long-term treatment-related neurotoxicity occurred in only 1.6% and 1.0% of patients in the docetaxel- and non-docetaxel-based regimens, respectively.

Although the addition of docetaxel to anthracycline-based adjuvant chemotherapy did not improve DFS or OS, the data suggested a benefit of sequential docetaxel in patients with highly proliferative ER-positive breast cancer, concluded Prof Sonnenblick.

Trial Will Evaluate Niraparib vs Placebo in Platinum-Sensitive Patients With Ovarian Cancer

Written by Maria Vinall

Niraparib is a potent oral PARP1 and PARP2 (poly [ADP-ribose] polymerase) inhibitor with antitumor activity in germline BRCA mutation (gBRCAmut) ovarian cancer and BRCA-negative (non-gBRCAmut) high-grade serous ovarian cancer (HGSOC).

Niraparib demonstrated antitumor activity in a recent phase 1 (dose-finding) trial of patients with advanced solid tumors (half the population enriched for *BRCA1* and *BRCA2* mutations) [Sandhu SK et al. *Lancet Oncol.* 2013]. Niraparib was well tolerated in this study, with a relatively low rate of grade 3 and 4 toxicities. The most common grade 3 or 4 treatment-related adverse events were anemia and thrombocytopenia (9% and 8% for grade 3 and 1% and 7% for grade 4, respectively) and 4% each for fatigue and neutropenia grade 3. Among study participants with sporadic HGSOC, 3 of 4 platinum-sensitive patients achieved RECIST responses (Response Evaluation Criteria in Solid Tumors). Based on these results, further trials were recommended.

Mansoor R. Mirza, MD, Oncology, Nordic Society of Gynaecologic Oncology and Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, presented the study design of an ongoing niraparib maintenance study examining platinum-sensitive patients with ovarian cancer and deleterious gBRCA^{mut} or high-grade serous histology non-gBRCA^{mut} (NOVA; NCT01847274).

The repeating 28-day maintenance cycle begins with screening and is followed by evaluation of gBRCA mutation status. From there, randomization occurs in 2 groups: gBRCA^{mut} (n = 180) and non- gBRCA^{mut} (n = 180). Each group is further divided into 2 groups: those receiving 300 mg of niraparib and those receiving placebo. After this, end points are assessed.

Women are eligible to participate in this phase 3 trial who are aged ≥ 18 years with histologically confirmed ovarian cancer, including either a tumor with HGSOC histology or known gBRCA^{mut}, and who have completed ≥ 2 courses of platinum-containing therapy with documented platinum sensitivity (complete or partial remission; no measurable lesion > 2 cm and normal CA125 or > 90% decrease during the last platinum regimen). Patients must also have an Eastern Cooperative Oncology Group score of 0 to 1 and normal organ function.

The primary study objective is to evaluate the effect of niraparib (300 mg, QD) on progression-free survival (PFS). Secondary objectives include additional measures of clinical benefit: patient-reported outcomes; PFS2, defined as the time from treatment randomization to the assessment of progression on a subsequent anticancer therapy or death by any cause; chemotherapy-free interval; and overall survival. Corrected QT intervals will be evaluated in a subset of patients. Other secondary objectives are to evaluate the safety and tolerability of niraparib versus placebo, the concordance of the centralized *BRCA* mutation test and a candidate companion diagnostic test with respect to gBCRA^{mut} patients, and the effects of food on the pharmacokinetics of niraparib.

The efficacy of oral niraparib will be determined by PFS as assessed by RECIST 1.1 via computed tomography or magnetic resonance imaging every 2 cycles through cycle 14, then every 3 cycles. Other end points are assessed by various targeted questionnaires. Analysis of 2 independent patient cohorts (deleterious gBRCA^{mut} and high-grade serous or high-grade predominantly serous histology non-gBRCA^{mut}) is being conducted under the hypothesis that patients with gBRCA mutations are enriched for responsiveness to niraparib. Pharmacokinetics will be assessed in all patients, and food effects will be assessed in a subset of patients who ingest a high-fat meal. This trial is being conducted in Europe, the United States, and Canada.

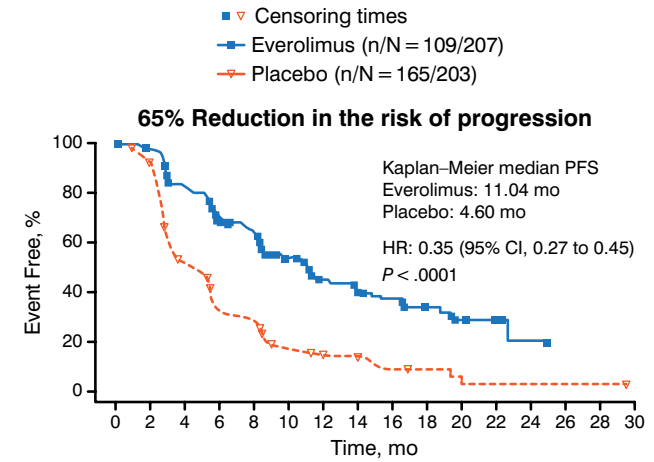
Niraparib is also being investigated in a phase 3 trial in patients with Her2-negative, germline *BRCA* mutation–positive breast cancer [BRAVO; NCT01905592].

Everolimus Safe and Effective for Advanced pNET: Final Results of RADIANT-3

Written by Brian Hoyle

Final overall survival (OS) and safety results of the phase 3 Everolimus and Octreotide in Patients With Advanced Carcinoid Tumor trial [RADIANT-3; NCT00412061] have bolstered previous findings that everolimus is effective and safe in the treatment of advanced pancreatic neuroendocrine tumors (pNET).

Figure 1. Primary End Point Data for RADIANT-3



No. of patients still at risk

Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

The *P* value was obtained from a stratified one-sided log-rank test and the HR was obtained from a stratified unadjusted Cox model.
PFS, progression-free survival.
From Yao JC et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–523. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

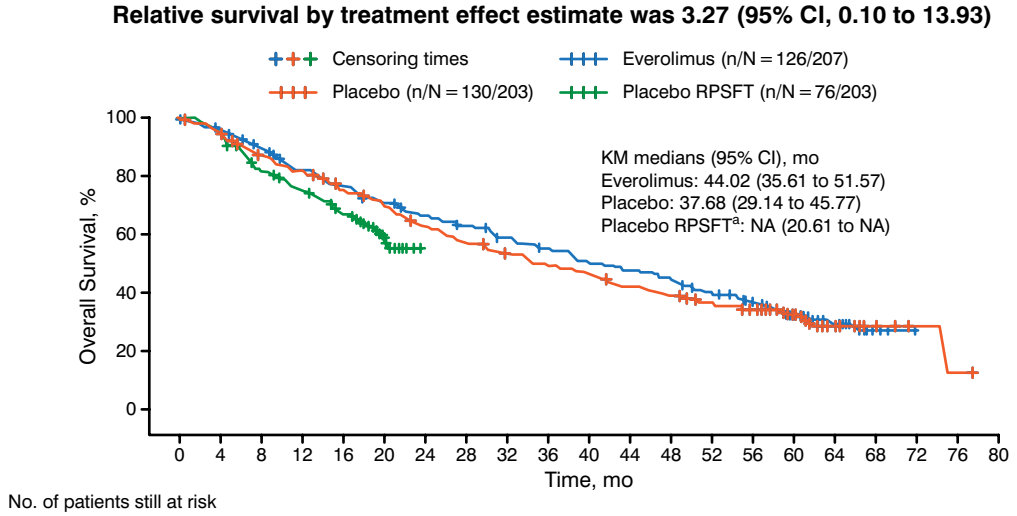
Prognosis is poor for patients with pNET, as the tumors are often advanced when diagnosed. In 2011, however, the RADIANT-3 trial investigators reported significantly improved median progression-free survival (PFS) in patients with advanced pNET treated using everolimus vs placebo (11.0 months vs 4.6 months) [Yao JC et al. *N Engl J Med.* 2011]. The present findings are the final OS and extended safety data including those from the open-label portion of the study.

RADIANT-3 investigators randomized 410 patients with advanced pNET in a 1:1 fashion to receive everolimus 10 mg/d (n = 207) or placebo (n = 203), both along with best supportive care, in the double-blind core phase of the study. In the open-label extension phase, crossover to the everolimus arm was allowed when disease progression occurred. The extension phase comprised 53 patients from the original everolimus arm and 172 crossover patients.

The primary end point was PFS according to RECIST 1.0 (Figure 1).

Secondary end points included OS as of the March 5, 2014 cutoff date after 256 events (deaths). The OS analysis

Figure 2. Final Overall Survival Analysis by RPSFT



No. of patients still at risk

Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0
Placebo RPSFT	203	189	159	143	125	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

KM Estimate (%, 95% CI)	Everolimus 10 mg	Placebo	Placebo Corrected by RPSFT[a]
12 mo	82.6 (76.6 to 87.2)	82.0 (75.9 to 86.7)	74.9
24 mo	67.7 (60.7 to 73.8)	64.0 (56.8 to 70.2)	≤ 55.6

Reproduced with permission from JC Yao, MD.
KM, Kaplan–Meier; RPSFT, rank-preserving structural failure time.
[a]Reconstructed placebo data as if never treated with everolimus.

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