**Phase II trial of afatinib in patients with advanced/metastatic urothelial carcinoma with genetic alterations in ERBB receptors 1–3 who failed on platinum-based chemotherapy**

**Trial objectives**

- To assess the efficacy and safety of afatinib monotherapy in patients with urothelial carcinoma (UC) and EGFR/ERBB2/ERBB3 mutations or ERBB2 amplification, who have progressed after platinum-based chemotherapy (CT).

**Background**

Bladder cancer is the most common cancer of the urinary tract, with 439,000 new cases and 135,000 deaths per year worldwide.

- ~15-20% experience metastatic disease.
- ~90% of bladder cancers are UC.

**Study design**

- All cohorts:
  - Adequate organ function
  - Measurable disease
  - ECOG PS 0 or 1
  - No concomitant chemotherapy
  - No radiotherapy within 6 weeks
  - No significant intercurrent condition

- Cohort A:
  - Local advanced/metastatic UC
  - Urothelial carcinoma (UC) and EGFR/ERBB2/ERBB3 mutations/amplyfications
  - Primary endpoint: PFS6
  - Secondary endpoints: ORR, DCR, DOR, tumor shrinkage

- Cohort B:
  - Local advanced/metastatic UC
  - ERBB3 amplification
  - Secondary endpoints: ORR, DCR, DOR, tumor shrinkage

- Trial commenced in June 2016.
- As of January 8, 2018, tumor samples from 287 patients have been analyzed.
- 26.1% of patients with tumors harboring genetic alterations potentially eligible for inclusion in Cohort A.
- 7.7% of patients with tumors harboring genetic alterations potentially eligible for inclusion in Cohort B.

**Rationale**

The ERBB pathway is a potential therapeutic target for patients with various UC subtypes, which frequently harbor EGFR receptor alterations including EGFR mutation or amplification, ERBB2 mutation, translocation, or amplification, and ERBB3 mutations/amplifications. Therefore, inhibition of this pathway is considered to be attractive therapeutic targets in UC.

**Methodology**

- As a Phase II trial for patients with non-small cell lung cancer harboring EGFR exon 19 deletion or exon 21 (L858R) substitution mutations.

**Endpoints and other assessments**

- Primary: PFS (Cohort A); ORR (Cohort B)
- Secondary: PFS, OS, DCR, DOR, tumor shrinkage (Cohort A)
- Safety: assessments and biomarker analysis will also be performed

**Patient eligibility criteria (Cont’d)**

- Age ≥ 18 years
- ECOG PS 0 or 1
- No prior CT within 4 weeks before start of study treatment
- No prior EGFR TKI
- No prior regimens targeting HER2
- No prior regimens targeting EGFR TKI and HER2

**Patient eligibility criteria**

- Age ≥ 18 years
- ECOG PS 0 or 1
- No prior CT within 4 weeks before start of study treatment
- No prior EGFR TKI
- No prior regimens targeting HER2
- No prior regimens targeting EGFR TKI and HER2

**Key inclusion criteria**

- Local or advanced/metastatic UC
- Presence of EGFR mutation or amplification
- Patients with different levels of disease burden
- Adequate organ function

**Key secondary efficacy/safety endpoints**

- PFS; OS; ORR; DCR; DOR; tumor shrinkage

**Targeting the whole ERBB family enhances the effect on metastatic UC**

- Afatinib demonstrated prolonged time to progression in patients with UC harboring EGFR mutations and/or ERBB3 gene amplifications, compared with patients without EGFR alteration (6.5 vs 1.4 months).

**References**


**Summary**

- Trial commenced in June 2016.
- As of January 8, 2018, tumor samples from 287 patients have been analyzed.
- 26.1% of patients with tumors harboring genetic alterations potentially eligible for inclusion in Cohort A.
- 7.7% of patients with tumors harboring genetic alterations potentially eligible for inclusion in Cohort B.
- 17 patients have received study treatment in Cohort A and 7 in Cohort B.
- Recruitment is currently ongoing in Spain, France, and Italy.