2 SYNOPSIS

Name of Sponsor/Company: Active Biotech AB Scheelevägen 22 Lund, Sweden	Individual Study Table Referring to Part Of the Dossier	(For National Authority Use Only)
Name of Finished Product: ANYARA	Volume:	
Name of Active Ingredient: ABR-217620 (naptumomab estafenatox)	Page:	

Title of Study: A randomized, open-label, multi-center, phase II/III study on treatment with ABR-217620 combined with IFN-α vs. IFN-α alone in patients with advanced renal cell carcinoma.

Investigators and Study Centers:
The study was conducted in 52 research centers in 5 countries: Bulgaria (6 centers), Romania (8 centers), Russia (19 centers), Ukraine (12 centers), and the United Kingdom (7 centers). Coordinating Investigator was Professor Robert Hawkins, Christie Hospital NHS Trust, Manchester, United Kingdom.

Publications Based on the Study:
Eisen T, Hedlund G, Forsberg G, Nordle Ö, Hawkins R. Baseline biomarker trend analysis of a randomized phase 2/3 study of naptumomab estafenatox plus IFN-α vs IFN-α in advanced renal cell carcinoma. European Cancer Congress (ECCO); 27 September–1 October 2013. Amsterdam, The Netherlands; Abstract ID: 2710.

Elkord E, Burt D, Sundstedt A, Nordle Ö, Hedlund G, Hawkins R. Immunological response and overall survival in a subset of advanced renal cell carcinoma patients from a randomized phase 2/3 study of naptumomab estafenatox plus IFN-α versus IFN-α. *Oncotarget*. 2015:1-12.

Hawkins R, Gore M, Shparyk Y, Bondar V, Gladkov O, Ganev T, et al. A randomized phase 2/3 study of naptumomab estafenatox plus IFN-α vs IFN-α in advanced renal cell carcinoma. American Society of Clinical Oncology annual meeting (ASCO) 2013; 31 May–4 June 2013. Chicago, Illinois; Abstract ID: 3073.

Study Period: Approximately 54 months
First patient, first visit: 12 March 2007
Last patient, last visit: 19 October 2010

Phase of Development: II/III

Objectives: The primary objective of the study was to evaluate the effect of ABR-217620 in combination with IFN-α on the survival of patients with locally advanced or metastatic renal cell carcinoma (RCC) when compared to patients receiving interferon-alpha (IFN-α alone).

The secondary objectives were:

- To compare progression-free survival in patients receiving combination therapy of ABR-217620 and IFN-α vs patients receiving IFN-α alone based on radiological data.
- To evaluate the effect of combination therapy of ABR-217620 and IFN-α on the tumor response and duration of tumor response vs therapy of IFN-α alone.

- To evaluate the immunological response in patients receiving combination therapy of ABR-217620 and IFN-α.
- To assess the safety and tolerability of ABR-217620 used in combination with IFN-α in patients with RCC compared to the therapy with IFN-α alone.
- To assess the pharmacokinetics (PK) of ABR-217620 in the different treatment cycles.

Methodology: This was a multinational, multicenter, randomized, open-label, parallel-group, Phase II/III study in patients with confirmed metastatic or inoperable locally advanced RCC eligible for standard therapy with IFN-α.

The study was initiated with a Safety Group of 6 patients; 3 patients received 10 µg/kg and 3 patients received 15 µg/kg. This initial phase of the study confirmed the safety of ABR-217620 at a dose of 15 µg/kg body weight in sequential combination with IFN-α that was planned for use in the randomized phase of the study. When the last patient in the Safety Group attended the Day 10 visit and it was determined that it was safe to proceed, randomization of patients into ABR-217620 in sequential combination with the IFN-α treatment arm and IFN-α alone treatment arm was to begin.

Number of Patients:
Planned: 524 patients (6-12 in the Safety Group; 512 randomized)
Randomized: 521 patients; analyzed for Safety: 519 patients, of which 513 patients were included in the efficacy group (intent-to-treat [ITT] population); Safety Group: 6 patients.

Diagnosis and Main Criteria for Inclusion:
To be enrolled in the study, the following criteria were met:

Main Inclusion Criteria:
- Histologically or cytologically confirmed clear cell or papillary type RCC; metastatic or inoperable locally advanced and eligible for therapy with IFN-α
- Karnofsky performance status ≥ 70
- Life expectancy > 3 months
- Acceptable levels of specific hematology and serum chemistry parameters

Main Exclusion Criteria:
- Currently on renal dialysis treatment
- Radiotherapy and/or major surgery or tumor embolization less than 4 weeks prior to the start of treatment
- History of exposure to murine monoclonal antibodies or known hypersensitivity to murine proteins
- Previous systemic antitumor therapy for RCC with the exception of oral antiangiogenic therapy

Test Product, Dose, and Mode of Administration, Batch Numbers:
Test product: ABR-217620; Dose (Safety Group): 10 µg/kg or 15 µg/kg; Dose (ABR-217620+IFN-α): 15 µg/kg on 4 consecutive days of Week 1, Week 9, and Week 17; Mode of Administration: 5-minute bolus intravenous injection.

Reference Therapy, Dose, and Mode of Administration, Batch No.:
Reference therapy: IFN-α; Dose: 3, 6, and 9 million international units 3 times/week; Mode of administration: Subcutaneous or intramuscular injection.

Duration of Treatment:
All patients received treatment for 72 weeks (unless prematurely withdrawn from the study).

CRITERIA FOR EVALUATION:
Efficacy:
Primary efficacy endpoint:

- Time to death

Secondary efficacy endpoints:

- Progression-free survival time (PFS)
- Objective tumor response rate
- Duration of response (DOR)
- Percent changes in sum of target lesions
- Immunological response to treatment in patients receiving combination therapy of ABR-217620 and IFN-α
- Pharmacokinetic parameters of ABR-217620

Pharmacokinetics: Plasma concentration time profile of ABR-217620. Standard PK parameters determined in patients included in the PK subgroup.

Safety: The following variables were assessed: Adverse events (AEs), laboratory assessments, physical examination, Karnofsky performance status, vital signs, and electrocardiogram (ECG).

Statistical Methods: The primary analysis on time to death was done with the log-rank-test adjusted for Memorial Sloan-Kettering Cancer Center (Motzer risk score) category**.** An interim analysis was conducted in the study.

All data collected in this study were summarized using frequencies and percentages for categorical variables, and using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for continuous variables. Changes from baseline to the various study time points were provided for all variables where appropriate. In addition, summaries were provided by dose group.

The following populations were analyzed: **Intent-to-Treat population (ITT)** (defined as all patients who were randomized to treatment and who have taken at least one dose of study drug); **Biomarker-Normal population (BMNORM)** (defined as all patients with normal/low biomarkers, where baseline interleukin-6 (IL-6) concentration and baseline anti-staphylococcal enterotoxin A/E-120 antibody (anti-SEA/E-120) concentration measurements exist and both are below or equal to the median of the ITT population). IL-6 and anti-SEA/E-120 were important prognostic and predictive baseline parameters. This important finding was realized during the study. Thus, this subset (BMNORM), not described in the protocol, was added to the statistical plan; **Per-Protocol population (PP)** (defined as all patients who fulfilled the inclusion/exclusion criteria and have valid data for tumor assessments before treatment and at Week 13/major protocol violators of inclusion/exclusion criteria or patients who have

received < 75% of study treatment up to the PP validating tumor assessment are excluded from this analysis); **PP population for BMNORM patients ([PP in BMNORM])** included patients who were included in both populations); and the **Safety population** (defined as all patients, including the initial Safety Group and the randomized patients, who have taken at least one dose of study drug).

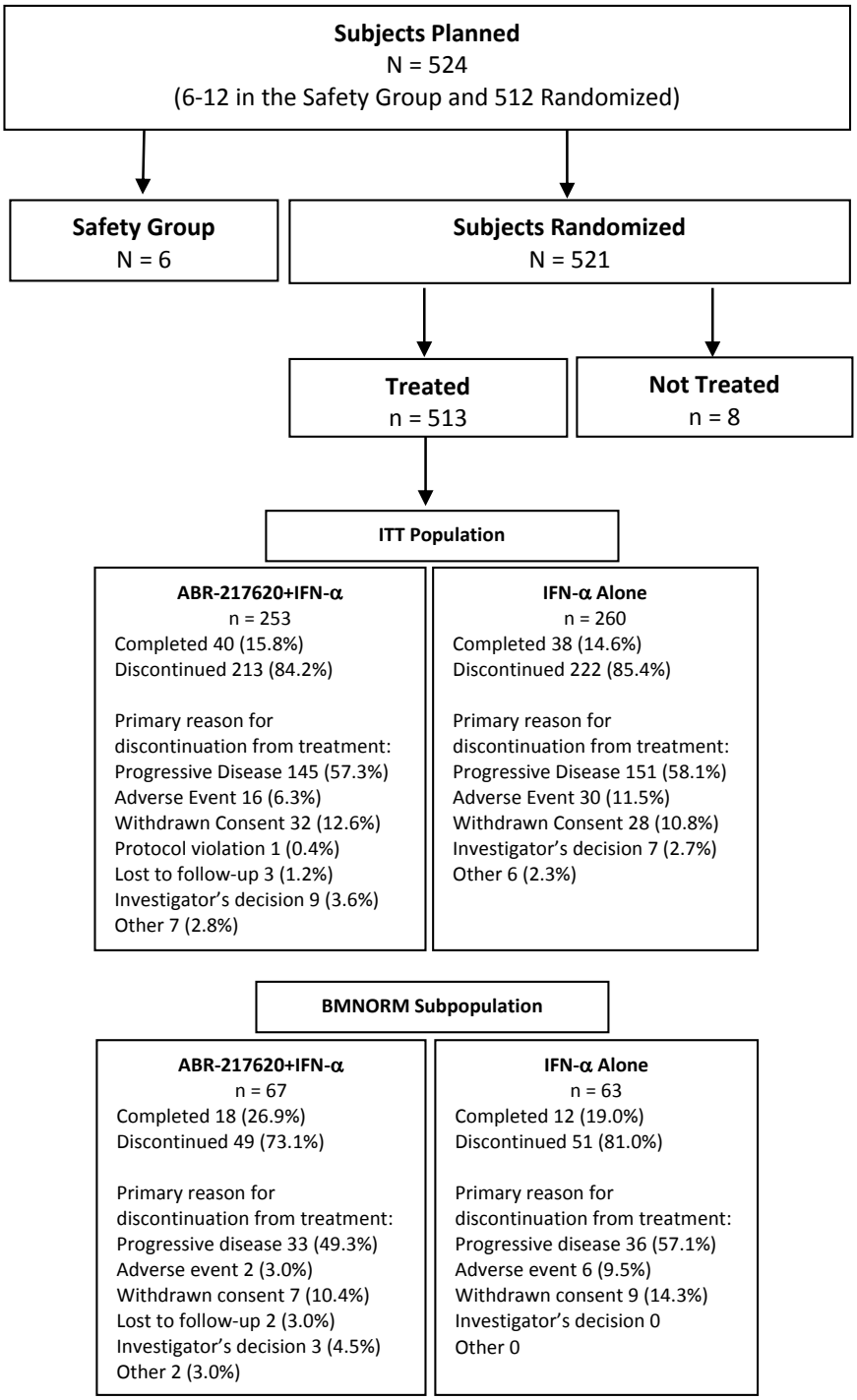
RESULTS

Disposition of Patients: Study 06762004 was conducted at 52 research centers in 5 countries (Bulgaria, Romania, Russia, Ukraine, and the United Kingdom). The number of patients planned was 524 patients (6 to 12 in the initial Safety Group and 512 randomized). A total of 521 patients were randomized; 519 patients (260 patients received ABR-217620+IFN-α and 259 patients received IFN-α alone) were analyzed for the Safety population, from which 6 patients were from the initial Safety Group and 513 patients were from the randomized group. Eight of the 521 patients were randomized to receive ABR-217620+IFN-α and did not take one dose of the study drug and were not analyzed.

The most frequent reason for study discontinuation was disease progression. Overall, 296 patients developed progressive disease: in the ABR-217620+IFN-α treatment arm (145 patients [57.3%]) and in the IFN-α alone treatment arm (151 patients [58.1%]), and in the ITT population, 46 patients were discontinued from the study due to AEs: 16 patients (6.3%) in the ABR-217620+IFN-α treatment arm and 30 patients (11.5%) in the IFN-α alone treatment arm. One patient (0.4%) in the IFN-α alone treatment arm died due to progressive disease. Twenty-six patients died during study treatment from AEs not related to study drug: 9 patients (3.6%) in the ABR-217620+IFN-α treatment arm, and 17 patients (6.5%) in the IFN-α alone treatment arm.

The disposition of all enrolled patients is displayed in Figure 1.

Figure 1: Patient Disposition and Primary Reason for Discontinuation From Study Treatment



Abbreviations: BMNORM = Biomarker-normal; IFN-α = interferon-alpha; ITT = intent-to-treat.
Sources: Tables 14.1.2.1.and 14.1.2.2.

Demography and Baseline Characteristics: The majority of patients in the ITT population were male (183 [72.3%] for ABR-217620+IFN-α treatment arm and 183 [70.4%] for the IFN-α alone treatment arm) and Caucasian (253 [100%] for ABR-217620+IFN-α treatment arm and 258 [99.2%] for the IFN-α alone treatment arm). The mean ±SD age at time of enrollment was 57.9 ± 9.52 years of age for ABR-217620+IFN-α treatment arm and 57.6 ± 9.89 years of age for the IFN-α alone treatment arm. Demographic and other baseline characteristics of the 2 treatment groups of the Safety population were similar.

The majority of patients in the BMNORM population were male (47 [70.1%] for the ABR-217620+IFN-α treatment arm and 40 [63.5%] for the IFN-α alone treatment arm) and Caucasian (67 [100%] for ABR-217620+IFN-α and 62 [98.4%] for IFN-α alone). The mean age at time of enrollment was 58.3 ± 9.72 years of age for ABR-217620+IFN-α treatment arm and 57.7 ± 9.71 years of age for the IFN-α alone treatment arm. Demographic and other baseline characteristics of the 2 treatment groups of the BMNORM population were similar.

Efficacy Results: The primary endpoint was overall survival (OS), defined as time to death. Primary analysis was performed in the ITT, BMNORM, PP, and PP in BMNORM populations. The secondary efficacy analyses were performed in the ITT and BMNORM populations and for selected secondary endpoints in the PP population and the PP in BMNORM population.

ITT population
Median OS for patients treated with ABR-217620+IFN-α was 17.1 vs 17.5 months for the patients receiving IFN-α alone (hazard ratio [HR]: 1.08; $P = .555$). The 12-month Kaplan-Meier estimate for survival rate was 0.60 for the patients treated with ABR-217620+IFN-α and 0.62 for the patients receiving IFN-α alone; the 24-month survival rates were 0.39 and 0.42, respectively. No difference of OS between treatment arms in the ITT population was detected, and accordingly the study did not reach its primary endpoint.

Median PFS for patients treated with ABR-217620 + IFN-α was the same (5.8 months) as for patients receiving IFN-α alone (HR: 0.92; $P = .405$).

Baseline IL-6 was shown to be a very important prognostic factor for OS and baseline anti-SEA/E-120 was shown to be a very important factor for systemic exposure of ABR-217620. A statistical analysis on PFS and OS, Cox Regression with interaction terms, was performed in order to evaluate the effect of those two biomarkers and treatment. The result indicated significant interactions with treatment showing that the effect of treatment varies dependent on the baseline plasma concentrations of the biomarkers.

Patients showing higher ABR-217620 plasma concentrations had favorable OS and PFS as compared to the patient populations having lower plasma concentrations. These trends within the ABR-217620+IFN-α treatment arm further support drug-induced treatment effects as impact on OS and PFS. All patients with normal/low baseline biomarkers, where IL-6 and anti-SEA/E-120 existed and both were below or equal to the median of the ITT population were included in the BMNORM population.

The tumor response was similar in the 2 treatment arms. The median DOR was recorded for 11.1 months in the ABR-217620+IFN-α treatment arm and 7.4 months in the IFN-α alone treatment arm (HR: 0.5; $P = .039$).

BMNORM population
Overall, median survival for patients treated with ABR-217620+IFN-α was 63.3 months vs 31.1 months for patients receiving IFN-α alone in the BMNORM population (*P* = .020). The HR was 0.59 (95% confidence interval [CI]: 0.37, 0.95), showing that risk of dying is significantly lower for patients in the ABR-217620+IFN-α arm than for those in the IFN-α alone treatment arm. The 12-month Kaplan-Meier survival rate was 0.92 (95% CI: 0.83, 0.97) for the patients treated with ABR-217620+IFN-α and 0.77 (95% CI: 0.64, 0.86) for the patients receiving IFN-α alone; the 24-month survival rate was 0.79 (95% CI: 0.67, 0.87) and 0.56 (0.43, 0.68), respectively. The differences in survival rates between patients treated with ABR-217620+IFN-α and patients receiving IFN-α alone were 0.16 at 12 months and 0.22 at 24 months.

Median PFS for patients treated with ABR-217620+IFN-α was 13.7 months vs 5.8 months for patients receiving IFN-α alone (HR: 0.62 [95% CI 0.42, 0.92]; *P* = .015).

The best overall tumor response analysis, confirmed and non-confirmed, favored the combined therapy of ABR-217620+IFN-α, and the Cochran-Armitage test for trend was significant, *P* = .008. There were 28.4% of patients who had CR or PR in the ABR-217620+IFN-α arm compared to 15.9% of patients in the IFN-α arm, *P* = .091.

The median duration of tumor response of complete response (CR) or partial response (PR), a trend was present (11.1 months vs 8.4 months, for the ABR-217620+IFN-α and IFN-α alone treatment arms, respectively), the total number of patients with repeated CT scans was small (n = 17) and therefore, no definitive conclusion can be made from these comparisons.

PP population
Overall, median survival for patients treated with ABR-217620+IFN-α was 23.5 months vs 21.2 months for patients receiving IFN-α alone in the PP population (HR: 0.95; *P* = .619). The 12-month Kaplan-Meier survival rate was 0.73 (95% CI: 0.66, 0.79) for patients treated with ABR-217620+IFN-α and 0.71 (95% CI: 0.64, 0.77) for patients receiving IFN-α alone; Kaplan-Meier estimates for 24-month survival rates were 0.50 (95% CI: 0.42, 0.57) and 0.47 (0.40, 0.54), respectively.

The median PFS for patients treated with ABR-217620+IFN-α was 8.5 months vs 6.5 months for patients receiving IFN-α alone (HR: 0.78 [95% CI 0.63, 0.97]; *P* = .025).

PP in BMNORM population
Overall, median survival for patients treated with ABR-217620+IFN-α was 63.3 months vs 32.2 months for patients receiving IFN-α alone (HR: 0.56; *P* = .019). The 12-month Kaplan-Meier survival rate was 0.95 (95% CI: 0.85, 0.98) for patients treated with ABR-217620+IFN-α and 0.83 (95% CI: 0.69, 0.91) for patients receiving IFN-α alone; the 24-month survival rates were 0.81 (95% CI: 0.69, 0.89) and 0.60 (0.45, 0.72), respectively.

The median PFS for patients treated with ABR-217620+IFN-α was 13.9 months vs 5.9 months for patients receiving IFN-α alone (HR: 0.58; *P* = .006).

Immunological Response: Antibodies binding to ABR-217620 (anti-SEA/E-120) may interfere with drug exposure and efficacy. Anti-SEA/E-120 has been analyzed at baseline and at several time points during the study.

The SEA/E-120 part of ABR-217620 binds to and activates T lymphocytes. Therefore, the cytokine response (eg, interleukin-2; IL-2) as measured in plasma is a pharmacological marker for drug activity and T cell activation. Plasma for analysis of the cytokines was collected at pre-dose and 3 hours post-dose Days 1 and 2 of the ABR-217620 treatment cycles.

Anti-SEA/E-120 Antibodies
Slightly increased baseline anti-SEA/E-120 antibody levels were detected in certain territories predicting for suboptimal exposure of ABR-217620. At baseline only low levels of human anti-mouse antibodies (HAMA) were detected. Anti-SEA/E-120 and HAMA concentrations were increased in the great majority of patients after the first treatment cycle. While the median baseline concentration of anti-SEA/E-120 in ITT patients treated with ABR-217620+IFN-α was 53.1 pmol/mL, the median concentrations at Cycle 2 (Week 9) and Cycle 3 (Week 17) were 17.5 nmol/mL and 15.9 nmol/mL, respectively, equalizing more than 300x increase. The BMNORM population showed slightly lower induction of anti-SEA/E-120 antibodies equalizing approximately 200x increase.

Cytokines
IL-2, -4, -6, -10, interferon-gamma (IFN-γ) and tumor necrosis factor–alpha (TNF-α) were analyzed at pre-injection and 3 hours after injection at Day 1 and Day 2 of the treatment Cycles (Weeks 1, 9, and 17). All cytokines were induced in a predicted pattern as compared to the results from Phase I studies with lower IL-2, -6 and TNF-α responses, similar IFN-γ response and higher IL-10 response Day 2 as compared to Day 1 in Cycle 1. Furthermore, patients being nephrectomized had a tendency to have higher induced cytokine concentrations as compared to non-nephrectomized patients.

Interleukin-2: In the ITT population the median IL-2 increased from below lower limit of quantification ([LLOQ] < 5.2 pg/mL) at pre-injection to 48.4 pg/mL 3 hours after injection Day 1 and from below LLOQ at pre-injection to 21.0 pg/mL 3 hours after injection Day 2 of Week 1. The BMNORM population showed higher median induction of IL-2 (153 pg/mL 3 hours after injection Day 1 and 32 pg/mL 3 hours after injection Day 2) as compared to the ITT population indicating higher frequency of patients having expected level of T cell activation. In general, no increase of IL-2 concentrations following treatment in Cycles 2 and 3 was recorded.

Interleukin-4: No increase of IL-4 concentrations following treatment in Cycles 1, 2, and 3 was recorded.

Interleukin-6: Although the median baseline concentration of IL-6 in the BMNORM population was lower than in the ITT group (< LLOQ: 6 pg/mL vs 8.4 pg/mL in the ITT population), the stimulated increase following the first treatment with ABR-217620 was higher in the BMNORM population (176.8 pg/mL vs 137.5 pg/mL in the ITT population at 3 hours after injection Day 1). In general, no increase of IL-6 concentrations following treatment in Cycles 2 and 3 was recorded.

Interleukin-10: In response to study treatment, significantly elevated concentrations of IL-10 were observed in both ITT and BMNORM populations during Cycle 1. The response increased Day 2 in both the ITT and the BMNORM patients. The highest IL-10 response was observed Day 2 in BMNORM patients. In general, no increase of IL-10 concentrations following treatment in Cycles 2 and 3 was recorded.

Interferon-γ: On Days 1 and 2 of Week 1, patients in both the ITT and BMNORM populations demonstrated elevations in IFN-γ concentrations following study drug administration. Patients in the

BMNORM population demonstrated a higher IFN-γ response than patients in the ITT population. In general, no increase of IFN-gamma concentrations following treatment in Cycles 2 and 3 was recorded.

Tumor necrosis factor-α: Increased median TNF-α concentrations were demonstrated in response to the first dose of study drug in both the ITT and BMNORM populations. Patients in the BMNORM population demonstrated a higher TNF-alpha response than patients in the ITT population. In general, no increase of TNF-alpha concentrations following treatment in Cycles 2 and 3 was recorded.

Pharmacokinetic Results: The plasma concentration data of ABR-217620 measured at 1 hour and 3 hours after the first injection of a dose of 15 µg/kg in Cycle 1 showed higher concentrations at the earlier time point. An approximately 2-fold higher median ABR-217620 plasma concentration was seen at 1 and 3 hours in the BMNORM population compared with the ITT population. In Cycles 2 and 3, markedly lower plasma concentrations of ABR-217620 were seen compared with Cycle 1, with median values below the lower limit of quantitation (1 ng/mL) both for the ITT and BMNORM populations.

A Spearman's rank correlation analysis showed a statistically significant ($P < .001$) inverse relationship between baseline anti-SEA/E-120 antibody concentration and plasma concentration of ABR-217620 in both the ITT and BMNORM populations at the 1-hour and 3-hour time points of the first day of the first treatment cycle. These results were indicative of potential drug exposure benefits from selecting patients for treatment with ABR-217620 on the basis of baseline anti-SEA/E-120 concentration.

The results of the PK subgroup evaluation showed a lower mean clearance and a smaller mean volume of distribution in the BMNORM population than in the ITT population. The clearance values seen in the BMNORM population confirmed results reported in previous clinical studies with ABR-217620.

Safety Results: Safety was evaluated in the Safety and the BMNORM populations.

In both populations the ABR-217620 TEAEs were generally mild and transient. The majority of the AEs resulting from treatment with ABR-217620 relates to increased levels of cytokines, and is expected as a part of the mechanism of action. Most of these AEs occurred during the ABR-217620 treatment Cycle 1 (Week 1) and were less pronounced during Cycle 2 and Cycle 3. During Cycle 1 TEAEs were slightly less pronounced in the Safety population compared to the BMNORM population (76.4% vs. 83.6%). During ABR-217620 treatment Cycle 2 (Week 9), back pain was the most common TEAE. The back pain could be attributed to immune complex formation in patients with increased anti-SEA/E-120.

There was no unexpected change or difference between treatment arms in the other safety parameters of the 2 populations (clinical laboratory assessments, body weight, vital signs, ECG, physical assessments).

Safety Population
A total of 519 patients (n = 260 for ABR-217620+IFN-α and n = 259 for IFN-α alone) were included in the Safety population, defined as all patients in the initial Safety Group and all randomized patients who received at least 1 dose of study drug. Of the 519 patients, 6 patients were from the initial Safety Group and 513 patients were from randomized group. There were 452 patients with TEAEs: 243 patients (93.5%) in the ABR-217620+IFN-α treatment arm and 209 patients (80.7%) in the IFN-α alone treatment arm. Grade 3 or 4 TEAEs were reported in 181 patients: 110 patients (42.3%) in ABR-217620+IFN-α treatment arm and 71 patients (27.4%) in the IFN-α alone treatment arm.

There were 13 patients (5.0%) with Grade 4 TEAEs in the ABR-217620+IFN-α treatment arm and 10 patients (3.9%) in the IFN-α alone treatment arm in the Safety population.

There were 103 patients with serious adverse events (SAEs) reported. Of these, 58 patients (22.3%) were in ABR-217620+IFN-α treatment arm and 45 patients (17.4%) were in the IFN-α alone treatment arm. Thirty (30) patients had SAEs that were assessed by the Investigator(s) as related to study drug: 24 patients (9.2%) in ABR-217620+IFN-α treatment arm and 6 patients (2.3%) in the IFN-α alone treatment arm.

There were 22 SAEs leading to death in the ABR-217620+IFN-α treatment arm and 27 deaths in the IFN-α alone treatment arm. Only 1 death in the ABR-217620+IFN-α treatment arm (due to mucosal inflammation and mouth ulceration) was considered possibly related to study drug. All other deaths, including one patient with a mass, duodenal perforation, intestinal hemorrhage, and peritonitis (majority of them due to disease progression and should not have been reported as SAEs) were considered to be unlikely related to study drug.

Overall, 55 patients were withdrawn from study treatment due to TEAEs in the Safety population: 22 patients (8.5%) in the ABR-217620+IFN-α treatment arm and 33 patients (12.7%) in the IFN-α alone treatment arm. There were 13 patients (5.0%) with Grade 4 TEAEs in ABR-217620+IFN-α treatment arm and 10 patients (3.9%) in the IFN-α alone treatment arm. The majority of Grade 5 TEAEs were related to disease progression.

The most commonly occurring TEAEs in ≥ 5% of patients and with a higher frequency in the ABR-217620+IFN-α treatment arm than in the IFN-α alone treatment arm included anemia, diarrhea, tachycardia, nausea, vomiting, chills, pyrexia, hyperthermia, hypersensitivity, back pain, headache, hypertension, and hypotension. Most of these AEs occurred during ABR-217620 treatment Cycle 1 (Week 1) and were less pronounced during Cycle 2 and Cycle 3. During ABR-217620 treatment Cycle 2 (Week 9), back pain was the most common TEAE.

BMNORM population
A total of 130 patients (n = 67 for ABR-217620+IFN-α and n = 63 for IFN-α alone) were included in the BMNORM population.

Treatment-emergent adverse events were reported in 111 patients. Of these, 63 patients (94.0%) were in ABR-217620+IFN-α treatment arm, and 48 patients (76.2%) were in the IFN-α alone treatment arm. Grade 3 or 4 TEAEs were reported in 34 patients: 19 patients (28.4%) in ABR-217620+IFN-α treatment arm and 15 patients (23.8%) in the IFN-α alone treatment arm. There were 2 patients (3.0%) with Grade 4 TEAEs in ABR-217620+IFN-α treatment arm and 3 patients (4.8%) in the IFN-α alone treatment arm.

Serious adverse events were reported in a total of 16 patients: 9 patients (13.4%) in ABR-217620+IFN-α treatment arm, and 7 patients (11.1%) in the IFN-α alone treatment arm. Three patients (4.8%) had TEAEs in the IFN-α alone treatment arm that were fatal, 2 were related to disease progression and 1 patient had a mass, duodenal perforation, intestinal hemorrhage, and peritonitis.

Eight patients were withdrawn from the study due to TEAEs: 3 patients (4.5%) in ABR-217620+IFN-α treatment arm and 5 patients (7.9%) in the IFN-α alone treatment arm.

The most commonly occurring TEAEs in ≥ 5% of patients and with a higher frequency in the ABR-217620+IFN-α treatment arm than in the IFN-α alone treatment arm were tachycardia, abdominal pain, constipation, diarrhea, nausea, vomiting chills, pyrexia, back pain, dizziness, and hypotension. There was a higher frequency (≥ 5%) of hyperthermia, weight decrease, and anorexia in the IFN-α alone treatment arm than in the ABR-217620+IFN-α treatment arm in the BMNORM population.

Clinical Laboratory Evaluations: In general, in the Safety population, there were more Grade 3 and Grade 4 laboratory abnormalities (increases from normal) in patients in the ABR-217620+IFN-α treatment arm than in the IFN-α alone treatment arm. There were several laboratory parameters where a shift from normal (Grade 0) to severe (Grade 4) was noted during the study. This included changes in bilirubin, calcium, potassium, and sodium levels. These shifts from normal were considered to be unrelated to the study drug and were not unexpected in this seriously ill patient population.

In the BMNORM population, there were several laboratory parameters where a shift from normal (Grade 0) to severe (Grade 4) was noted during the study. This included changes in bilirubin, calcium, potassium, and sodium levels. These shifts from normal were considered to be unrelated to study drug and were not unexpected in this seriously ill patient population.

Vital Signs: In the Safety population (at Week 3 and Week 5), hypotension was reported as a TEAE for 28 (10.8%) patients in the ABR-217620+IFN-α treatment arm and for 2 (0.8%) patients in the IFN-α alone treatment arm.

In the BMNORM population, hypotension was reported as a TEAE for 10 (14.9%) patients in the ABR-217620+IFN-α treatment arm. There were no reports of hypotension in this population in the IFN-α alone treatment arm.

Beside these differences, changes in vital signs were similar between the treatment arms, in both populations, with a pattern as expected for this seriously ill patient population.

Physical Findings: In the Safety population, patients in both treatment arms lost weight at similar rates during study participation. The frequencies of new abnormal findings from baseline to each assessment were similar at Week 9 (8.8% and 7.8%), but were different at Week 25 (3.2% and 9.6%) for the patients in the ABR-217620+IFN-α treatment arm and patients in the IFN-α alone treatment arm, respectively.

In the BMNORM population, patients in both treatment arms also lost weight at similar rates during study participation. The frequencies of new abnormal findings from baseline to each assessment were similar at Week 9 (7.7% and 8.8%), but were significantly different at Week 25 (1.9% and 7.7%) for the patients in the ABR-217620+IFN-α treatment arm and patients in the IFN-α alone treatment arm, respectively, in the BMNORM population.

Electrocardiogram Findings: In the Safety population, the percentage of patients with a change in ECG assessment (from normal at baseline to abnormal at Week 25 and at the end of the study) was 2.4% and 3.9%, respectively, in the ABR-217620+IFN-α treatment arm; and 1.5% and 4.4%, respectively, in the IFN-α alone treatment arm.

In the BMNORM population, the percentage of patients with a change in ECG assessment (from normal at baseline to abnormal at Week 25 and at the End of Study) was 0.0% and 1.8%, respectively, in the ABR-217620+IFN-α treatment arm; and 2.6% and 7.4%, respectively, in the IFN-α alone treatment arm.

Karnofsky Performance Status: As expected for this seriously ill patient population, there was a trend toward more patients having a decrease in performance status than an increase in performance over time.

CONCLUSION

The primary endpoint of the study, prolongation of overall survival (OS) in RCC patients treated with ABR-217620+IFN-α as compared to patients treated with IFN-α alone, was not met (hazard ratio [HR]: 1.08; $P = .555$). Progression free survival (PFS) was also similar in the two treatment arms (HR: 0.92; $P = .405$). However, the addition of ABR-217620 to IFN-α improved OS (HR: 0.59; $P = .020$) and PFS (HR: 0.62; $P = .015$) in a subgroup of patients, BMNORM, with low baseline IL-6 and normal levels of anti-SEA/E-120 antibodies. The addition of ABR-217620 to IFN-α resulted in predicted transient immune-related AEs and the combination regimen had an acceptable safety profile. These results warrant further studies with ABR-217620 in the baseline defined BMNORM subgroup of RCC patients.

DATE OF THE REPORT: 03 June 2015