42	33	26
Median age [years] (IQR)	72 (68.5 – 78)	75 (68 – 81)	73 (70 – 79)	77 (71.3 – 79)
Number patients ≥ 75 years (%)	16 (41.0)	22 (52.4)	12 (36.4)	15 (57.7)
Baseline ECOG performance status (%) †				
0 – 1	20 (51.3)	23 (54.8)	18 (54.5)	11 (42.3)
2 – 3	<5	10 (23.8)	5 (15.2)	7 (26.9)
Gleason score at diagnosis (%) †				
≤ 7	11 (28.2)	8 (19.0)	<5	<5
≥ 8	19 (48.7)	19 (45.2)	23 (69.7)	13 (50.0)
Number prior docetaxel cycles				
Median (IQR)	4 (2 – 9.5)	0	5 (2 – 8)	0
Range	1 – 12	0	1 – 10	0
Baseline PSA [µg/L]				
Median (IQR)	214.8 (91.3 – 551.2)	50.2 (19.8 – 94.9)	128.6 (28.8 – 312.2)	79.4 (40.5 – 244.0)
Range	0.1 – 7571.0	0.4 – 6567.6	5.1 – 1913.8	2.1 – 3689.3
Baseline haemoglobin [g/L]				
Median (IQR)	105 (93 – 117)	119.0 (108.5 – 130.5)	109.5 (99.8 – 123.5)	124.0 (112.8 – 129.0)
Range	77 – 164	74 – 147	67 – 149	85 – 164
Baseline alkaline phosphatase [IU/L]				
Median (IQR)	194.5 (111.5 – 359.2)	153.0 (83.5 – 277.5)	167.0 (106.2 – 305.0)	148 (114 – 371)
Range	67 – 1126	49 – 2172	54 – 1013	63 – 1903
Baseline albumin [g/L]				
Median (IQR)	27.0 (24.3 – 31.8)	33.0 (30.5 – 37.5)	30.0 (26.8 – 34.0)	34 (32 – 37)
Range	16 – 41	22 – 42	20 – 43	25 – 41

†- Percentages do not match up to 100% due to missing values

ECOG – Eastern Cooperative Oncology Group; IQR – interquartile range; PSA – prostate-specific antigen

Table S4: Complete case analysis – multivariable survival models

	Post-chemotherapy					Pre-chemotherapy				
Variable	**No. pat.**	**Person years follow-up**	**No. deaths**	**Adjusted HR (95% CI)**	**p-value**	**No. pat.**	**Person years follow-up**	**No. deaths**	**Adjusted HR (95% CI)**	**p-value**
Medication prescribed										
Abiraterone	29	22.5	28	1						
Enzalutamide	35	37.6	29	0.94 (0.47 – 1.86)	0.86					
ECOG performance status										
0-1	57	58.7	50	1		40	45.5	21	1	
2-3	7	1.5	7	2.78 (0.96 – 8.01)	0.06	12	10.6	8	2.19 (0.81 – 5.96)	0.12
Charlson comorbidity index score										
0	41	42.7	35	1						
1	11	8.1	11	0.99 (0.42 – 2.35)	0.99					
2+	12	9.4	11	0.74 (0.33 – 1.64)	0.45					
Number of medicines prescribed concomitantly										
≤10	9	13.0	7	1		14	18.3	5	1	
11-15	21	26.5	16	0.60 (0.21 – 1.69)	0.33	16	17.2	8	1.12 (0.34 – 3.66)	0.85
16-20	6	3.8	6	1.55 (0.44 – 5.50)	0.49	8	6.8	6	0.93 (0.20 – 4.35)	0.93
21+	28	16.9	28	1.90 (0.68 – 5.27)	0.22	14	13.9	10	2.27 (0.72 – 7.14)	0.16
Gleason score										
≤7	21	14.5	21	1						
8+	43	45.6	36	0.63 (0.31 – 1.29)	0.20					
Baseline PSA [µg/L]										
≤70	25	27.4	21	1		31	36.1	13	1	
71+	39	32.7	36	1.44 (0.76 – 2.70)	0.26	21	20.0	16	2.28 (0.94 – 5.50)	0.07
Baseline albumin [g/L]										
≤34	40	33.5	36	1		24	19.8	18	1	
35+	24	26.7	21	1.09 (0.49 – 2.39)	0.84	28	36.3	11	0.43 (0.18 – 1.04)	0.06
Baseline alkaline phosphatase [IU/L]										
≤155	28	35.6	24	1		31	38.7	14	1	
156+	36	24.5	33	1.73 (0.83 – 3.62)	0.14	21	17.4	15	2.17 (0.82 – 5.77)	0.12
Baseline haemoglobin [g/L]										
≤120	39	27.6	37	1		23	21.1	17	1	
121+	25	32.5	20	0.55 (0.22 – 1.36)	0.19	29	35.1	12	0.99 (0.35 – 2.83)	0.99

CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; HR – hazard ratio; PSA – prostate-specific antigen