time of the third interim analysis [Rathkopf DE et al. *Eur Urol.* 2014].

The final analysis consisted of data from a median follow-up of 49.2 months. At this time, 92% of patients in the abiraterone arm and 100% in the placebo arm had discontinued therapy, most often for radiographic progression. Median OS was 34.7 months in the abiraterone arm and 30.3 months in the placebo arm, corresponding to a 19% relative reduction in the risk of death (HR, 0.81; $P = .0033$). The treatment effect of abiraterone was more pronounced when adjusting for the 44% of patients receiving prednisone who subsequently received abiraterone (HR, 0.74). More than one-fourth of patients randomized into the abiraterone arm have survived for 48 months or longer, noted Dr Ryan.

The final analysis also demonstrated a significant improvement in median time to opiate use for cancer-related pain when comparing abiraterone versus placebo (median, 33.4 vs 23.4 months, respectively; HR, 0.72; $P < .00001$). With 2 additional years of follow-up since the previous clinical cutoff, the safety profile of abiraterone remained unchanged. No new safety signals emerged despite the longer duration of therapy and follow-up compared with prior analyses.

ERA 223 to Study Radium-223 and Abiraterone in Combination in mCRPC

Written by Nicola Parry

Matthew R. Smith, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts, USA, discussed the Phase III Randomized, Double-Blind, Placebo-Controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-Naïve Subjects With Bone Predominant Metastatic Castration-Resistant Prostate Cancer (CRPC) trial [ERA 223; NCT02043678] that is now recruiting patients with bone metastases and CRPC.

According to Dr Smith, skeletal metastases are common in prostate cancer, occurring in approximately 90% of men with advanced disease. Bone metastases result in decreased quality of life by causing problems such as bone pain, morbidity, pathologic fracture, and spinal cord compression [Autio K, Morris MJ. *Clin Adv Hematol Oncol.* 2013].

Although approximately half of patients with metastatic prostate cancer are asymptomatic and may not be good candidates for immediate chemotherapy, they may benefit from alternate therapies [National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Prostate Cancer* v2. 2014; Cookson MS et al. *Castration-Resistant Prostate Cancer: American Urological Association (AUA) Guideline.* 2014].

A first-in-class α-radiopharmaceutical that selectively targets bone metastases, radium-223 has gained US Food and Drug Administration approval for use based primarily on increased overall survival (OS) demonstrated in the large, randomized, placebo-controlled phase 3 ALSYMPCA trial [Parker C et al. *N Engl J Med.* 2013; http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm352393.htm].

Compared with placebo, radium-223 prolonged OS by 3.6 months and delayed time to first symptomatic skeletal event (SSE) by 5.8 months in patients with CRPC with symptomatic bone metastases when added to best standard of care [Parker C et al. *N Engl J Med.* 2013]. It also demonstrated a favorable safety profile with low rates of myelosuppression, which supports combining it with other agents, noted Dr Smith.

He added that abiraterone plus prednisone is a standard of care for patients with CRPC who are not eligible for docetaxel because they are asymptomatic or mildly symptomatic. Abiraterone produces OS and radiographic progression-free survival benefits, and significantly delays clinical deterioration and initiation of chemotherapy in patients with metastatic CRPC (mCRPC) [Ryan CJ et al. *N Engl J Med.* 2014].

According to Dr Smith, the different modes of action of radium-223 and abiraterone, and their non-overlapping toxicity profiles, suggest that a combination of the 2 treatment options will prolong SSE-free survival compared with abiraterone alone.

Consequently, ERA 223 was designed to prospectively evaluate combination therapy with abiraterone acetate and prednisone in combination with radium-223 in men with asymptomatic or mildly symptomatic, chemotherapy-naïve, bone-predominant mCRPC.

The study will accrue patients with bone metastases (both symptomatic and asymptomatic) and CRPC. It will include men (≥18 years with a life expectancy ≥6 months) with pathologically confirmed prostatic adenocarcinoma that is castration-resistant, with ≥2 bone metastases within 4 weeks prior to randomization.

Exclusion criteria include prior treatment with abiraterone or cytotoxic chemotherapy, and a history of visceral or brain metastasis.

Approximately 800 eligible subjects will be randomized 1:1 to abiraterone acetate (1000 mg QD) and oral prednisone (5 mg BID) plus radium-223 (50 kBq/kg body weight intravenously, every 4 weeks for 6 cycles) or abiraterone acetate and prednisone plus placebo.

The primary end points are SSE-free survival, with a key secondary end point of OS. In order to determine safety and OS, the long-term follow up consisted of a phone call every 6 months until 7 years after the last dose of radium-223 or death.

During the study, patients will be evaluated at each treatment visit for efficacy, safety, and health-related quality of life. Disease progression and long-term safety will also be assessed every 3 months. Upon completion of radium-223 treatment, all subjects will continue to receive abiraterone plus prednisone until occurrence of an SSE or death.

This trial is currently recruiting participants, with 74 enrolled as of September 5, 2014, concluded Dr Smith.

Enzalutamide Plus Radiation Therapy for High-Risk Localized Prostate Cancer

Written by Maria Vinall

Adjuvant androgen deprivation therapy (ADT), including a luteinizing hormone-releasing hormone analogue (LHRHA) for 2 to 3 years, is the standard of care before, during, and after radiotherapy for patients with localized prostate cancer at high risk of recurrence. Although outcomes in patients receiving long-term ADT (18 to 36 months) are superior to those seen in patients receiving 6 months of treatment, the optimal regimen remains unclear.

Scott Williams, PhD, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, presented the design and objectives for a phase 3 trial of Enzalutamide in Androgen Deprivation Therapy with Radiation Therapy for High Risk, Clinically Localized, Prostate Cancer [ENZARAD; Australian New Zealand Clinical Trials Registry ACTRN12614000126617; Williams S et al. *Ann Oncol.* 2014], which is currently enrolling patients.

Enzalutamide is a new second-generation androgen receptor inhibitor that improves survival in metastatic castration-resistant prostate cancer; it is more potent and binds with a higher affinity to androgen receptors than do conventional nonsteroidal antiandrogens (NSAAs).

ENZARAD is an open-label intergroup trial open to adult men who have localized prostate cancer that is of high risk of recurrence and who are suitable for external beam radiation therapy (EBRT) with the intent to cure. Participants are stratified by Gleason score (7 vs 8 to 10), clinical stage (T1 to T2 vs T3 to T4), prostate-specific antigen (PSA) levels ≥10 ng/mL or ≥20 ng/mL, and study site. Patients are then randomized 1:1 to either enzalutamide (160 mg, daily) for 24 months or conventional NSAAs for 6 months. All participants will receive LHRHA for 24 months and EBRT (78 Gy/39 F) starting after week 16.

The primary study end point is overall survival. Secondary end points include cause-specific survival, PSA progression-free survival, clinical progression-free survival, time to subsequent hormonal therapy, health-related quality of life, adverse events, and health outcomes relative to cost. A tertiary objective is to identify biomarkers that are prognostic or predictive of response to treatment. Study assessments will be conducted at baseline; weeks 4, 12, 16, 20, and 24; then every 3 to 4 months until year 5, every 6 months until year 7, and annually thereafter. Computed tomography and magnetic resonance imaging and bone scan will be performed at baseline, then as clinically indicated. The tertiary objective will be assessed through archival tumor tissue and data from fasting blood collected at baseline, 24 weeks, 5 years, and first evidence of progression.

This study opened for recruitment in March 2014, with a planned duration of recruitment of 2 years. As of September 27, 2014, 9 sites were open to recruitment; 84 patients had been screened; and 20 patients had been randomized to treatment. Sites continue to be opened for recruitment in Australia, New Zealand, Ireland, the United Kingdom, and Europe.

Additional information on this study is available by e-mail (enzarad@ctc.usyd.edu.au) or from the study website: http://www.anzup.org.au/.

RAM Fails to Improve OS as Second-Line Treatment for Hepatocellular Cancer

Written by Wayne Kuznar

As second-line therapy for hepatocellular carcinoma (HCC), ramucirumab (RAM) did not improve overall survival (OS) compared with placebo (PBO) in a phase 3 randomized study, but benefit was observed in a selected population with an elevated baseline level of alpha-fetoprotein (AFP). The results of the randomized, phase 3 Ramucirumab Second-Line Treatment in Patients With Hepatocellular Carcinoma After First-Line Therapy With Sorafenib study [REACH; NCT01140347] were presented by Andrew X. Zhu, MD, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA.

Currently, no treatment has demonstrated a survival benefit in a second-line setting (after sorafenib) in HCC [Zhu AX et al. *JAMA*. 2014; Llovet JM et al. *J Clin Oncol.* 2013]. Vascular endothelial growth factor (VEGF)