SUPPLEMENTAL TEXT

Subgroup analysis by tumor histology

Unlike many clinical trials with stringent selection criteria, EU-ARCCS enrolled patients with diverse tumor histologies, a known prognostic factor for RCC. Small subpopulations of patients in the study had clear-cell RCC with sarcomatoid features (n=53), with papillary features (n=112), with other histologic features (n=66), and other histologies (n=10); the majority of patients in the ITT population had pure clear-cell RCC (79%; n=909). Patients with sarcomatoid histologic features tended to have a worse baseline ECOG PS (ECOG PS 0 [clear-cell RCC with sarcomatoid features vs patients with pure clear-cell RCC or clear-cell RCC with papillary or other histologic features]: 19% vs 38%-41%, respectively). Patients with clear-cell RCC with sarcomatoid features were generally younger than patients with pure clear-cell RCC or clear-cell RCC histology with papillary features (patients <70 years of age: 76% vs 87%-88%, respectively).

Sorafenib treatment was generally well tolerated in patients in EU-ARCCS, regardless of histology, and the safety profile was generally similar to the ITT population. Patients with sarcomatoid histology had a slightly higher rate of fatigue and oral cavity mucositis than did patients with nonsarcomatoid histology (42% vs 30%-34%, and 49% vs 23%-27%, respectively), but a lower incidence of constipation (2% of patients with sarcomatoid histology vs 7-9% of nonsarcomatoid histology). The incidence of drug-related SAEs (DRSAEs) was 8%, 16%, 11%, and 14% of patients with pure clear-cell histology, clear-cell with sarcomatoid histology, clear-cell with papillary histology, and pure clear-cell RCC with other histologic features, respectively.
Given their baseline ECOG PS and the prognosis associated with sarcomatoid histology, it is not surprising that patients with pure clear-cell RCC had a longer median PFS (7.4 months [95% CI 6.6, 8.2]) vs papillary (5.7 months [95% CI 4.5, 6.7]) or sarcomatoid features (4.0 months [95% CI 2.8, 4.8]). DCRs at 8 and 12 weeks were also higher for patients with pure clear-cell RCC histology than those with other histologic features (87% vs 50%-82%, and 80% vs 50%-73%, respectively).

**Safety and efficacy data from subgroup analysis by prior therapy**

The sorafenib safety profile in these subgroups was similar to that in the overall ITT study population (94% across all populations). The most common AEs included HFSR, diarrhea, fatigue, and hypertension. Drug-related SAEs in patients with prior nephrectomy, prior systemic anticancer therapy, or prior cytokine therapy included fatigue (1.3%, 1.0%, and 0.9%, respectively), and rash/desquamation (1.0%, 1.1%, and 1.2%, respectively).

Sorafenib was effective in patients with advanced RCC, regardless of prior treatments. The median PFS in patients with prior nephrectomy, systemic anticancer therapy, or cytokine therapy was similar to that in the overall ITT study population (Figure 3; 6.9, 6.8, and 6.9 months, respectively, vs 6.6 months). The DCRs at 8 and 12 weeks were similar in patients with prior nephrectomy, systemic anticancer, or cytokine therapies, and were similar to that of the overall ITT study population (DCR at 8 weeks: approximately 85% across all groups; DCR at 12 weeks in patients with prior nephrectomy, prior systemic anticancer, prior cytokine therapy, and the overall ITT study population: 78%, 77%, 78%, and 78%, respectively).
**Subgroup analysis by number of tumor sites and sites of metastases**

Many (47%; n=539) of the patients in the EU-ARCCS ITT population had ≥3 sites of metastases at baseline; 24% (n=272) had 1 site and 29% (n=338) had 2 sites. Baseline patient characteristics were somewhat unbalanced between the subpopulations by the lower proportion of patients with ≥3 tumor sites who had a good ECOG PS than patients with 1 or 2 tumor sites (ECOG PS 0: 34% vs 45% and 46%, respectively). Metastasis to the lung was predominant in patients with ≥3 sites of disease at baseline (84%). Other baseline characteristics were similar, regardless of the number of metastases. Patients with metastases to the lung (73%), liver (28%), or bone (32%) exhibited uniform baseline characteristics (Table 1), although patients with brain metastasis tended to be younger (89% of patients <70 years of age), have pure clear-cell RCC histology (89%), and additional metastasis to the lung (82%).

Regardless of the number of tumor sites and sites of metastasis at baseline, treatment with sorafenib was well tolerated. The incidence rates of AEs were similar in the tumor-site subpopulations and the overall ITT study population (96%, 94%, and 92% of patients with 1, 2, and ≥3 sites of disease at baseline, respectively). Overall rates of AEs were similar in the metastases subpopulations (lung: 94%; liver: 93%; bone: 89%; brain: 93%) and the overall ITT study population (94%). The most common AEs were consistent with the safety profile of sorafenib, and included HFSR, diarrhea, fatigue, hypertension, and rash/desquamation.

The rates of drug-related SAEs were low for patients with 1, 2, or ≥3 sites of disease at baseline and included: cardiac ischemia (0.6–1.5%), hypertension (0–1.1%), fatigue (0.6–1.9%), fever (0–1.1%), HFSR (0.7–1.2%), rash/desquamation (1.1–1.5%), and diarrhea (0.3–1.5%). Drug-related SAEs were reported for 13% to
18% of patients with metastases to the lung, liver, bone, or brain. Fatigue, rash/desquamation, and hypertension were experienced by 1.6%, 1.6%, and 1.3% of patients with liver metastasis, respectively; the most common SAEs in patients with lung metastases were fatigue and rash/desquamation (1.4% and 1.2%, respectively). Fatigue was an SAE in 1.1% of patients with bone metastasis.

Patients with ≥3 tumor sites had a shorter median PFS (5.9 months [95% CI 5.2, 6.4]) than those with one (8.9 months [95% CI 8.2, 11.2]) or two (6.6 months [95% CI 5.8, 8.0]) tumor sites at baseline. DCRs at 8 and 12 weeks were also higher for patients with 1 tumor site at baseline than for those with 2 or ≥3 disease sites (8 weeks: 92% vs 83% for both 2 or ≥3 disease sites, respectively; 12 weeks: 86% vs 76% and 75% for 2 and ≥3 disease sites, respectively).

Sorafenib demonstrated efficacy in patients with advanced RCC, regardless of metastases to the lung, liver, bone, or brain. The PFS was similar across subgroups (lung: 6.5 months; liver: 5.4 months; bone: 6.0 months; brain: 7.1 months) and was comparable with the overall ITT population (6.6 months). Patients with metastases to the liver and brain tended to have a lower DCR than patients with metastases to the lung or bone and the overall ITT patient population (at 8 weeks: liver: 78%; brain: 79% vs lung: 86%; bone: 83%; ITT: 85%; and at 12 weeks: liver: 69%; brain: 64% vs lung: 79%; bone: 75%; ITT: 78%).