**Supplementary information**

**Safety analyses**

**Methods**

Treatment interruptions and dose reductions with afatinib could be implemented when necessary for the management of treatment-related adverse events (TRAEs), as follows:

* Any drug-related grade ≥3 adverse event (AE)
* Grade ≥2 diarrhea persisting ≥48 hours despite adequate treatment
* Reduced renal function (grade ≥2), as measured by serum creatinine, proteinuria or >50% reduction in glomerular filtration rate versus baseline.

If treatment interruption was required, afatinib was suspended until AE severity decreased to grade ≤1 or baseline severity. If recovery was achieved within 6 weeks, afatinib was re-introduced at a lower dose (reduced by 10 mg/day decrements to a minimum of 20 mg/day; afatinib dose could not be increased after a dose reduction). If recovery was not achieved within 6 weeks of treatment interruption, afatinib was discontinued.

Safety endpoints were analyzed in an exploratory manner and included the incidence of serious adverse events (SAEs) and the number of patients with TRAEs. Safety endpoints were analyzed descriptively.

**Safety outcomes**

All 64 patients included in the biomarker analysis group experienced at least 1 AE. AEs leading to a dose reduction with afatinib occurred in 25.0% of patients, and those leading to treatment discontinuation occurred in 10.9% of patients. TRAEs leading to treatment discontinuation were reported in 6.3% of patients, SAEs developed in 23.4% of patients and fatal SAEs occurred in 6.3% of patients. The majority of TRAEs were grade 1-2 (52%); grade 3, 4 and 5 AEs occurred in 37.5%, 4.7% and 6.3% of patients, respectively.

Among SAEs, the most frequently reported were cerebral infarction (4.7%), malignant neoplasm progression (3.1%) and metastases to the central nervous system (CNS) (3.1%). Six patients (9.4%) experienced a total of 7 SAEs that were assessed as drug-related – decreased appetite, diarrhea, gastritis, gastrointestinal disorder, ileus and intestinal obstruction (two events in one patient) and interstitial lung disease. Among TRAEs, the most commonly reported were diarrhea (98.4%), rash/acne (81.3%) and stomatitis (71.9%) (Supplementary Table 1).

There were four deaths reported in the biomarker analysis group, although three were not considered related to afatinib: one due to cancer progression alone, one due to cancer progression and lung infection and one due to metastases to the CNS. One death due to decreased appetite was considered treatment-related.