**PFIZER INC.**

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

**GENERIC DRUG NAME / COMPOUND NUMBER:** Figitumumab / CP-751,871

**PROTOCOL NO.:** A4021011

**PROTOCOL TITLE:** A Phase 2, Randomized, Non-Comparative, Two-Arm Open Label, Multiple-Center Study of CP-751,871 in Combination With Docetaxel/Prednisone in Chemotherapy-Naive (Arm A) and Docetaxel/Prednisone Refractory (Arm B) Patients With Hormone Insensitive Prostate Cancer

**Study Centers:** Sixteen (16) centers took part in the study and enrolled subjects with 5 centers in the United States (US), 3 centers each in the United Kingdom (UK) and Spain, 2 centers in Canada, 2 centers in Germany and 1 center in Switzerland.

**Study Initiation Date, Primary Completion Date, and Final Completion Date:**
Study Initiation Date: 09 May 2006 (First Subject First Visit)
Primary Completion Date: 08 August 2011 (Database snapshot for primary clinical study report) and
Final Completion Date: 14 December 2011 (Last Subject Last Visit).

**Phase of Development:** Phase 2

**Study Objectives:**

Primary Objectives:

- Arm A: To assess the efficacy, in terms of prostate-specific antigen (PSA) response rate, of multiple doses of figitumumab in combination with docetaxel and prednisone in chemotherapy-naive subjects with hormone refractory (androgen independent) progressive prostate cancer (HRPC).

- Arm B: To assess the efficacy, in terms of PSA response rate, of the addition of figitumumab to the treatment of HRPC subjects that progress on docetaxel/prednisone.

Secondary Objectives:

- To assess efficacy in terms of progression free survival (PFS).

- To assess the safety and tolerability of multiple doses of figitumumab in combination with docetaxel and prednisone.

- To assess population pharmacokinetics (PK) of figitumumab when used in combination with docetaxel and prednisone.

- To evaluate the effect of figitumumab in combination with docetaxel and prednisone on biomarkers.

- To test for the occurrence of human anti-human antibodies (HAHA) response to figitumumab.

- The feasibility of performing quality of life and pain questionnaires in the subject population were to be investigated.

## METHODS

**Study Design:** This was a multicenter, open-label, 2-arm, randomized, noncomparative Phase 2 study to evaluate the efficacy of figitumumab given as an infusion in combination with docetaxel and prednisone as treatment for HRPC. Subjects were randomized (1:1) to receive either figitumumab in combination with docetaxel and prednisone (Arm A) or docetaxel and prednisone alone (Arm B).

Subjects in Arm B who experienced progression of their disease while on chemotherapy received additional cycles of docetaxel and prednisone in combination with figitumumab. In order to be eligible to receive combination treatment, subjects in Arm B were required to satisfy at least 1 of the following criteria within 6 weeks from the last docetaxel administration:

- Disease progression demonstrated by 2 or more new bone lesions.

- Disease progression demonstrated by computed tomography scan according to the response evaluation criteria in solid tumors criteria (with the exception of 1 new bone lesion).

- PSA progression at Cycle 3 or beyond (post Cycle 3 dosing).

- Increase of pain at the site of metastatic disease requiring either use of narcotics for a period longer than 2 weeks, or radiation or doubling of current corticosteroid dose.

The duration of the study was approximately 48 months. The schedule of activities is presented in the Table 1 and Table 2.

## Table 1. Visit Schedule

| Observation (Time Relative to Start of Study Treatment) | Screen | Day 1 (PreDose) | Day 1 (Postdose) | Day 8 | Day 15 | End of Treatment[a] (EOT) | Follow-Up[a] |
|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | |
| Complete medical history | X | | | | | | |
| Baseline signs and symptoms | X | | | | | | |
| ECOG performance status (PS) | X | X[b] | | | | | |
| Vital signs (temp, BP, pulse) | X | X[b] | | | | X | X |
| Weight | X | X | | | | | |
| Height | X | | | | | | |
| Physical examination[c] | X | X[b] | | | | X | X |
| Patient questionnaires[c] | X | X | | | | X | |
| Electrocardiogram[d] | X | X | | | | X | X |
| Hematology[e] | X | X[b] | | | X | X | X |
| Chemistry[e] | X | X[b] | | | X | X | X |
| Coagulation[e] | X | X[b] | | | | | |
| Urinalysis[e] | X | X[b] | | | | | |
| Testosterone[e] | X | | | | | X | |
| Total IgG[e] | | X | | | | X | |
| PSA levels | X[f] | X[b] | | | X[f] | X | X |
| Genotyping sample | | X | | | | | |
| Biomarkers[g] | Check Table 2 | | | | | | |
| Safety evaluation (AE monitoring) | Assessed at each study visit, and as clinically indicated | | | | | | |
| Drugs administration[h] | | | X | | | | |
| Tumor imaging[i] | X[i] | | | | X | | X |
| PK figitumumab[j] | | X | X | X | X | | X |
| HAHA sample[k] | | X | | | | | X |

## Table 1. Visit Schedule

AE = adverse events; BID = twice a day; BP = blood pressure; CRF = case report form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HAHA = human anti-human antibodies; IGF-1R = Insulin-like Growth Factor 1 receptor; IgG = immunoglobulin G; PK = pharamacokinetic; PSA = prostate specific antigen.

a. An EOT visit took place 28 days after the last dose or sooner if subject withdrew form study. Follow-up visits were scheduled once a month. However, additional follow-up study visits were scheduled, as needed, to monitor for any sustained, treatment emergent adverse events or efficacy. In particular, for subjects who go off treatment prior to progression, follow-up for progression was continued. PK and HAHA samples were collected for subjects in Arm A or subjects in Arm B receiving figitumumab during the fourth scheduled follow-up visit.

b. Beginning in Cycle 2, predose activities (except for the collection of the biomarker samples and PK) were done up to 72 h predose. Physical exam and ECOG PS were done up to 1 week before dosing. Vital signs were repeated postdose, if clinically indicated.

c. Pain was assessed using a modified brief pain inventory-short form questionnaire. Daily analgesic use was recorded on the CRF. The quality of life was assessed using the functional assessment of cancer therapy-prostate questionnaire. Pain and quality of life was assessed at Screening, on Day 1 for each cycle and EOT. Subjects completed the questionnaires.

d. Arm A and B: One (1) ECG was done at Screening. For subjects in Arm A additional ECGs was done at Cycle 2 Day 1 predose (up to 72 hours) and EOT. Subjects in Arm B who had figitumumab added to their regimen had ECG done within 72 hours before the second figitumumab infusion and 1 at the end of the study. Additional ECGs were done if medically required.

e. Hematology, coagulation, chemistry, and urinalysis were done within 2 weeks (72 hours preferable) prior to dosing on Cycle 1 and 1 or 2 days prior to dosing in all other cycles. Day 15 hematology testing was performed at the judgment of the Investigator at Cycle 2 and beyond. Total IgG were measured only for subjects in Arm A at Cycle 1 predose and End of the Study. Additional safety tests were done as per institutional standard of care. Results of these additional tests were recorded on the CRF.

f. Three measurements were taken, at least 1 week apart, to confirm progressive disease before enrollment. One additional measurement was taken at Day 1 predose only in Cycle 1 (baseline reference value). Day 15 measurement was taken 1-2 days prior to Day 15 or up to 7 days before redosing. For each subject, samples collected for on study PSA measurements were analyzed at the same local laboratory.

g. Arm A: Paraffin blocks from previous diagnostic biopsy (1 optional sample) and pre and post treatment tumor biopsy (optional samples).
Arm A and B: Circulating Tumor Cells (CTCs), IGF-1R positive CTCs, IGF-2 and IGF-BP2. Blood samples for CTCs, and IGF-1R positive CTCs were taken at Screening, at each odd-numbered cycle (Cycles 1, 3, 5, etc) on Day 1 predosing and EOT. Serum samples for the measurement of IGF-2 and IGF-BP2 were collected at Cycle 1 predose, Cycle 3 predose and either at Cycle 5 predose or EOT, whichever occurs first.

h. The pre-medication regimen for docetaxel included 8-mg oral dexamethasone given at 12 (Day -1), 3 and 1 hour prior to docetaxel administration. Either docetaxel and figitumumab (Arm A) or docetaxel alone (Arm B) were administered on Day 1. Prednisone was administered BID starting on Day 1, Cycle 1.

i. Screening tumor assessments (eg, CT scan, bone scans, metastatic X-ray series) were done within 4 weeks prior to the first dose. Results from CT and bone scans generated either on study or as part of standard clinical follow-up of the subjects, were recorded on the CRF.

j. Arm A: Blood samples for evaluation of figitumumab plasma PK were collected approximately 30 minutes prior to docetaxel infusion in Cycles 1, 2, 4, and 5 and at 1 hour post the end of figitumumab infusion in Cycles 1 and 4. Additional PK blood samples were collected in Cycle 4 at Day 8 and 15 and at the last (fourth) scheduled follow-up visit.
Arm B: Subjects in Arm B that received treatment with figitumumab had a PK sample drawn during the first cycle of combined treatment prior to docetaxel infusion. An additional PK sample was collected at the fourth scheduled follow-up visit. Every effort was made to collect the last PK follow-up sample.

k. Arm A: Serum samples for measurement of HAHA were collected prior to docetaxel infusion in Cycle 1 and at the last follow-up visit.
Arm B: HAHA samples were collected from subjects in Arm B, only if figitumumab was added to the regimen. Samples were collected during the first cycle of combined treatment, prior to docetaxel infusion and the fourth scheduled follow-up visit. Every effort was made to collect this follow-up sample.

## Table 2. Biomarkers Time Points

| | Screen | Cycle 1 | Odd Numbered Cycles (1, 3, 5, etc) | End of Treatment |
|---|---|---|---|---|
| | | Predose | Predose | |
| CTCs | X | X | X | X |
| IGF-1R positive CTCs | X | X | X | |
| IGF2 and IGF-BP2 | | X | X[a] | X[a] |

BP = blood pressure; CTCs = circulating tumor cells; IGF-1R = Insulin-Like Growth Factor 1 receptor; IGF2 = Insulin-Like Growth Factor 2.

a. Samples were collected either at Cycle 5 predose or at the End of the Study, whichever occurs first.

**Number of Subjects (Planned and Analyzed):** The study initially planned to accrue approximately 120 subjects (60 in each arm), providing sufficient power to test the primary hypothesis of PSA response. Approximately 200 subjects (100 in each arm) was planned to also allow the assessment of PFS. The actual numbers of subjects randomized country-wise were 67 from the UK; 57 from Spain; 40 from the US; 23 from Canada; 10 from Switzerland; 8 from Germany.

**Diagnosis and Main Criteria for Inclusion:** The study included adult male subjects diagnosed with metastatic, progressive hormone refractory prostate cancer and with adequate bone marrow, liver, and kidney function. Subjects with previous treatment with chemotherapy were excluded from study.

**Study Treatment:** Standard doses of docetaxel and prednisone used during the study were 75 mg/m$^2$ once every 3 weeks and 5 mg twice a day, respectively. The dose of figitumumab was 20 mg/kg either as single agent or in combination with docetaxel/prednisone. The treatment was given in 3-week cycles (21-day cycles).

The contribution of figitumumab to the standard regimen of docetaxel and prednisone was investigated in the following 2 ways:

- Concurrent administration of figitumumab with docetaxel/prednisone in chemo-naive subjects (Arm A).

- Subsequent administration of figitumumab/docetaxel/prednisone combination regimen in subjects that failed to respond to docetaxel/prednisone alone (Arm B).

In Arm A; figitumumab was administered as a 1-hour intravenous (IV) infusion following docetaxel administered as a 1-hour IV infusion on Day 1. However, dosing of figitumumab could have been delayed up to 7 days. Prednisone was given daily, starting on Day 1.

In Arm B docetaxel was administered as a 1-hour IV infusion on Day 1 and prednisone was given daily, starting on Day 1. In the study prednisolone or equivalent could also be employed.

Figitumumab was added to the dosage regimen of subjects in Arm B if disease progression was noticed; this treatment group was designated as Arm B2. Arm B2 is used to indicate the

subset of B1 subjects who received figitumumab/docetaxel/prednisone combination regimen after being treated on docetaxel/prednisone alone and progressing. Arm B1 is used to refer to all subjects who initially received docetaxel/prednisone alone.

**Efficacy, Pharmacokinetic, Pharmacodynamics, Safety, or Outcomes Research Endpoints:**

Primary Endpoint:

- PSA Response.

Secondary Endpoints:

- PFS.
- Safety and tolerability.
- Population PK parameters of figitumumab.
- HAHA.
- Total number of circulating tumor cells (CTCs) and CTCs expressing Insulin-Like Growth Factor 1 receptor (IGF-1R).
- Pain measured by the modified brief pain inventory-short form (BPI-sf modified Sponsor) and quality of life measured by the functional assessment of cancer treatment-prostate.

**Safety Evaluations:** All subjects who started treatment in either arm were considered evaluable for safety. Safety evaluations included adverse events (AE), serious adverse events (SAEs), clinical examination (including blood pressure and pulse rate), laboratory tests (hematology, chemistry, coagulation function, and urinalysis), and 12-lead electrocardiograms.

**Statistical Methods:**

Analysis Populations: Full analysis set included all enrolled subjects. Per protocol analysis set included all enrolled subjects who had the disease under study and who started treatment on the assigned arm. Safety analysis set included all enrolled subjects who started treatment.

Statistical Hypotheses: The primary endpoint for each arm was confirmed PSA response. The hypotheses planned to be tested on Arm A were $H_0$: p=0.45 versus $H_A$: p=0.6, while the hypotheses for Arm B2 were $H_0$: p=0.05 versus $H_A$: p=0.2.

Statistical Decision Rules: For Arm A, if the null hypothesis was rejected at the 0.05 level in favor of the alternative after accrual was complete, the regimen was to be considered for further development in subjects with chemotherapy naïve HRPC. If $H_0$ was rejected at the 0.01 level after response was determined in the first 50 subjects, consideration was given to

initiating Phase 3 planning activities. For treatment B2, if the null hypothesis was rejected at the 0.05 level in favor of the alternative after the second stage of accrual was complete, the regimen was to be considered for further development in HRPC subjects who had progressed on docetaxel/prednisone.

## RESULTS

**Subject Disposition and Demography:** Subject disposition is summarized in Table 3. A total of 204 subjects were enrolled (102 subjects in each Arm A and Arm B).

### Table 3. Subject Disposition and Subjects Analyzed

| Number of Subjects (%) | | Arm A | Arm B1 | Arm B2 |
|---|---|---|---|---|
| Assigned to study treatment | 204 | | | |
| Treated | | 97 | 102 | 37 |
| Completed[a] | | 27 (27.8) | 23 (22.5) | 9 (24.3) |
| Discontinued | | 70 (72.2) | 42 (41.2) | 27 (73.0) |
| Subject died | | 8 (8.2) | | 0 |
| Related to study drug | | 15 (15.5) | | 4 (10.8) |
| Adverse event | | 15 (15.5) | | 4 (10.8) |
| Not related to study drug | | 65 (67.0) | | 27 (73.0) |
| Adverse event | | 9 (9.3) | | 1 (2.7) |
| Global deterioration of health status | | 9 (9.3) | | 3 (8.1) |
| Objective progression or relapse | | 27 (27.8) | | 19 (51.4) |
| Other | | 16 (16.5) | | 3 (8.1) |
| Subject refused continued treatment for reason other than adverse event | | 4 (4.1) | | 1 (2.7) |
| Ongoing at date of cut-off | | 0 | 0 | 1 (2.7) |
| Crossover | | 0 | 37 (36.3) | 0 |
| Evaluability | | | | |
| With the disease under study | | 97 (100.0) | 102 (100.0) | 37 (100.0) |
| No first cycle major deviation[b] | | 97 (100.0) | 102 (100.0) | 37 (100.0) |
| Analyzed for safety | | | | |
| Adverse events | | 97 (100.0) | 102 (100.0) | 37 (100.0) |
| Laboratory data | | 96 (99.0) | 101 (99.0) | 37 (100.0) |

a. A 'completer' was defined as a subject who completed 17 cycles.
b. First cycle major deviations include: <50% of the planned Cycle 1 dose of figitumumab (provided the reduction is not due to toxicity); >150% of the planned Cycle 1 dose of figitumumab; docetaxel or prednisone not given in Cycle 1 (provided omission is not due to toxicity).

Of the 102 subjects, 97 were treated as per treatment regimen of Arm A. All 102 subjects received treatment in Arm B. Thirty-seven (37) subjects in Arm B received additional cycles of docetaxel and prednisone in combination with figitumumab after experiencing progression of their disease while on chemotherapy alone (Arm B2).

Demographic and other baseline characteristics are presented in Table 4.

## Table 4. Demographic Characteristics

| Characteristics | Arm A | Arm B |
|---|---|---|
| | Male | Male |
| Number of subjects (%) | 102 | 102 |
| Age (years): | | |
| <18 | 0 | 0 |
| 18-44 | 0 | 1 (1.0) |
| 45-64 | 26 (25.5) | 32 (31.4) |
| ≥65 | 76 (74.5) | 69 (67.6) |
| Mean | 68.9 | 67.9 |
| SD | 7.4 | 7.5 |
| Range | 45-84 | 42-82 |
| Race | | |
| White | 94 (92.2) | 97 (95.1) |
| Black | 4 (3.9) | 2 (2.0) |
| Other | 4 (3.9) | 3 (2.9) |
| Weight (kg) | | |
| Mean | 84.5 | 84.6 |
| SD | 17.0 | 13.7 |
| Range | 52.9-152.4 | 51.3-117.3 |
| N | 101 (99.0) | 102 (100.0) |
| Height (cm) | | |
| Mean | 172.8 | 173.1 |
| SD | 8.7 | 7.4 |
| Range | 151.0-210.8 | 153.0-193.0 |
| N | 101 (99.0) | 102 (100.0) |

N = number of subjects; SD = standard deviation.

### Efficacy, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Results:

The primary efficacy endpoint of this study was confirmed PSA response. A subject was considered PSA responder, if the PSA response was either confirmed PSA normalization (PN) or Partial PSA Response (PR). PN was defined as 2 or more sequential PSA objective statuses of normalization at least 3 weeks (21 days) apart documented prior to PSA progression. PR was defined as 2 or more sequential PSA objective statuses of partial PSA response or better at least 3 weeks (21 days) apart documented prior to PSA progression and not qualifying as normalization. Response rate was determined as the number of responding subjects divided by the number of evaluable subjects.

Summary of PSA best overall response is presented in Table 5.

**Table 5. Summary of Best Overall Response – PSA Evaluable Population**

| | Arm A (N=87) | Arm B1 (N=98) | Arm B2 (N=32) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| PSA normalization | 0 | 3 (3.1) | 1 (3.1) |
| Partial PSA response | 45 (51.7) | 56 (57.1) | 8 (25.0) |
| Stable PSA response | 27 (31.0) | 21 (21.4) | 9 (28.1) |
| PSA progression | 5 (5.7) | 8 (8.2) | 8 (25.0) |
| Objective disease progression | 1 (1.1) | 1 (1.0) | 1 ( 3.1) |
| Symptomatic deterioration | 6 (6.9) | 0 | 0 |
| Early death | 2 (2.3) | 1 (1.0) | 0 |
| Indeterminate | 1 (1.1) | 8 (8.2) | 5 (15.6) |
| Objective response rate (PN + PR) | 45 (51.7) | 59 (60.2) | 9 (28.1) |
| 90% exact CI[a] | 42.4, 61.0 | 51.4, 68.5 | 15.5, 43.9 |

CI = confidence interval; N = total number of subjects; n = number of subjects; PN = PSA normalization; PR = partial PSA response; PSA = prostate specific antigen.
a. Using exact method based on binomial distribution.

Progression Free Survival: For the secondary objective of comparing PFS in Arm A with PFS in Arm B1, summary of PSA PFS is presented in Table 6.

**Table 6. Summary of Progression-Free Survival**

| | Arm A (N=97) | Arm B1 (N=102) | Arm B2 (N=37) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Number with event | 88 (90.7) | 83 (81.4) | 31 (83.8) |
| Type of event | | | |
| Objective progression | 87 (89.7) | 78 (76.5) | 30 (81.1) |
| Symptomatic deterioration without objective progression | 0 | 0 | 0 |
| Death without objective progression or symptomatic deterioration | 0 | 2 (2.0) | 0 |
| Started new treatment with progression unknown | 1 (1.0) | 3 (2.9) | 1 (2.7) |
| Number censored | 9 (9.3) | 19 (18.6) | 6 (16.2) |
| Reason for censorship | | | |
| In follow-up for progression | 8 (8.2) | 18 (17.6) | 6 (16.2) |
| Withdrew consent for additional follow-up | 1 (1.0) | 1 (<1.0) | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Started new treatment without progression | 0 | 0 | 0 |
| Probability of being event free at Month 6[a] (95% CI[b]) | 39.3 (29.3, 49.3) | 61.0 (51.2, 70.7) | |
| Kaplan-Meier estimates of time to event (month) | | | |
| Quartiles (95% CI)[c] | | | |
| 25% | 2.5 (2.1, 3.5) | 2.9 (2.3, 4.3) | 2.3 (1.4, 3.5) |
| 50% | 4.9 (4.1, 5.9) | 7.7 (6.1, 8.9) | 4.0 (3.3, 4.8) |
| 75% | 8.8 (7.2, 10.2) | 10.2 (9.2, 13.0) | 6.2 (4.4, 6.7) |
| Versus Arm B1 | | | |
| Hazard ratio[d] | 1.415 | | |
| 95% CI of hazard ratio | 1.047-1.914 | | |

CI = confidence interval; N = total number of subjects, n = number of subjects; PSA = prostate specific antigen.
a. Using exact method based on binomial distribution.
b. Calculated based on a normal distribution.
c. p-Value is from a Pearson chi-square test.
d. Based on the Cox Proportional hazards model.

No statistical analysis was performed for the PK data and the data were reported separately.

HAHA results are summarized in the Table 7.

**Table 7. Summary of Immunoglobulin G (HAHA)**

| Visit | | Arm A (N=97) | Arm B1 (N=102) | Arm B2 (N=37) |
|---|---|---|---|---|
| Cycle 1 Day 1 (Baseline) | | | | |
| | n | 49 | 41 | |
| | Mean | 1130.3 | 1338.1 | |
| | SD | 406.49 | 804.3 | |
| | Max | 2800 | 4900 | |
| | Min | 27 | 575 | |
| | 95% CI | (1013.50, 1247.02) | (1084.28, 1592.02) | |
| | Median | 1051 | 1180 | |
| | 25% quartile | 899 | 935 | |
| | 75% quartile | 1360 | 1459 | |
| End of treatment | | | | |
| | n | 32 | 13 | 14 |
| | Mean | 944.81 | 819 | 970.86 |
| | SD | 946.42 | 487.94 | 295.28 |
| | Max | 6000 | 2300 | 1570 |
| | Min | 468 | 448 | 352 |
| | 95% CI | (603.59, 1286.03) | (524.14, 1113.86) | (800.37, 1141.35) |
| | Median | 737 | 668 | 962.5 |
| | 25% quartile | 625.5 | 533 | 790 |
| | 75% quartile | 922 | 853 | 1117 |

CI = confidence interval; HAHA = human anti-human antibodies; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in each group; SD = standard deviation.

In the screening ADA assay, none of the samples collected after start of figitumumab dosing was positive for ADA, as indicated by a titer measurement of <6.64. There was 1 sample collected prior to the first figitumumab dose that showed a low titer measurement of 10.85 for 1 subject in Cycle 1 predose; this low titer ADA measurement was likely a false positive result from the assay.

CTC summary statistics and change from Baseline for enrolled subjects is presented in Table 8.

## Table 8. Circulating Tumor Cells (CTC) Summary Statistics and Change From Baseline - Enrolled

| Visit | | Arm A (N=102) | Arm B (N=102) |
|---|---|---|---|
| Number of subjects with a Cycle 1 Day 1 CTC measurement ≥0 | n | 91 | 91 |
| Cycle 1 Day 1(Baseline)[a] | n | 46 | 39 |
| | Mean | 105.17 | 213.23 |
| | SD | 259.60 | 555.82 |
| | Max, Min | 1347.0, 5.0 | 2805.0, 5.0 |
| | 95% CI | (28.08, 182.26) | (33.05, 393.41) |
| | Median | 16.5 | 52.0 |
| | 25% quartile | 10.0 | 20.0 |
| | 75% quartile | 73.0 | 192.0 |
| Cycle 3 Day 1[b] | n | 28 | 29 |
| | Mean | 6.39 | 12.21 |
| | SD | 11.39 | 27.52 |
| | Max, Min | 57.0, 0.0 | 146.0, 0.0 |
| | 95% CI | (1.98, 10.81) | (1.74, 22.68) |
| | Median | 2.0 | 3.0 |
| | 25% quartile | 0.0 | 1.0 |
| | 75% quartile | 8.5 | 11.0 |
| Percent change from Baseline at Cycle 3 Day 1[b] | n | 28 | 29 |
| | Mean | -78.84 | -84.73 |
| | SD | 40.25 | 25.18 |
| | Max, Min | 100.0, -100.0 | -5.6, -100.0 |
| | 95% CI | (-94.45, -63.23) | (-94.31, -75.16) |
| | Median | -89.0 | -96.6 |
| | 25% quartile | -100.0 | -99.8 |
| | 75% quartile | -80.0 | -84.9 |
| Cycle 5 Day 1[b] | n | 25 | 23 |
| | Mean | 15.20 | 17.78 |
| | SD | 46.40 | 28.11 |
| | Max, Min | 226.0, 0.0 | 109.0, 0.0 |
| | 95% CI | (-3.95, 34.35) | (5.63, 29.94) |
| | Median | 0.0 | 3.0 |
| | 25% quartile | 0.0 | 1.0 |
| | 75% quartile | 4.0 | 21.0 |
| Percent change from Baseline at Cycle 5 Day 1[b] | n | 25 | 23 |
| | Mean | -23.49 | -41.32 |
| | SD | 300.38 | 156.85 |
| | Max, Min | 1407.0, -100 | 626.7, -100 |
| | 95% CI | (-147.48, 100.50) | (-109.14, 26.51) |
| | Median | -100.0 | -94.3 |
| | 25% quartile | -100.0 | -99.2 |
| | 75% quartile | -90.9 | -72.1 |

CI = confidence interval; CTC = circulating tumor cells; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects; SD = standard deviation.

a. Subjects with (baseline CTC ≥5).

b. Arm A subjects with (baseline CTC ≥5), CTC ≥0 at the visit; Arm B subjects with (baseline CTC ≥5), CTC ≥0 at the visit, and have not started figitumumab at the visit.

Similar results for IGF-1R positive CTC summary statistics and change from Baseline for enrolled subjects is presented in Table 9.

## Table 9. Circulating Tumor Cells (IGF-1R-Positive) Summary Statistics and Change From Baseline - Enrolled

| Visit | | Arm A (N=102) | Arm B (N=102) |
|---|---|---|---|
| Number of subjects with a Cycle 1 Day 1 CTC measurement ≥0 | n | 91 | 90 |
| Cycle 1 Day 1 (Baseline)[a] | n | 22 | 18 |
| | Mean | 24.73 | 54.94 |
| | SD | 25.32 | 55.52 |
| | Max, Min | 86.0, 5.0 | 186.0, 5.0 |
| | 95% CI | (13.50, 35.95) | (27.34, 82.55) |
| | Median | 12.0 | 27.0 |
| | 25% quartile | 5.0 | 15.0 |
| | 75% quartile | 37.0 | 98.0 |
| Cycle 3 Day 1[b] | n | 12 | 15 |
| | Mean | 2.33 | 4.93 |
| | SD | 4.48 | 7.74 |
| | Max, Min | 15.0, 0.0 | 29.0, 0.0 |
| | 95% CI | (-0.51, 5.18) | (0.65, 9.22) |
| | Median | 0.5 | 2.0 |
| | 25% quartile | 0.0 | 0.0 |
| | 75% quartile | 2.0 | 5.0 |
| Percent change from Baseline at Cycle 3 Day 1[b] | n | 12 | 15 |
| | Mean | -92.23 | -85.65 |
| | SD | 10.12 | 20.82 |
| | Max, Min | -76.7, -100 | -37.0, -100.0 |
| | 95% CI | (-98.66, -85.79) | (-97.18, -74.12) |
| | Median | -98.9 | -96.5 |
| | 25% quartile | -100.0 | -100.0 |
| | 75% quartile | -81.0 | -77.8 |
| Cycle 5 Day 1[b] | n | 11 | 10 |
| | Mean | 2.00 | 3.90 |
| | SD | 4.49 | 6.03 |
| | Max, Min | 14.0, 0.0 | 17.0, 0.0 |
| | 95% CI | (-1.02, 5.02) | (-0.41, 8.21) |
| | Median | 0.0 | 2.0 |
| | 25% quartile | 0.0 | 0.0 |
| | 75% quartile | 1.0 | 3.0 |
| Percent change from Baseline at Cycle 5 Day 1[b] | n | 11 | 10 |
| | Mean | -92.56 | -89.51 |
| | SD | 16.43 | 13.96 |
| | Max, Min | -46.2, -100.0 | -60.0, -100.0 |
| | 95% CI | (-103.60, -81.53) | (-99.49, -79.53) |
| | Median | -100.0 | -95.8 |
| | 25% quartile | -100.0 | -100.0 |
| | 75% quartile | -88.9 | -85.1 |

CI = confidence interval; CTC = circulating tumor cells; IGF-1R = Insulin-like Growth Factor 1 receptor; Max = maximum; Min = minimum; N = total number of subjects, n = number of subjects; SD = standard deviation.

a. Subjects with (baseline CTC/IGF-1R ≥5).

b. Arm A subjects with (baseline CTC/IGF-1R ≥5), CTC/IGF-1R ≥0 at the visit; Arm B subjects with (baseline CTC/IGF-1R ≥5), CTC /IGF-1R ≥0 at the visit, and have not started figitumumab at the visit.

No statistical analysis was performed for BPI–sf and the results are not provided here.

**Safety Results:** The treatment-emergent all-causality non serious AE are presented in the Table 10.

## Table 10. Treatment Emergent Non Serious Adverse Events for Events Having a Frequency Rate ≥5

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Number (%) of subjects: | | | |
| Evaluable for adverse events | 97 | 102 | 37 |
| With adverse events | 96 (99.0) | 100 (98.0) | 37 (100.0) |
| Number (%) of subjects with adverse events by: | | | |
| System organ class and MedDRA (v14.0) Preferred term | | | |
| Blood and lymphatic system disorders | 48 (49.5) | 49 (48.0) | 19 (51.4) |
| Anaemia | 13 (13.4) | 21 (20.6) | 11 (29.7) |
| Leukopenia | 22 (22.7) | 24 (23.5) | 4 (10.8) |
| Lymphopenia | 8 (8.2) | 10 (9.8) | 4 (10.8) |
| Neutropenia | 34 (35.1) | 37 (36.3) | 10 (27.0) |
| Thrombocytopenia | 5 (5.2) | 1 (1.0) | 1 (2.7) |
| Ear and labyrinth disorders | 25 (25.8) | 6 (5.9) | 4 (10.8) |
| Deafness | 7 (7.2) | 1 (1.0) | 1 (2.7) |
| Ear discomfort | 6 (6.2) | 0 | 0 |
| Hypoacusis | 7 (7.2) | 0 | 0 |
| Eye disorders | 25 (25.8) | 21 (20.6) | 10 (27.0) |
| Conjunctivitis | 6 (6.2) | 5 (4.9) | 2 (5.4) |
| Lacrimation increased | 9 (9.3) | 8 (7.8) | 6 (16.2) |
| Vision blurred | 5 (5.2) | 5 (4.9) | 2 (5.4) |
| Gastrointestinal disorders | 89 (91.8) | 70 (68.6) | 28 (75.7) |
| Abdominal pain | 8 (8.2) | 2 (2.0) | 3 (8.1) |
| Abdominal pain upper | 6 (6.2) | 2 (2.0) | 0 |
| Anal fissure | 5 (5.2) | 0 | 0 |
| Constipation | 22 (22.7) | 17 (16.7) | 8 (21.6) |
| Diarrhoea | 64 (66.0) | 38 (37.3) | 14 (37.8) |
| Dry mouth | 6 (6.2) | 4 (3.9) | 3 (8.1) |
| Dyspepsia | 8 (8.2) | 6 (5.9) | 3 (8.1) |
| Dysphagia | 2 (2.1) | 3 (2.9) | 2 (5.4) |
| Faecal incontinence | 2 (2.1) | 2 (2.0) | 2 (5.4) |
| Flatulence | 1 (1.0) | 2 (2.0) | 2 (5.4) |
| Gingival pain | 5 (5.2) | 1 (1.0) | 0 |
| Gingival ulceration | 1 (1.0) | 1 (1.0) | 2 (5.4) |
| Haemorrhoids | 5 (5.2) | 3 (2.9) | 2 (5.4) |
| Nausea | 34 (35.1) | 28 (27.5) | 10 (27.0) |
| Proctalgia | 5 (5.2) | 2 (2.0) | 3 (8.1) |
| Rectal haemorrhage | 10 (10.3) | 6 (5.9) | 2 (5.4) |
| Stomatitis | 18 (18.6) | 8 (7.8) | 3 (8.1) |
| Vomiting | 19 (19.6) | 12 (11.8) | 10 (27.0) |
| General disorders and administration site conditions | 77 (79.4) | 79 (77.5) | 28 (75.7) |
| Asthenia | 38 (39.2) | 33 (32.4) | 13 (35.1) |
| Chest pain | 2 (2.1) | 3 (2.9) | 2 (5.4) |
| Chills | 6 (6.2) | 6 (5.9) | 3 (8.1) |
| Fatigue | 40 (41.2) | 36 (35.3) | 14 (37.8) |
| General physical health deterioration | 2 (2.1) | 0 | 2 (5.4) |
| Mucosal inflammation | 15 (15.5) | 12 (11.8) | 1 (2.7) |
| Oedema peripheral | 10 (10.3) | 28 (27.5) | 4 (10.8) |
| Pain | 6 (6.2) | 3 (2.9) | 4 (10.8) |
| Pyrexia | 12 (12.4) | 13 (12.7) | 4 (10.8) |
| Infections and infestations | 47 (48.5) | 46 (45.1) | 12 (32.4) |
| Nasopharyngitis | 7 (7.2) | 11 (10.8) | 4 (10.8) |
| Onychomycosis | 2 (2.1) | 5 (4.9) | 2 (5.4) |
| Respiratory tract infection | 4 (4.1) | 3 (2.9) | 2 (5.4) |
| Rhinitis | 3 (3.1) | 6 (5.9) | 2 (5.4) |

## Table 10. Treatment Emergent Non Serious Adverse Events for Events Having a Frequency Rate ≥5

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Upper respiratory tract infection | 4 (4.1) | 6 (5.9) | 0 |
| Urinary tract infection | 12 (12.4) | 7 (6.9) | 2 (5.4) |
| Injury, poisoning and procedural complications | 26 (26.8) | 10 (9.8) | 6 (16.2) |
| Contusion | 7 (7.2) | 4 (3.9) | 2 (5.4) |
| Fall | 9 (9.3) | 0 | 3 (8.1) |
| Investigations | 47 (48.5) | 30 (29.4) | 16 (43.2) |
| Alanine aminotransferase increased | 7 (7.2) | 1 (1.0) | 0 |
| Blood alkaline phosphatase increased | 1 (1.0) | 4 (3.9) | 3 (8.1) |
| Blood creatinine increased | 9 (9.3) | 0 | 2 (5.4) |
| Blood glucose increased | 4 (4.1) | 3 (2.9) | 3 (8.1) |
| Blood urea increased | 4 (4.1) | 1 (1.0) | 2 (5.4) |
| Weight decreased | 18 (18.6) | 8 (7.8) | 6 (16.2) |
| Metabolism and nutrition disorders | 77 (79.4) | 50 (49.0) | 26 (70.3) |
| Decreased appetite | 56 (57.7) | 32 (31.4) | 20 (54.1) |
| Hypercholesterolaemia | 2 (2.1) | 1 (1.0) | 2 (5.4) |
| Hyperglycaemia | 34 (35.1) | 15 (14.7) | 14 (37.8) |
| Hypokalaemia | 7 (7.2) | 4 (3.9) | 2 (5.4) |
| Hyponatraemia | 5 (5.2) | 1 (1.0) | 1 (2.7) |
| Musculoskeletal and connective tissue disorder | 67 (69.1) | 60 (58.8) | 30 (81.1) |
| Arthralgia | 10 (10.3) | 15 (14.7) | 10 (27.0) |
| Back pain | 20 (20.6) | 13 (12.7) | 11 (29.7) |
| Bone pain | 5 (5.2) | 7 (6.9) | 1 (2.7) |
| Groin pain | 3 (3.1) | 2 (2.0) | 2 (5.4) |
| Joint swelling | 3 (3.1) | 2 (2.0) | 2 (5.4) |
| Muscle spasms | 19 (19.6) | 7 (6.9) | 6 (16.2) |
| Muscular weakness | 13 (13.4) | 11 (10.8) | 6 (16.2) |
| Musculoskeletal chest pain | 2 (2.1) | 3 (2.9) | 3 (8.1) |
| Musculoskeletal pain | 14 (14.4) | 8 (7.8) | 5 (13.5) |
| Myalgia | 6 (6.2) | 13 (12.7) | 4 (10.8) |
| Pain in extremity | 14 (14.4) | 18 (17.6) | 10 (27.0) |
| Nervous system disorders | 69 (71.1) | 75 (73.5) | 31 (83.8) |
| Amnesia | 5 (5.2) | 1 (1.0) | 2 (5.4) |
| Dizziness | 10 (10.3) | 16 (15.7) | 6 (16.2) |
| Dysgeusia | 37 (38.1) | 37 (36.3) | 12 (32.4) |
| Headache | 9 (9.3) | 7 (6.9) | 1 (2.7) |
| Hypoaesthesia | 3 (3.1) | 8 (7.8) | 2 (5.4) |
| Lethargy | 15 (15.5) | 16 (15.7) | 5 (13.5) |
| Neuropathy peripheral | 16 (16.5) | 22 (21.6) | 12 (32.4) |
| Neurotoxicity | 9 (9.3) | 3 (2.9) | 0 |
| Paraesthesia | 7 (7.2) | 15 (14.7) | 5 (13.5) |
| Peripheral sensory neuropathy | 2 (2.1) | 5 (4.9) | 4 (10.8) |
| Spinal cord compression | 0 | 0 | 2 (5.4) |
| Tremor | 6 (6.2) | 2 (2.0) | 1 (2.7) |
| Psychiatric disorders | 32 (33.0) | 22 (21.6) | 4 (10.8) |
| Anxiety | 7 (7.2) | 2 (2.0) | 1 (2.7) |
| Depression | 7 (7.2) | 1 (1.0) | 2 (5.4) |
| Disorientation | 8 (8.2) | 0 | 0 |
| Insomnia | 6 (6.2) | 12 (11.8) | 1 (2.7) |
| Renal and urinary disorders | 32 (33.0) | 31 (30.4) | 16 (43.2) |
| Dysuria | 5 (5.2) | 3 (2.9) | 2 (5.4) |
| Haematuria | 7 (7.2) | 3 (2.9) | 3 (8.1) |
| Nocturia | 8 (8.2) | 9 (8.8) | 4 (10.8) |
| Pollakiuria | 5 (5.2) | 4 (3.9) | 2 (5.4) |
| Polyuria | 4 (4.1) | 0 | 2 (5.4) |
| Proteinuria | 1 (1.0) | 3 (2.9) | 3 (8.1) |

**Table 10. Treatment Emergent Non Serious Adverse Events for Events Having a Frequency Rate ≥5**

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Urinary incontinence | 7 (7.2) | 4 (3.9) | 3 (8.1) |
| Urinary retention | 7 (7.2) | 2 (2.0) | 1 (2.7) |
| Urine flow decreased | 1 (1.0) | 0 | 2 (5.4) |
| Reproductive system and breast disorders | 2 (2.1) | 12 (11.8) | 5 (13.5) |
| Pelvic pain | 1 (1.0) | 4 (3.9) | 3 (8.1) |
| Respiratory, thoracic and mediastinal disorders | 51 (52.6) | 56 (54.9) | 19 (51.4) |
| Cough | 15 (15.5) | 13 (12.7) | 5 (13.5) |
| Dysphonia | 5 (5.2) | 11 (10.8) | 1 (2.7) |
| Dyspnoea | 15 (15.5) | 23 (22.5) | 10 (27.0) |
| Dyspnoea exertional | 4 (4.1) | 3 (2.9) | 3 (8.1) |
| Epistaxis | 21 (21.6) | 15 (14.7) | 7 (18.9) |
| Oropharyngeal pain | 5 (5.2) | 6 (5.9) | 1 (2.7) |
| Pleural effusion | 0 | 1 (1.0) | 2 (5.4) |
| Productive cough | 5 (5.2) | 5 (4.9) | 0 |
| Rhinorrhoea | 8 (8.2) | 5 (4.9) | 2 (5.4) |
| Skin and subcutaneous tissue disorders | 70 (72.2) | 80 (78.4) | 27 (73.0) |
| Alopecia | 46 (47.4) | 51 (50.0) | 17 (45.9) |
| Dry skin | 9 (9.3) | 14 (13.7) | 4 (10.8) |
| Ecchymosis | 5 (5.2) | 0 | 2 (5.4) |
| Erythema | 8 (8.2) | 10 (9.8) | 2 (5.4) |
| Hyperhidrosis | 1 (1.0) | 3 (2.9) | 2 (5.4) |
| Nail disorder | 7 (7.2) | 15 (14.7) | 7 (18.9) |
| Nail toxicity | 6 (6.2) | 6 (5.9) | 0 |
| Pruritus | 7 (7.2) | 4 (3.9) | 2 (5.4) |
| Purpura | 3 (3.1) | 0 | 2 (5.4) |
| Rash | 9 (9.3) | 7 (6.9) | 2 (5.4) |
| Skin lesion | 1 (1.0) | 0 | 3 (8.1) |
| Skin ulcer | 3 (3.1) | 0 | 4 (10.8) |
| Vascular disorders | 29 (29.9) | 27 (26.5) | 8 (21.6) |
| Flushing | 3 (3.1) | 8 (7.8) | 1 (2.7) |
| Haematoma | 5 (5.2) | 2 (2.0) | 1 (2.7) |
| Hot flush | 1 (1.0) | 6 (5.9) | 0 |
| Hypertension | 3 (3.1) | 4 (3.9) | 2 (5.4) |
| Hypotension | 8 (8.2) | 5 (4.9) | 1 (2.7) |
| Pallor | 8 (8.2) | 1 (1.0) | 3 (8.1) |

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

The treatment-related AEs are presented in the Table 11. A clinically meaningful number of more subjects reported AE for the following terms more commonly in Arm A than subjects in Arm B1 respectively: diarrhea, decreased appetite, fatigue, asthenia, hyperglycemia, stomatitis, muscle spasm, febrile neutropenia.

## Table 11. Treatment-Emergent Adverse Events by Decreasing Frequency (Treatment-Related) for a Frequency Rate ≥3

| MedDRA (v14.0) Preferred Term | Arm A | | Arm B1 | | Arm B2 | |
|---|---|---|---|---|---|---|
| | n | n (%) | n | n (%) | n | n (%) |
| Diarrhoea | 56 | 57.7 | 34 | 33.3 | 10 | 27 |
| Decreased appetite | 48 | 49.5 | 26 | 25.5 | 17 | 45.9 |
| Alopecia | 46 | 47.4 | 51 | 50 | 17 | 45.9 |
| Fatigue | 41 | 42.3 | 35 | 34.3 | 13 | 35.1 |
| Neutropenia | 39 | 40.2 | 39 | 38.2 | 10 | 27 |
| Dysgeusia | 36 | 37.1 | 37 | 36.3 | 12 | 32.4 |
| Asthenia | 35 | 36.1 | 28 | 27.5 | 13 | 35.1 |
| Hyperglycaemia | 32 | 33 | 14 | 13.7 | 14 | 37.8 |
| Nausea | 28 | 28.9 | 26 | 25.5 | 8 | 21.6 |
| Leukopenia | 22 | 22.7 | 25 | 24.5 | 3 | 8.1 |
| Stomatitis | 18 | 18.6 | 8 | 7.8 | 2 | 5.4 |
| Mucosal inflammation | 15 | 15.5 | 12 | 11.8 | 1 | 2.7 |
| Muscle spasms | 15 | 15.5 | 5 | 4.9 | 5 | 13.5 |
| Neuropathy peripheral | 14 | 14.4 | 21 | 20.6 | 12 | 32.4 |
| Febrile neutropenia | 12 | 12.4 | 7 | 6.9 | 2 | 5.4 |
| Lethargy | 12 | 12.4 | 15 | 14.7 | 5 | 13.5 |
| Vomiting | 12 | 12.4 | 9 | 8.8 | 7 | 18.9 |
| Constipation | 9 | 9.3 | 8 | 7.8 | 3 | 8.1 |
| Epistaxis | 9 | 9.3 | 8 | 7.8 | 3 | 8.1 |
| Pyrexia | 9 | 9.3 | 6 | 5.9 | 0 | - |
| Weight decreased | 9 | 9.3 | 7 | 6.9 | 5 | 13.5 |
| Disorientation | 8 | 8.2 | 0 | - | 0 | - |
| Lymphopenia | 8 | 8.2 | 9 | 8.8 | 4 | 10.8 |
| Neurotoxicity | 8 | 8.2 | 3 | 2.9 | 0 | - |
| Lacrimation increased | 7 | 7.2 | 7 | 6.9 | 5 | 13.5 |
| Muscular weakness | 7 | 7.2 | 4 | 3.9 | 4 | 10.8 |
| Nail disorder | 7 | 7.2 | 15 | 14.7 | 7 | 18.9 |
| Rash | 7 | 7.2 | 7 | 6.9 | 1 | 2.7 |
| Alanine aminotransferase increased | 6 | 6.2 | 1 | 1 | 0 | - |
| Anaemia | 6 | 6.2 | 16 | 15.7 | 6 | 16.2 |
| Dry skin | 6 | 6.2 | 10 | 9.8 | 3 | 8.1 |
| Dyspepsia | 6 | 6.2 | 3 | 2.9 | 1 | 2.7 |
| Dyspnoea | 6 | 6.2 | 16 | 15.7 | 3 | 8.1 |
| Ear discomfort | 6 | 6.2 | 0 | - | 0 | - |
| Erythema | 6 | 6.2 | 9 | 8.8 | 1 | 2.7 |
| Nail toxicity | 6 | 6.2 | 6 | 5.9 | 0 | - |
| Oedema peripheral | 6 | 6.2 | 17 | 16.7 | 3 | 8.1 |
| Deafness | 5 | 5.2 | 0 | - | 1 | 2.7 |
| Dry mouth | 5 | 5.2 | 3 | 2.9 | 3 | 8.1 |
| Paraesthesia | 5 | 5.2 | 13 | 12.7 | 4 | 10.8 |
| Thrombocytopenia | 5 | 5.2 | 1 | 1 | 0 | - |
| Abdominal pain | 4 | 4.1 | 2 | 2 | 0 | - |
| Abdominal pain upper | 4 | 4.1 | 1 | 1 | 0 | - |
| Blood glucose increased | 4 | 4.1 | 1 | 1 | 3 | 8.1 |
| Chills | 4 | 4.1 | 4 | 3.9 | 3 | 8.1 |
| Dizziness | 4 | 4.1 | 8 | 7.8 | 4 | 10.8 |
| Gingival pain | 4 | 4.1 | 1 | 1 | 0 | - |
| Headache | 4 | 4.1 | 2 | 2 | 0 | - |
| Neutrophil count decreased | 4 | 4.1 | 2 | 2 | 0 | - |
| Onycholysis | 4 | 4.1 | 6 | 5.9 | 1 | 2.7 |
| Oral candidiasis | 4 | 4.1 | 4 | 3.9 | 0 | - |
| Oropharyngeal pain | 4 | 4.1 | 2 | 2 | 0 | - |
| Rhinorrhoea | 4 | 4.1 | 4 | 3.9 | 1 | 2.7 |
| White blood cell count decreased | 4 | 4.1 | 3 | 2.9 | 0 | - |
| Contusion | 3 | 3.1 | 1 | 1 | 0 | - |
| Dehydration | 3 | 3.1 | 1 | 1 | 1 | 2.7 |

**Table 11. Treatment-Emergent Adverse Events by Decreasing Frequency (Treatment-Related) for a Frequency Rate ≥3**

| MedDRA (v14.0) Preferred Term | Arm A | | Arm B1 | | Arm B2 | |
|---|---|---|---|---|---|---|
| Ecchymosis | 3 | 3.1 | 0 | - | 2 | 5.4 |
| Gamma-glutamyltransferase increased | 3 | 3.1 | 3 | 2.9 | 1 | 2.7 |
| Hypoaesthesia | 3 | 3.1 | 8 | 7.8 | 2 | 5.4 |
| Hypoglycaemia | 3 | 3.1 | 1 | 1 | 1 | 2.7 |
| Hyponatraemia | 3 | 3.1 | 0 | - | 0 | - |
| Insomnia | 3 | 3.1 | 7 | 6.9 | 0 | - |
| Myopathy | 3 | 3.1 | 1 | 1 | 0 | - |
| Palmarplantar erythrodysaesthesia syndrome | 3 | 3.1 | 1 | 1 | 0 | - |
| Presyncope | 3 | 3.1 | 0 | - | 0 | - |
| Tinnitus | 3 | 3.1 | 0 | - | 0 | - |
| Trigger finger | 3 | 3.1 | 1 | 1 | 0 | - |
| Vision blurred | 3 | 3.1 | 4 | 3.9 | 2 | 5.4 |
| Candidiasis | 2 | 2.1 | 4 | 3.9 | 0 | - |
| Dysphonia | 2 | 2.1 | 6 | 5.9 | 1 | 2.7 |
| Flushing | 2 | 2.1 | 7 | 6.9 | 1 | 2.7 |
| Myalgia | 2 | 2.1 | 9 | 8.8 | 2 | 5.4 |
| Onychomycosis | 2 | 2.1 | 4 | 3.9 | 2 | 5.4 |
| Peripheral sensory neuropathy | 2 | 2.1 | 4 | 3.9 | 4 | 10.8 |
| Purpura | 2 | 2.1 | 0 | - | 2 | 5.4 |
| Arthralgia | 1 | 1 | 3 | 2.9 | 3 | 8.1 |
| Conjunctivitis | 1 | 1 | 1 | 1 | 2 | 5.4 |
| Cough | 1 | 1 | 2 | 2 | 2 | 5.4 |
| Gingival ulceration | 1 | 1 | 1 | 1 | 2 | 5.4 |
| Pain in extremity | 1 | 1 | 7 | 6.9 | 3 | 8.1 |
| Gait disturbance | 0 | - | 1 | 1 | 2 | 5.4 |
| Nocturia | 0 | - | 2 | 2 | 2 | 5.4 |
| Oral pain | 0 | - | 4 | 3.9 | 0 | - |

AEs and SAEs are not separated out in the table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; SAEs = serious adverse events; v = version.

The serious AEs reported in the study are presented in the Table 12.

## Table 12. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Number (%) of subjects: | | | |
| Evaluable for adverse events | 97 | 102 | 37 |
| With adverse events | 64 (66.0) | 37 (36.3) | 20 (54.1) |
| Blood and lymphatic system disorders | 23 (23.7) | 10 (9.8) | 3 (8.1) |
| Anaemia | 2 (2.1) | 1 (1.0) | 1 (2.7) |
| Febrile neutropenia | 12 (12.4) | 7 (6.9) | 2 (5.4) |
| Leukopenia | 1 (1.0) | 1 (1.0) | 0 |
| Neutropenia | 10 (10.3) | 2 (2.0) | 0 |
| Thrombocytopenia | 1 (1.0) | 0 | 0 |
| Cardiac disorders | 3 (3.1) | 5 (4.9) | 2 (5.4) |
| Acute coronary syndrome | 0 | 0 | 1 (2.7) |
| Acute myocardial infarction | 0 | 1 (1.0) | 0 |
| Atrial fibrillation | 0 | 0 | 1 (2.7) |
| Cardiac failure | 1 (1.0) | 1 (1.0) | 0 |
| Cardiogenic shock | 1 (1.0) | 0 | 0 |
| Cardiopulmonary failure | 0 | 1 (1.0) | 0 |
| Myocardial infarction | 0 | 1 (1.0) | 0 |
| Myocardial ischaemia | 1 (1.0) | 1 (1.0) | 0 |
| Endocrine disorders | 1 (1.0) | 0 | 0 |
| Hypercalcaemia of malignancy | 1 (1.0) | 0 | 0 |
| Eye disorders | 1 (1.0) | 0 | 0 |
| Vitreous haemorrhage | 1 (1.0) | 0 | 0 |
| Gastrointestinal disorders | 14 (14.4) | 2 (2.0) | 5 (13.5) |
| Abdominal pain | 1 (1.0) | 0 | 0 |
| Anal fissure | 0 | 0 | 1 (2.7) |
| Colitis ischaemic | 1 (1.0) | 0 | 0 |
| Diarrhoea | 9 (9.3) | 0 | 1 (2.7) |
| Dysphagia | 0 | 1 (1.0) | 1 (2.7) |
| Faecaloma | 1 (1.0) | 0 | 0 |
| Intestinal perforation | 0 | 1 (1.0) | 0 |
| Nausea | 1 (1.0) | 0 | 1 (2.7) |
| Rectal haemorrhage | 1 (1.0) | 0 | 0 |
| Stomatitis | 0 | 1 (1.0) | 0 |
| Upper gastrointestinal haemorrhage | 0 | 0 | 1 (2.7) |
| Vomiting | 4 (4.1) | 0 | 1 (2.7) |
| General disorders and administration site conditions | 20 (20.6) | 5 (4.9) | 8 (21.6) |
| Asthenia | 4 (4.1) | 0 | 1 (2.7) |
| Chest pain | 1 (1.0) | 0 | 0 |
| Death | 2 (2.1) | 0 | 0 |
| Disease progression | 8 (8.2) | 3 (2.9) | 6 (16.2) |
| Drug interaction | 1 (1.0) | 0 | 0 |
| Fatigue | 5 (5.2) | 0 | 3 (8.1) |
| Pyrexia | 1 (1.0) | 2 (2.0) | 0 |
| Immune system disorders | 1 (1.0) | 1 (1.0) | 0 |
| Hypersensitivity | 1 (1.0) | 1 (1.0) | 0 |
| Infections and infestations | 16 (16.5) | 11 (10.8) | 5 (13.5) |
| Abscess | 1 (1.0) | 0 | 0 |
| Candidiasis | 0 | 1 (1.0) | 0 |
| Cellulitis | 1 (1.0) | 0 | 0 |
| Clostridial infection | 1 (1.0) | 0 | 0 |
| Diverticulitis | 4 (4.1) | 1 (1.0) | 0 |
| Endocarditis bacterial | 0 | 1 (1.0) | 0 |
| Gastroenteritis | 1 (1.0) | 0 | 0 |
| Gastrointestinal fungal infection | 1 (1.0) | 0 | 0 |
| Infection | 0 | 0 | 1 (2.7) |

## Table 12. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Localised infection | 0 | 0 | 1 (2.7) |
| Lower respiratory tract infection | 1 (1.0) | 2 (2.0) | 0 |
| Neutropenic sepsis | 3 (3.1) | 3 (2.9) | 0 |
| Peridiverticular abscess | 1 (1.0) | 0 | 0 |
| Pneumonia | 2 (2.1) | 4 (3.9) | 2 (5.4) |
| Salmonellosis | 0 | 1 (1.0) | 0 |
| Septic shock | 1 (1.0) | 0 | 1 (2.7) |
| Soft tissue infection | 0 | 0 | 1 (2.7) |
| Subcutaneous abscess | 1 (1.0) | 0 | 0 |
| Urinary tract infection | 4 (4.1) | 1 (1.0) | 0 |
| Injury, poisoning and procedural complications | 2 (2.1) | 5 (4.9) | 0 |
| Fall | 1 (1.0) | 2 (2.0) | 0 |
| Femoral neck fracture | 0 | 1 (1.0) | 0 |
| Foot fracture | 0 | 1 (1.0) | 0 |
| Joint dislocation | 0 | 1 (1.0) | 0 |
| Rib fracture | 1 (1.0) | 0 | 0 |
| Investigations | 2 (2.1) | 1 (1.0) | 0 |
| Blood creatinine increased | 1 (1.0) | 0 | 0 |
| Troponin T increased | 0 | 1 (1.0) | 0 |
| Weight decreased | 1 (1.0) | 0 | 0 |
| Metabolism and nutrition disorders | 17 (17.5) | 2 (2.0) | 4 (10.8) |
| Decreased appetite | 2 (2.1) | 1 (1.0) | 0 |
| Dehydration | 4 (4.1) | 1 (1.0) | 1 (2.7) |
| Diabetic ketoacidosis | 0 | 0 | 1 (2.7) |
| Hyperglycaemia | 11 (11.3) | 0 | 1 (2.7) |
| Hyperkalaemia | 1 (1.0) | 0 | 0 |
| Hypoglycaemia | 0 | 1 (1.0) | 0 |
| Hyponatraemia | 1 (1.0) | 0 | 1 (2.7) |
| Musculoskeletal and connective tissue disorders | 2 (2.1) | 6 (5.9) | 6 (16.2) |
| Arthralgia | 0 | 0 | 1 (2.7) |
| Arthropathy | 1 (1.0) | 0 | 0 |
| Back pain | 0 | 2 (2.0) | 0 |
| Bone pain | 0 | 1 (1.0) | 1 (2.7) |
| Flank pain | 0 | 0 | 1 (2.7) |
| Muscular weakness | 0 | 1 (1.0) | 1 (2.7) |
| Myopathy | 1 (1.0) | 0 | 0 |
| Osteonecrosis | 0 | 1 (1.0) | 1 (2.7) |
| Pain in extremity | 1 (1.0) | 0 | 0 |
| Pathological fracture | 0 | 1 (1.0) | 0 |
| Spinal column stenosis | 0 | 0 | 1 (2.7) |
| Nervous system disorders | 8 (8.2) | 4 (3.9) | 2 (5.4) |
| Cerebral infarction | 0 | 1 (1.0) | 0 |
| Cerebrovascular accident | 0 | 1 (1.0) | 0 |
| Cognitive disorder | 1 (1.0) | 0 | 0 |
| Convulsion | 1 (1.0) | 0 | 0 |
| Dizziness | 1 (1.0) | 0 | 0 |
| Lethargy | 0 | 0 | 1 (2.7) |
| Mental impairment | 1 (1.0) | 0 | 0 |
| Peripheral motor neuropathy | 1 (1.0) | 0 | 1 (2.7) |
| Presyncope | 1 (1.0) | 0 | 0 |
| Speech disorder | 1 (1.0) | 0 | 0 |
| Spinal cord compression | 2 (2.1) | 0 | 0 |
| Syncope | 0 | 2 (2.0) | 0 |
| Psychiatric disorders | 5 (5.2) | 1 (1.0) | 0 |
| Confusional state | 2 (2.1) | 1 (1.0) | 0 |
| Major depression | 1 (1.0) | 0 | 0 |

**Table 12. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)**

| | Arm A n (%) | Arm B1 n (%) | Arm B2 n (%) |
|---|---|---|---|
| Mental status changes | 2 (2.1) | 0 | 0 |
| Suicide attempt | 1 (1.0) | 0 | 0 |
| Renal and urinary disorders | 8 (8.2) | 3 (2.9) | 4 (10.8) |
| Bladder tamponade | 1 (1.0) | 0 | 0 |
| Haematuria | 1 (1.0) | 1 (1.0) | 0 |
| Renal failure | 4 (4.1) | 0 | 1 (2.7) |
| Renal failure acute | 1 (1.0) | 1 (1.0) | 0 |
| Renal impairment | 1 (1.0) | 0 | 0 |
| Urethral obstruction | 1 (1.0) | 0 | 0 |
| Urinary retention | 0 | 1 (1.0) | 2 (5.4) |
| Urinary tract obstruction | 0 | 0 | 1 (2.7) |
| Respiratory, thoracic and mediastinal disorders | 9 (9.3) | 4 (3.9) | 2 (5.4) |
| Dyspnoea | 2 (2.1) | 0 | 0 |
| Epistaxis | 0 | 0 | 1 (2.7) |
| Hypoxia | 0 | 0 | 1 (2.7) |
| Pharyngeal inflammation | 0 | 1 (1.0) | 0 |
| Pneumonia aspiration | 1 (1.0) | 0 | 0 |
| Pulmonary embolism | 6 (6.2) | 2 (2.0) | 1 (2.7) |
| Respiratory failure | 0 | 1 (1.0) | 0 |
| Vascular disorders | 3 (3.1) | 1 (1.0) | 2 (5.4) |
| Deep vein thrombosis | 1 (1.0) | 0 | 1 (2.7) |
| Haematoma | 1 (1.0) | 0 | 0 |
| Hypotension | 0 | 0 | 1 (2.7) |
| Hypovolaemic shock | 1 (1.0) | 0 | 0 |
| Vasculitis | 0 | 1 (1.0) | 0 |

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

A summary of treatment-emergent SAEs (All causalities, treatment-related) are presented in Table 13.

## Table 13. Treatment-Emergent Treatment-Related Serious Adverse Events

| System Organ Class<br>Preferred Term | Arm A<br>n (%) | Arm B1<br>n (%) | Arm B2<br>n (%) |
|---|---|---|---|
| Any AEs | 40 (41.2) | 15 (14.7) | 10 (27.0) |
| Blood and lymphatic system disorders | 22 (22.7) | 9 (8.8) | 2 (5.4) |
| Febrile neutropenia | 12 (12.4) | 7 (6.9) | 2 (5.4) |
| Leukopenia | 1 (1.0) | 1 (1.0) | 0 |
| Neutropenia | 10 (10.3) | 2 (2.0) | 0 |
| Thrombocytopenia | 1 (1.0) | 0 | 0 |
| Cardiac disorders | 1 (1.0) | 1 (1.0) | 0 |
| Myocardial infarction | | 1 (1.0) | 0 |
| Myocardial ischaemia | 1 (1.0) | 0 | 0 |
| Gastrointestinal disorders | 9 (9.3) | 1 (1.0) | 1 (2.7) |
| Colitis ischaemic | 1 (1.0) | 0 | 0 |
| Diarrhoea | 6 (6.2) | 0 | 1 (2.7) |
| Dysphagia | 0 | 1 (1.0) | 0 |
| Nausea | 1 (1.0) | 0 | 0 |
| Stomatitis | 1 (1.0) | 0 | 0 |
| Vomiting | 4 (4.1) | 0 | 0 |
| General disorders and administration site conditions | 9 (9.3) | 0 | 3 (8.1) |
| Asthenia | 4 (4.1) | 0 | 1 (2.7) |
| Drug interaction | 1 (1.0) | 0 | |
| Fatigue | 5 (5.2) | 0 | 3 (8.1) |
| Infections and infestations | 5 (5.2) | 6 (5.9) | 1 (2.7) |
| Candidiasis | | 1 (1.0) | 0 |
| Diverticulitis | 2 (2.1) | 1 (1.0) | 0 |
| Gastroenteritis | 1 (1.0) | 0 | 0 |
| Gastrointestinal fungal infection | 1 (1.0) | 0 | 0 |
| Neutropenic sepsis | 2 (2.1) | 3 (2.9) | 0 |
| Pneumonia | 0 | 1 (1.0) | 0 |
| Soft tissue infection | 0 | 0 | 1 (2.7) |
| Investigations | 1 (1.0) | 0 | 0 |
| Weight decreased | 1 (1.0) | 0 | 0 |
| Metabolism and nutrition disorders | 14 (14.4) | 1 (1.0) | 2 (5.4) |
| Decreased appetite | 2 (2.1) | | 0 |
| Dehydration | 2 (2.1) | 1 (1.0) | 1 (2.7) |
| Hyperglycaemia | 10 (10.3) | 0 | 1 (2.7) |
| Hyponatraemia | 1 (1.0) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 1 (1.0) | 0 | 2 (5.4) |
| Arthralgia | 0 | 0 | 1 (2.7) |
| Arthropathy | 1 (1.0) | 0 | 0 |
| Bone pain | 0 | 0 | 1 (2.7) |
| Myopathy | 1 (1.0) | 0 | 0 |
| Nervous system disorders | 4 (4.1) | 0 | 2 (5.4) |
| Cognitive disorder | 1 (1.0) | 0 | 0 |
| Dizziness | 1 (1.0) | 0 | 0 |
| Lethargy | 0 | 0 | 1 (2.7) |
| Peripheral motor neuropathy | 1 (1.0) | 0 | 1 (2.7) |
| Presyncope | 1 (1.0) | 0 | 0 |
| Psychiatric disorders | 2 (2.1) | 0 | 0 |
| Major depression | 1 (1.0) | 0 | 0 |
| Mental status changes | 1 (1.0) | 0 | 0 |
| Suicide attempt | 1 (1.0) | 0 | 0 |
| Renal and urinary disorders | 2 (2.1) | 0 | 0 |
| Haematuria | 1 (1.0) | 0 | 0 |
| Renal failure | 1 (1.0) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 2 (2.1) | 1 (1.0) | 0 |
| Dyspnoea | 1 (1.0) | 0 | 0 |
| Pharyngeal inflammation | 0 | 1 (1.0) | 0 |
| Pulmonary embolism | 1 (1.0) | 0 | 0 |
| Vascular disorders | 1 (1.0) | 0 | 1 (2.7) |

**Table 13. Treatment-Emergent Treatment-Related Serious Adverse Events**

| System Organ Class<br>Preferred Term | Arm A<br>n (%) | Arm B1<br>n (%) | Arm B2<br>n (%) |
|---|---|---|---|
| Hypovolaemic shock | 1 (1.0) | 0 | 0 |
| Hypotension | 0 | 0 | 1 (2.7) |

MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Discontinuations

The total number of discontinuations due to deaths during the study were 22 (22.7%), 8 (7.8%) and 6 (16.2%) in Arm A, Arm B1 and Arm B2, respectively. The majority of discontinuations were not reported to be related to the study treatment. The other reasons for discontinuation of subjects were 'lost to follow-up', 'no longer willing to participate in the study' and 'other'. Of these, the most frequent cause of discontinuation was attributed to be 'Other'. A summary of reasons for discontinuation from the study phase is presented in Table 14.

**Table 14. Discontinuations From Study**

| Discontinuations | Arm A<br>(N=97) | Arm B1<br>(N=102) | Arm B2<br>(N=37) |
|---|---|---|---|
| Patient died | 22 (22.7) | 8 (7.8) | 6 (16.2) |
| Not related to study drug | 48 (49.5) | 34 (33.3) | 21 (56.8) |
| Lost to follow-up | 0 | 3 (2.9) | 0 |
| No longer willing to participate in study | 3 (3.1) | 1 (1.0) | 3 (8.1) |
| Other[a] | 45 (46.4) | 30 (29.4) | 18 (48.6) |
| Total | 70 (72.2) | 42 (41.2) | 27 (73.0) |

Subjects whose death records were entered after end of study (7, 11 and 6 in Arm A, B1 and B2, respectively) were not included.
N = total number of subjects.
a. The composition of other included disease progression, adverse events, starting on another anticancer therapy, and Principal Investigator decision.

Summary of deaths/follow-up subject status are presented in Table 15. Of the total 97 subjects in Arm A, 29 (29.9%) subjects died during the study of which 9 (9.3%) subjects died on-study (ie, after the first dose of study drug and within 28 days of last dose), and 20 (20.6%) subjects died during the follow-up (ie, after 28 days of last dose). Similarly, 19 (18.6%) subjects died in Arm B1 and 12 (32.4%) subjects died in Arm B2 during the study treatment defined as the period after the first dose of study drug up to 28 days after last dose of study drug. Fourteen subjects in Arm B1 (13.7%) and 10 (27.0%) subjects in Arm B2 died during the safety follow-up period.

The major reason of death was reported to be 'disease under study'. Overall, 3 (3.1%) subjects died on-study due to disease under study and 12 (12.4%) subjects died during follow-up phase due to disease under study in Arm A; and 1 patient each in Arm B1 and Arm B2 died on-study due to disease under study while 13 (12.7%) in Arm B1 and 10 (27.0%) subjects in Arm B2 died during follow-up due to existing disease condition. Only 1 death in Arm A was due to 'study treatment toxicity'.

**Table 15. Summary of Deaths/Follow-Up Subject Status**

| Number (%) of Subjects | Arm A (N=97) | Arm B1[a] (N=102) | Arm B2[a] (N=37) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Alive | 65 (67.0) | 78 (76.5) | 22 (59.5) |
| Dead | 29 (29.9) | 19 (18.6) | 12 (32.4) |
| Lost to follow-up | 0 | 3 (2.9) | 0 |
| Subject no longer willing to participate | 3 (3.1) | 2 (2.0) | 3 (8.1) |
| Subjects who died while on-study[b] | 9 (9.3) | 5 (4.9) | 2 (5.4) |
| Disease under study | 3 (3.1) | 1 (<1.0) | 1 (2.7) |
| Study treatment toxicity | 1 (1.0) | 0 | 0 |
| Unknown | 1 (1.0) | 0 | 0 |
| Other | 4 (4.1) | 4 (3.9) | 1 (2.7) |
| Subjects who died during follow-up[c] | 20 (20.6) | 14 (13.7) | 10 (27.0) |
| Disease under study | 12 (12.4) | 13 (12.7) | 10 (27.0) |
| Study treatment toxicity | 0 | 0 | 0 |
| Unknown | 4 (4.1) | 0 | 0 |
| Other | 4 (4.1) | 1 (<1.0) | 0 |

The subjects whose death records were entered after End of Study (7, 11 and 6 subjects in Arm A, B1 and B2, respectively).
N = total number of subjects; n = number of subjects.
a. Deaths on Arm B are included in only 1 of Arm B1 and Arm B2.
b. On-study deaths are those that occurred after the first dose of study drug and within 28 days of last dose. No subjects died within 28 days of last dose on Arm B1 while on Arm B2.
c. Follow-up deaths are those that occurred after 28 days of last dose. Subjects in Arm B2 were not included in Arm B1 follow-up.

## CONCLUSIONS:

Efficacy: The null hypothesis that Arm A PSA response rate was 45% was not rejected and the primary objective of the study was not met.

It was observed that 9 of 32 evaluable subjects were PSA responders, corresponding to a 1-sided p-value of 0.00002 in Arm B2. Hence, it was concluded that addition of figitumumab to the treatment of HRPC subjects that progressed on docetaxel/prednisone was significantly >0.05.

The secondary objective of PFS was not met as the estimated hazard ratio of Arm A versus Arm B1 was 1.415 (95% CI, 1.047 to 1.914; p-value=0.989). Values above 1 favor Arm B1.

Safety: The combination of figitumumab/docetaxel/prednisone (Arm A or Arm B2) was tolerated but tolerated less well than the combination of docetaxel/prednisone alone (Arm B1).

The majority of subjects in Arm A (58.8%) and B2 (70.3%) experienced figitumumab related treatment emergent AEs (any grade all cycles).

More Grade 3/4 (combined) all causality/treatment-related AE events were reported for Arm A (88.7%; 75.3%) than Arm B1 (73.5%; 55.9%) subjects, respectively. For the following events, more subjects in Arm A than Arm B1 reported clinically meaningful higher

frequency of all causality adverse events: diarrhea, decreased appetite, fatigue, asthenia, hyperglycemia, stomatitis, muscle spasm, and febrile neutropenia.

More subjects in Arm A (66.0%; 41.2%) than those in Arm B1 (36.3%; 14.7%) reported all causality or treatment-related SAEs, respectively.