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Bridging the Gap From Knowledge to Practice in Castration-Resistant Prostate Cancer

A CME Activity

Overview

The selection of therapy for patients with castration-resistant prostate cancer (CRPC) remains challenging. Review answers to some of the most important questions posed by your oncology and urology colleagues from a series of live Tumor Boards.

Content Areas:

- Androgen deprivation resistance
- Prechemotherapy vs postchemotherapy
- Sequencing therapy
- Shared decision making

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CE/CME Information

Target Audience

This activity was developed for hospital-based oncologists and urologists, community cancer center oncologists, oncology fellows and other health care professionals involved in the management of patients with castration-resistant prostate cancer (CRPC).

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Evaluate the clinical data for therapies currently available for the treatment of CRPC
- Synthesize the clinical efficacy and safety data on therapies currently under investigation for the treatment of CRPC
- Design individualized treatment algorithms for CRPC patients that may include the use of combination and sequencing strategies
- Employ effective communication strategies and shared decision making with CRPC patients

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The estimated time to complete the activity is 1.0 hour.

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Question #1: Which patients are candidates for treatment with sipuleucel-T?

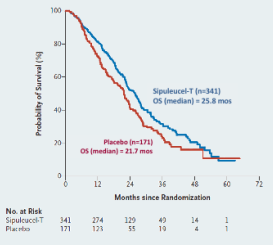
Answer: The efficacy of sipuleucel-T in improving overall survival (OS) but not time to disease progression in men with metastatic castration-resistant prostate cancer (mCRPC) was first demonstrated in 2 small phase 3 trials.[1,2] To confirm these findings, the phase 3 Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial randomized 512 patients in a 2:1 ratio to sipuleucel-T or placebo administered every 2 weeks for a total of 3 infusions.[3] Initially, only men with Gleason score ≤7 and no symptoms were enrolled, but these criteria were amended following further analysis of the earlier studies to include men with any Gleason score and whose disease was minimally symptomatic. Patients could have undergone no more than 2 chemotherapy regimens.

After a median follow-up of 34.1 months in the IMPACT trial, death occurred in 61.6% of the patients in the sipuleucel-T group and 70.8% in the placebo group (hazard ratio [HR] 0.78; *P*=0.03).[3] The median survival was 25.8 months vs 21.7 months and time to objective disease progression was 14.6 weeks vs 14.4 weeks, respectively. Reduction of the prostate specific antigen (PSA) level ≥50% occurred in 2.6% and 1.3% of sipuleucel-T and placebo patients, respectively. The most common adverse events (sipuleucel-T vs placebo) were: chills (54.1% vs 12.5%), fatigue (39.1% vs 38.1%), fever (29.3% vs 13.7%), nausea (28.1% vs 20.8%), and headache (16.0% vs 4.8%). A grade ≥3 adverse event occurred in 6.8% and 1.8% of sipuleucel-T and placebo patients, respectively, of which chills and fatigue were the most common.

Subsequent analysis of the IMPACT results showed that the PSA level was the strongest baseline prognostic factor for OS.[4] The OS benefit with sipuleucel-T was greater for patients in the lowest baseline PSA quartile (≤22.1 ng/mL) (HR 0.51; 95% confidence interval [CI] 0.31-0.85) compared with the highest PSA quartile (>134 ng/mL) (HR 0.84, 95% CI 0.55-1.29). This result may be due to lower tumor burden in the lowest PSA quartile. It is also noted that the greatest difference in OS was seen at 3 years following treatment, even though only about a third of the study population experienced a survival of this length. Although not prospectively validated, these data suggest that sipuleucel-T should be used selectively for asymptomatic patients with more indolent, lower volume mCRPC as opposed to patients with rapid progression or extensive disease.

Sipuleucel-T Survival Benefit

- Sipuleucel-T was approved based on HR of 0.775 (~4-month OS benefit)
- Survival curves separated after 6 months
- Significant PSA decline rate ~3%
- No improvement in time to progression
- Very few side effects



Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer, Kantoff PW, et al. *N Engl J Med.* 2010;363:411-422. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Survival Benefit of Sipuleucel-T Is Greater When PSA Is Lower

IMPACT: OS by Baseline PSA

Median OS, mo	Baseline PSA (ng/mL) (N=128 for all categories)			
	≤22.1	>22.1–50.1	>50.1–134.1	>134.1
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	**13.0**	**7.1**	**5.4**	**2.8**
HR (95% CI)	**0.51 (0.31-0.85)**	**0.74 (0.47-1.17)**	**0.81 (0.52-1.24)**	**0.84 (0.55-1.29)**

OS, overall survival; PSA, prostate specific antigen.
Schellhammer PF, et al. *Urology.* 2013;81:1297-1302.

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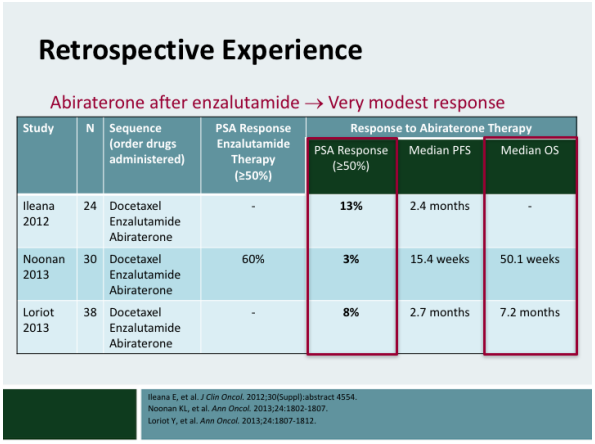
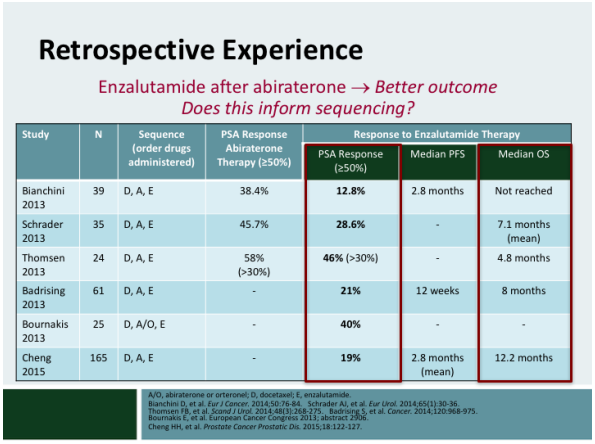
Question #2: If a patient progresses on either abiraterone or enzalutamide, should he be switched to the other or move on to a therapeutic agent with a very different mechanism of action?

Answer: Algorithms such as the one developed by the National Comprehensive Cancer Center[5] provide guidance regarding systemic therapy for metastatic castration-resistant prostate cancer (mCRPC), but the question of sequencing remains challenging. Results of 3 trials have shown a prostate specific antigen (PSA) response ≥50% ranging from 3% to 13% with abiraterone in patients who have progressed on second-line enzalutamide.[6–8] Median overall survival (OS) ranged from 7 to nearly 12 months.[7,8] Trials utilizing enzalutamide after progressing on docetaxel and/or abiraterone have shown better, albeit modest response.[9–14] PSA response ≥50% ranged from 13% to 40%, with 46% experiencing a 30% PSA response in 1 trial.[12] Median OS ranged from 4.8 months to 12.2 months in 5 of the 6 trials and was not reached in the other trial.[9]

These results do not provide a clear pathway for sequencing. Consequently, treatment should be initiated with the most effective treatment with the least toxicity. When disease progresses, it is reasonable to switch class of therapy, eg, hormone to chemotherapy, and to avoid overlapping treatments that may be antagonistic, eg, steroids and vaccines. Consideration should also be given to offering the patient the option to enroll in a clinical trial.





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Question #3: Should radium-223 be used before or after chemotherapy?

Answer: Radium-223 is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease.[15] The phase 3 Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial showed a survival benefit vs placebo in patients with ≥2 bone metastases but no known visceral metastases (14.9 months vs 11.3 months; hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.58-0.83).[16] The survival benefit vs placebo was similar in patients who had been (HR 0.70, 95% CI 0.56-0.88) and who had not been (HR 0.69, 95% CI 0.52-0.92) pretreated with docetaxel.

The previous docetaxel subgroup had a higher incidence of adverse events after receiving radium-223 than the no previous docetaxel subgroup (95% vs 90%, respectively).[16,17] A grade 3/4 adverse event occurred in 62% and 54% of patients, respectively. The previous docetaxel group had a higher incidence of grade 3/4 thrombocytopenia with radium-223 than with placebo (9% vs 3%, respectively). In contrast, the incidences of grade 3/4 anemia and neutropenia were similar between radium-223 and placebo within each docetaxel subgroup.

Logistic regression analyses identified significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223.[18] Predictors for anemia were extent of disease (6-20 vs <6 bone metastases, odds ratio [OR] 2.76; *P*=0.022), total alkaline phosphatase (OR 2.00; *P*=0.019), and elevated prostate specific antigen (PSA) level (OR 1.65; *P*=0.006). Predictors for thrombocytopenia were elevated PSA level (OR 1.83; *P*=0.016), prior docetaxel (OR 2.16; *P*=0.035), decreased hemoglobin (OR 1.35; *P*=0.008), and decreased platelets (OR 1.44; *P*=-0.030).

Taken together, these data suggest that adequate hematologic parameters are a more important criterion for choosing radium-223 than a prior history of docetaxel.

Thus, strict eligibility criteria for radium-223 include an initial absolute neutrophil count (ANC) ≥1500/μL, platelet count ≥100,000/μL, and hemoglobin ≥10 g/dL. Prior to subsequent administration of radium-223, the ANC should be ≥1000/μL and platelet count ≥50,000/μL.[15]

ALSYMPCA: Predisposing Factors for Hematologic Toxicity

Parameter estimates for maximum percentage decrease from baseline during on-treatment period in Hb, neutrophils and platelets

	Hemoglobin (n=870)		Neutrophils (n=867)		Platelets (n=870)	
Baseline variable	Parameter estimates	*P* value	Parameter estimates	*P* value	Parameter estimates	*P* value
Study tx (Ra-223/Pbo)	-1.57	0.027	-18.56	<0.0001	-10.18	<0.0001
Current use of bisphosphonates (Y/N)	-1.21	NS	-0.08	NS	-1.22	NS
Prior Docetaxel (Y/N)	-1.32	NS	-3.04	0.023	-6.04	<0.0001
EOD ≥ 6 mets including superscan (Y/N)	-2.54	0.008	-3.45	NS	-6.59	0.001
Prior EBRT to bone for pain (Y/N)	2.21	0.001	3.91	0.003	2.30	NS
Total ALP (≥220 U//L / <220 U/L/)	-3.07	<0.0001	-2.11	NS	-4.91	0.001

ALP, alkaline phosphatase; EBRT, external beam radiation therapy; EOD, extent of disease; PBO, placebo.
Parker C, et al. *J Clin Oncol.* 2013;31:abstract 5060.

Radium-223 Before or After Chemotherapy? Practical Considerations

- Only FDA-approved for patients who lack visceral metastasis
- Stringent eligibility requirements for treatment
  - Initial ANC ≥1,500/L with subsequent ≥1,000/L
  - Hb ≥10 g/dL
  - PLT ≥100,000/L with subsequent ≥50,000/L
- Requires preauthorization, while chemotherapy with docetaxel does not

ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelets.

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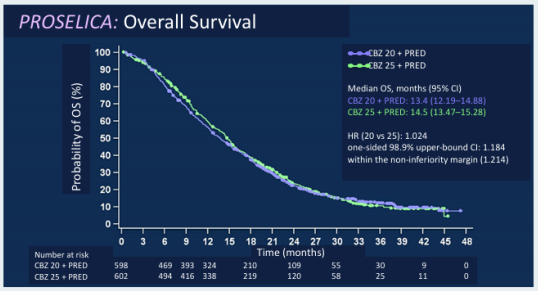
Question #4: How do you manage cabazitaxel-related toxicity?

Answer: In phase 3 clinical trials of cabazitaxel in patients with metastatic castration-resistant prostate cancer (mCRPC), the most common adverse events were febrile neutropenia, diarrhea, and hematuria.[19–21]

Febrile neutropenia is best managed with prophylactic granulocyte colony stimulating factor as recommended in the 2015 American Society of Clinical Oncology guidelines.[22] Administration of pegfilgrastim the same day as cabazitaxel, compared with 24 hours after cabazitaxel, has been shown to significantly reduce the infection rate during cycle 1 (6% vs 26%, respectively; *P*=0.01).[23]

The toxicities associated with cabazitaxel also can be managed by using a dose of 20 mg/m^2 rather than 25 mg/m^2 since the incidences of most adverse events are less with the lower dose.[20,21] In the PROSELICA trial, for example, overall survival (OS) was similar at the 2 dose levels (13.4 vs 14.5 months), but grade 3/4 adverse events were more frequent with the higher dose (39.7% vs 54.5%).[20] The most frequent grade 3/4 adverse events in the 20 mg/m^2 vs 25 mg/m^2 groups were febrile neutropenia (2.1% vs 9.2%), hematuria (1.9% vs 4.2%), and diarrhea (1.4% vs 4.0%). In the FRISTANA trial, efficacy outcomes of median OS (24.5 months vs 25.2 months) and progression-free survival (4.4 months vs 5.1 months) were similar in the lower and higher dose groups, while febrile neutropenia, diarrhea, and hematuria were more frequent with the 25 mg/m^2 dose. Grade 3/4 adverse events occurred in 41.2% and 60.1% of patients treated with 20 mg/m^2 compared with 25 mg/m2, respectively.[21]

The PROSELICA Study–Cabazitaxel 20 vs 25 mg/m²



De Bono JS, et al. *J Clin Oncol.* 2016;34(Suppl):abstract 5008.

The PROSELICA Study – Adverse Events

PROSELICA: Treatment-Emergent Adverse Events

Patients, n (%)	CBZ 20 + PRED N = 580	CBZ 25 + PRED N = 595
Any Grade TEAE	529 (91.2)	559 (93.9)
Grade 3–4 TEAE	230 (39.7)	324 (54.5)
Serious TEAE	177 (30.5)	257 (43.2)
TEAE leading to permanent treatment discontinuation	95 (16.4)	116 (19.5)
Most frequent Grade 3–4 TEAEs reported in ≥ 5% pts, n (%)		
Febrile neutropenia	12 (2.1)	55 (9.2)
Hematuria	11 (1.9)	25 (4.2)
Diarrhea	8 (1.4)	24 (4.0)
Fatigue	15 (2.6)	22 (3.7)
Urinary tract infection	10 (1.7)	13 (2.2)
Bone pain	10 (1.7)	13 (2.2)
Asthenia	11 (1.9)	12 (2.0)
Vomiting	7 (1.2)	8 (1.3)
Nausea	4 (0.7)	7 (1.2)

De Bono JS, et al. *J Clin Oncol.* 2016;34(Suppl):abstract 5008.

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Question #5: When do you worry about small cell or neuroendocrine prostate cancer?

Neuroendocrine prostate cancer (NEPC) is an aggressive variant of prostate cancer in patients with metastatic castration-resistant prostate cancer (mCRPC) following androgen deprivation therapy (ADT).[24,25] Overall survival is typically less than 1 year from time of detection.[26]

NEPC tumors appear to arise clonally from a prostate adenocarcinoma precursor, thereby retaining many of the common prostate cancer genomic alterations; however, new molecular alterations occur as well.[25] Treatment-emergent NEPC may occur in 30% to 40% of patients with mCRPC, including 10% to 15% with pure small cell histology and about 25% with a phenotype intermediate between adenocarcinoma and small cell.[26]

Presentation of NEPC is more likely in the setting of predominant visceral metastases, ie, liver metastases, bulky lymphadenopathy, low prostate specific antigen (PSA) level despite high volume disease and/or predominantly lytic rather than blastic bone metastases.[24] Clinically, NEPC should be suspected in patients who have particularly aggressive mCRPC who have failed to respond to typical prostate cancer therapies, with progression in the setting of a low or nonrising PSA.[24] Metastatic tumor biopsy is needed to make a definitive diagnosis by morphology or immunohistochemical staining for neuroendocrine markers like chromogranin A or synaptophysin. By themselves, serum neuroendocrine markers have limited sensitivity.

The choice of systemic therapy depends on the clinical context (de novo vs treatment-emergent) and pathologic findings (small cell vs focal neuroendocrine differentiation). When biopsy reveals pure small cell differentiation, cytotoxic chemotherapy is preferred over androgen pathway inhibitors, such as abiraterone or enzalutamide. If the biopsy also reveals concomitant persistent androgen receptor expression, carboplatin plus docetaxel is reasonable for patients who are deemed fit. In cases with minimal evidence of dependence on AR signaling, a platinum-etoposide doublet may be preferred. If the biopsy reveals high-grade adenocarcinoma with focal neuroendocrine differentiation or intermediate phenotypic features without frank small cell morphology, cytotoxic chemotherapy and/or androgen signaling inhibitors can be used.[5,27] Alternatively, a taxane plus carboplatin can be considered for patients who are fit. However, given the relatively poor outcomes and aggressive clinical course, participation in a prospective clinical trial is encouraged.

Situations to Perform a Metastatic Biopsy

- Visceral lesions especially liver metastasis
- Extremely bulky lymph nodes (>5 cm)
- Low PSA in the setting of very high volume disease
- Predominantly lytic rather than blastic bone metastases

Neuroendocrine/Small-Cell Prostate Cancer

- De novo presentation rare (<1% new diagnoses)
- May arise as a mechanism of resistance to ADT
- Metastatic disease, including unusual sites of metastases
- Low or modestly rising PSA
- Paraneoplastic syndromes (uncommon)
- Elevated CEA or serum neuroendocrine markers (chromogranin, neuron-specific enolase) can support the diagnosis
- Tissue IHC expresses chromogranin A and synaptophysin
- Treated like small-cell lung cancer platinum-doublet chemotherapy, eg, cisplatin or carboplatin with (etoposide)

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Case Study

A 55-year-old male presents with de novo prostate cancer that has metastasized to the bones diffusely and multiple retroperitoneal lymph nodes. He initially received androgen deprivation therapy (ADT) with 6 cycles of docetaxel chemotherapy. He had a good initial response with an undetectable prostate specific antigen (PSA) level. However, soon after completion of docetaxel, his PSA rose rapidly, indicating castration-resistant disease. He briefly responded to 5 months of treatment with abiraterone/prednisone, but then progressed with a rising PSA, multiple new bone metastases, and new bone pain.

Because of his rapid progression after docetaxel for hormone-sensitive disease, he was given cabazitaxel plus prednisone. His PSA declined slightly over the first 3 cycles but then started to rise slightly to 5.3 ng/mL. Imaging revealed multiple new liver metastases. A metastatic liver biopsy revealed no small cell morphology; immunohistochemistry was negative for chromogranin A and synaptophysin. His biopsy tissue was sent for commercial next-generation sequencing which revealed genetic alterations in *BRCA2*. This was surprising since he had no family history of prostate, breast, or ovarian cancer. Since he was not able to travel, enrollment into a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor clinical trial was not considered. Instead, treatment with a regimen of docetaxel plus carboplatin was initiated. His liver metastases decreased in size and his bone pain improved.

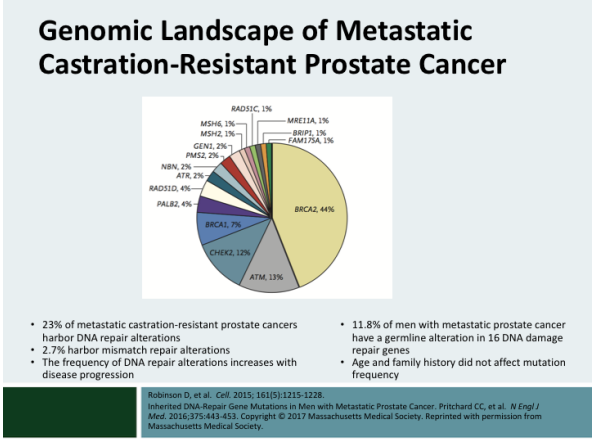
Discussion

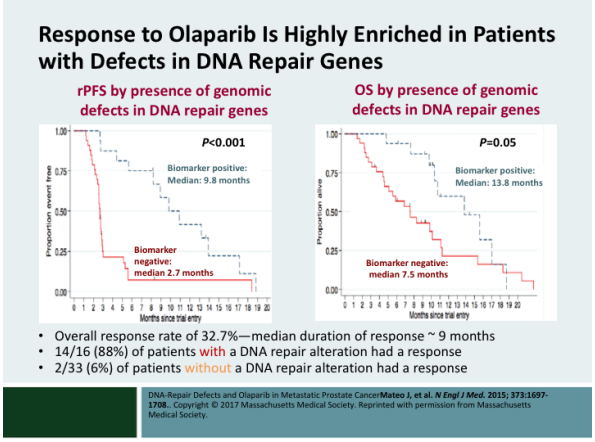
Disease progression is common in men with castration-resistant prostate cancer (CRPC) requiring thoughtful use of sequential therapy based on evolving evidence.[5] Increasingly, this evidence includes genomic profiling to identify the molecular subtype. One recent investigation found that approximately 90% of patients with metastatic prostate cancer (mCRPC) harbor clinically actionable molecular mutations, with 23% having DNA repair pathway and 8% harbor germline mutations.[28] The most frequent aberrant genes were androgen receptor (62.7%), E26 transformation-specific fusion (56.7%), *TP53* (53.3%), and *PTEN* (40.7%).

Another recent investigation found that 11.8% of men with metastatic prostate cancer harbored germline DNA-repair gene mutations.[29] The most common mutation occurred in the *BRCA2* gene (5.3% of men). Mutation frequencies did not differ according to family history or age at diagnosis. Family genetic counseling is important when germline alterations are suspected.

Having a DNA repair gene abnormality may predispose to increased response to agents like PARP inhibitors or other agents that induce double-strand breaks like platinum chemotherapy.[30–32] A recent phase 2 trial showed that 14 of 16 evaluable patients (88%) with heavily pretreated mCRPC and a DNA repair mutation had a response to the PARP inhibitor olaparib compared with 2 of 33 (6%) patients without a DNA repair mutation.[33] The 14 patients with a DNA repair mutation included all 7 with *BRCA2* loss (4 with biallelic somatic loss and 3 with germline mutations) and 4 of 5 with *ATM* mutations.

Although further study of patients with DNA repair abnormalities are ongoing, the preliminary data suggest that there is likely to be clinical benefit seen with platinum agents and PARP inhibitors. Furthermore, tumor and germline DNA sequencing should be considered in the management of mCRPC to identify patients who are likely to derive benefit from this approach.





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