Table 1. Kaplan–Meier Overall Survival Estimate for Everolimus vs Placebo

Time Point, mo	Everolimus	Placebo	Placebo Corrected by RPSFT
12	82.6 (76.6 to 87.2)	82.0 (75.9 to 86.7)	74.9
24	67.7 (60.7 to 73.8)	64.0 (56.8 to 70.2)	≤55.6
36	56.7 (49.4 to 63.3)	50.9 (43.6 to 57.7)	
48	46.9 (39.7 to 53.8)	41.3 (34.3 to 48.1)	
60	34.7 (27.7 to 41.7)	35.5 (28.7 to 42.4)	

Data are presented as hazard ratios (95% CIs). Adverse events (n = 221) during the open-label phase continued the pattern of the core phase, and most commonly included stomatitis (47%), diarrhea (44%), and rash (40%).

RPSFT, rank-preserving structural failure time.

involved a stratified log-rank test in the intent-to-treat population of 410 randomized patients.

Of the 410 patients, 225 ultimately received everolimus; this included most of the patients initially randomized to the placebo arm (172 of 203, 85%). The median length of exposure to open-label everolimus following crossover was 44.0 weeks (range, 0 to 261 weeks) in patients originally randomized to placebo and 67.1 weeks (range, 1 to 189 weeks) in those originally randomized to the drug. At the OS cutoff, 126 of 207 patients (61%) in the everolimus arm and 130 of 203 patients (64%) in the placebo arm had died. In the latter, 23 of 130 deaths occurred before crossover. The median OS was 44.02 months (95% CI, 35.6 to 51.8 months) for the everolimus arm and 37.68 months (95% CI, 29.1 to 45.8 months) for the placebo arm. The results indicated a benefit for everolimus (HR, 0.94; 95% CI, 0.73 to 1.20) although statistical significance was not achieved ($P = .30$; significance boundary 0.0249) (Figure 2), likely due to crossover of 85% of patients originally randomized to placebo.

To account for the bias due to the large number of crossovers, the investigators conducted rank-preserving structural failure time (RPSFT) analysis, which corrects for the effect of crossover by estimating the multiplicative factor that estimates the effect of each day of everolimus treatment on overall survival and subsequently adjusts for the effect of everolimus received after crossover in the placebo arm.

The Kaplan–Meier and RPSFT-corrected survival estimates for five different time points are shown in Table 1. The hazard ratio was 0.90 (95% CI, 0.71 to 1.16), adjusted for baseline age, sex, region, and prior use of somatostatin analog.

The median OS of 44 months for everolimus-treated patients is the longest reported for progressive advanced pNET in a phase 3 study. The investigators noted that the improvement of 6.3 months in median OS vs placebo was clinically important.

Abiraterone Significantly Extends Survival in mCRPC

Written by Wayne Kuznar

Abiraterone acetate as therapy for chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) improved overall survival (OS) compared with placebo in the final OS analysis of the phase 3 COU-AA-302 clinical trial.

Charles J. Ryan, MD, University of California, San Francisco, San Francisco, California, USA, presented data from more than 4 years of follow-up from the international, randomized, double-blind, placebo-controlled COU-AA-302. Abiraterone is an orally available inhibitor of the CYP17 enzyme complex, a key regulator of androgen synthesis.

Eligible patients for the trial were required to have mCRPC and to be free of disease-related symptoms that would lead to a requirement for opiate analgesic use. The study included 1088 men with mCRPC who were randomized in a 1:1 fashion to receive abiraterone acetate 1000 mg QD with concurrent prednisone 5 mg BID, or placebo plus prednisone 5 mg BID. The co-primary end points were radiographic progression-free survival (rPFS) and OS.

The study was unblinded on the recommendation of the Independent Data Safety Monitoring Committee after the second interim analysis based on a significant difference in rPFS as well as an emerging trend for OS in favor of abiraterone. After unblinding, the study was not discontinued. A subsequent protocol amendment allowed patients in the placebo arm to receive abiraterone. The current analysis incorporated survival and other data after the observation of 741 deaths.

Treatment arms were evenly matched with respect to common clinical and prognostic variables. The median PSA level was approximately 40 ng/mL in both arms. Approximately half of the patients enrolled had 10 or more bone metastases.

Eighty percent of patients in the placebo arm and 67% in the abiraterone arm received subsequent therapy for mCRPC prior to unblinding of the study. The most common subsequent therapy was docetaxel (about 60% in each arm).

Three interim analyses were conducted. As assessed by investigator review, abiraterone doubled the time to rPFS from 8.2 to 16.5 months (HR, 0.52; $P < .0001$) at the

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.