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)

and VEGF receptor-2 (VEGFR-2)-mediated signaling and angiogenesis are likely contributors to HCC tumor growth. RAM is a human immunoglobulin G1 monoclonal antibody that binds to the extracellular domain of VEGFR-2, preventing ligand binding and receptor activation. Preliminary evidence of RAM's anticancer activity was demonstrated in patients with treatment-naïve HCC in a single-arm phase 2 study [Zhu AX et al. *Clin Cancer Res.* 2013].

REACH evaluated the safety and efficacy of RAM in 565 patients with advanced HCC following first-line therapy with sorafenib. The primary end point was OS with progression-free survival (PFS), objective response rate (ORR), and safety included as secondary end points. Eligible patients had advanced HCC confirmed by histology or radiographic imaging to be Barcelona Clinic Liver Cancer stage C or B, were refractory or not amenable to locoregional therapy, were Child-Pugh Class A, and had disease progression during or following sorafenib therapy (or were intolerant to sorafenib). Patients were randomized to RAM 8 mg/kg intravenously (n = 283) plus best supportive care (BSC), or PBO (n = 282) plus BSC every 2 weeks per cycle, until disease progression or unacceptable toxicity. Baseline demographics and characteristics were balanced between the 2 arms.

The safety population consisted of 553 patients (277 in the RAM arm and 276 in the PBO arm). Grade ≥ 3 treatment-related adverse events reported in ≥ 3% of patients in the RAM arm included hypertension (12% in the RAM arm vs 4% in the PBO arm), thrombocytopenia (5% vs < 1%), hepatic encephalopathy (3% vs < 1%), and neutropenia (3% vs 1%). Bleeding or hemorrhage of any grade occurred in 33% of the RAM group and 20% of the PBO group; liver injury or failure in 51% and 37%, respectively; and proteinuria in 17% and 5%, respectively (Table 1).

In the intention-to-treat population, median OS was 9.2 months in the RAM arm and 7.6 months in the PBO arm (HR, 0.866; $P = .1391$). Median PFS was 2.8 months in the RAM arm and 2.1 months in the PBO arm (HR, 0.625; $P < .0001$). The median time to progression was 3.5 months in the RAM arm vs 2.6 months in the PBO arm ($P < .0001$). The 6-month PFS rates were 37.0% in RAM recipients and 14.9% in PBO recipients, and the 9-month PFS rates were 27.0% and 10.8%, respectively.

Table 1. Adverse Events of Special Interest in REACH

	Ramucirumab (n = 277), n (%)		Placeb (n = 276), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Liver injury or failure[a]	140 (51)[b]	58 (21)	103 (37)	65 (24)
Bleeding or hemorrhage[a]	90 (33)[b]	17 (6)	55 (20)	21 (8)
Epistaxis	38 (14)[b]	0	17 (6)	0
GI hemorrhage[a]	25 (9)	11 (4)	23 (8)	17 (6)
Hepatic hemorrhage[a]	2 (< 1)	2 (< 1)	2 (< 1)	2 (< 1)
Pulmonary hemorrhage[a]	9 (3)	1 (< 1)	4 (1)	2 (< 1)
Hypertension[a]	56 (20)[b]	35 (13)[b]	20 (7)	10 (4)
Proteinuria[a]	48 (17)[b]	6 (2)[b]	13 (5)	0
Renal failure[a]	20 (7)	6 (2)	18 (7)	3 (1)
Infusion-related reaction[a]	20 (7)[b]	3 (1)	2 (< 1)	0
Venous thromboembolic[a]	6 (2)	2 (< 1)	4 (1)	4 (1)
Arterial thromboembolic[a]	2 (< 1)	0	4 (1)	1 (< 1)
Congestive heart failure[a]	0	0	2 (< 1)	1 (< 1)
Healing complication[a]	0	0	1 (< 1)	0

GI, gastrointestinal; REACH, the Ramucirumab Second-Line Treatment in Patients With Hepatocellular Carcinoma After First-Line Therapy With Sorafenib study.

[a]Pooled adverse event terms.

[b]$P < .05$; P value is based on Fisher exact test comparing ramucirumab to placebo.

Reproduced with permission from AX Zhu, MD.

Table 2. Tumor Response Rates in REACH

	Ramucirumab, n = 283	Placebo, n = 282	*P* Value
Objective response (CR + PR), n (%)	20 (7.1)	2 (0.7)	< .0001
Disease control rate (CR + PR + SD), n (%)	159 (56.2)	129 (45.7)	.0110
CR, n (%)	1 (0.4)	0	
PR, n (%)	19 (6.7)	2 (0.7)	
SD, n (%)	139 (49.1)	127 (45.0)	
PD, n (%)	97 (34.3)	129 (45.7)	
Not evaluable, n (%)	27 (9.5)	24 (8.5)	

CR, complete response; PD, progressive disease; PR, partial response; REACH, the Ramucirumab Second-Line Treatment in Patients With Hepatocellular Carcinoma After First-Line Therapy With Sorafenib study; SD, stable disease.

Reproduced with permission from AX Zhu, MD.

The objective response rates were 7.1% in the RAM arm and 0.7% in the PBO arm ($P < .0001$), and the disease control rates were 56.2% and 45.7% ($P = .0110$), respectively (Table 2).

Two hundred and fifty patients had a baseline AFP level ≥ 400 ng/mL. In a prespecified analysis of OS in this subgroup, the OS HR in the RAM group compared with PBO was 0.674 ($P = .0059$), with a median OS of 7.8 months in the RAM group vs 4.2 months in the PBO group.

Dr Zhu concluded that although REACH did not demonstrate a significant improvement in OS with RAM in the intent-to-treat population, an elevated baseline AFP may select a population likely to benefit. Further investigation of RAM is warranted based on the REACH results and the unmet need in this disease.

Phase 3 Trial to Compare Postoperative Chemotherapy With Observation in Stage I or II Endometrial Cancer

Written by Maria Vinall

Patients with stage I or II endometrial cancer are generally treated with surgery. Despite radical surgery, however, patients with medium- or high-risk stage I and II endometrial cancers are still at significant risk of local and distant progression. Adjuvant radiotherapy has not been shown to improve survival, and adjuvant chemotherapy alone has shown greater survival benefit in patients with more advanced disease [Creutzberg CL et al. Curr Oncol Rep. 2011]. The current phase 3 study [NCT01244789] is preparing to evaluate whether survival can be improved in intermediate- and high-risk early-stage patients by offering postoperative chemotherapy instead of postoperative observation alone (standard strategy).

Frederic Amant, MD, EORTC and University of Leuven, Leuven, Belgium, presented the design of the study, which will evaluate this premise in patients with medium- or high-risk node-negative stage I or II endometrial cancer. Eligible patients must have a diagnosis of stage I grade 3, stage II, or stage I or II type 2 endometrioid adenocarcinoma and have undergone hysterectomy and bilateral salpingo- oophorectomy and pelvic lymphadenectomy (LNE; minimum, 12 pelvic nodes; para-aortic LNE optional). All patients are required to be World Health Organization performance status 0 to 2.

Eligible patients will be stratified by histology (endometrioid vs nonendometrioid), stage (1a vs 1b vs 2 disease), para-aortic (≥ 10) and pelvic (≥ 20) LNE versus lesser LNE, and brachytherapy (planned yes/no); they will then be randomized (1:1) to postoperative adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC5) every 3 weeks for a total of 6 courses or postoperative follow-up without any further treatment. Adjuvant brachytherapy is permitted in both arms; external beam radiotherapy is not allowed. All patients will be followed for a minimum of 3 years.

The primary study end point is overall survival. Secondary end points include disease-specific survival, progression-free survival, toxicity, quality of life based on patient-reported outcomes (EORTC QLQ-C30 and QLQ-EN24—quality-of-life questionnaires for cancer and endometrial cancer), as well as the rates of isolated