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

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Albert Font,[1*] Javier Puente,[2] Daniel Castellano,[3] Francisco X. Real,[4,5] Miguel Ángel Climent,[6] Aránzazu Gonzalez del Alba,[7] Stéphane Oudard,[8] Federico J. Vazquez Mazon,[9] Rafael Morales Barrera,[10] Juan Antonio Virizuela,[11] Nuria Sala,[12] Begoña Pérez-Valderrama,[13] Xavier Garcia del Muro,[14] Pedro L. Fernandez,[15] Pedro Jares,[15] Iban Aldecoa,[15] Neil Gibson,[16] Josep Serra,[17] Esteban Rodrigo Imedio,[18] Begoña Mellado[15]

[1]Institut Català d'Oncologia, Hospital Universitari Germans Trias i Pujol (HUGTiP), Badalona, Barcelona, Spain; [2]Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), CIBERONC, Madrid, Spain; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Centro Nacional de Investigaciones Oncológicas, Madrid, Spain; [5]Universitat Pompeu Fabra, Barcelona, Spain; [6]Instituto Valenciano de Oncología (IVO), València, Spain; [7]Medical Oncology Department, Hospital Universitario Son Espases, Palma de Mallorca, Spain; [8]Medical Oncology Department, Hôpital Européen George Pompidou, Paris, France; [9]Hospital General Universitario de Elche, Elche, Spain; [10]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [11]Hospital Universitario Virgen Macarena, Seville, Spain; [12]Institut Català Oncologia (ICO) Girona, Hospital Josep Trueta, Girona, Spain; [13]Hospital Universitario Virgen del Rocío, Seville, Spain; [14]Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain; [15]Hospital Clínic de Barcelona, Barcelona, Spain; [16]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [17]Boehringer Ingelheim España, S.A., Barcelona, Spain; [18]Boehringer Ingelheim Ltd, Bracknell, UK

Trial objectives

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

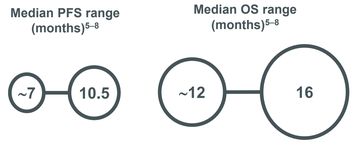
Background

- Bladder cancer is the most common cancer of the urinary tract, with ~380,000 new cases and ~150,000 deaths per year worldwide[1]

~15-20% experience metastatic disease[2,3]

>90% of bladder cancers are UC[2,3]

- First-line treatment of advanced/metastatic UC consists of platinum-based CT[4]



- Although some CT agents (vinflunine and docetaxel) have been included in clinical guidelines, no CT agent has improved OS compared to best supportive care in a platinum refractory UC patient population[4-9]

NO US FDA-approved CT

for patients with platinum-refractory locally advanced or metastatic UC; vinflunine is approved by EMA only, and not by the US FDA[4]

- Checkpoint inhibitors (anti-PD-1 and anti-PD-L1), such as atezolizumab, pembrolizumab, nivolumab, avelumab, and durvalumab have demonstrated benefit in patients with platinum refractory UC;[10-13] including a significant OS benefit with pembrolizumab versus second-line CT[11]
- However, no other targeted therapies have shown significant clinical activity to-date

CT, chemotherapy; EMA, European Medicines Agency; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; US FDA, United States Food and Drug Administration; UC, urothelial carcinoma

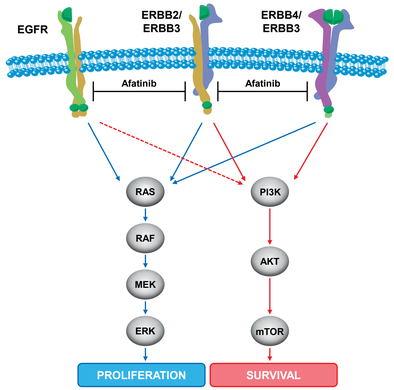
Rationale

- The ERBB pathway is of particular significance for patients with various UC subtypes, which frequently harbor ERBB receptor alterations including *EGFR* mutation or amplification, *ERBB2* mutation, translocation, or amplification, and *ERBB3* mutations[14,15]
- Therefore, inhibitors of this pathway are considered to be attractive therapeutic targets in UC

Afatinib

- An orally available ERBB family blocker that irreversibly inhibits signaling via ERBB1 (EGFR), ERBB2 (HER2) and ERBB4 pathways and blocks transphosphorylation of ERBB3[16] (Figure 1)
- Approved as a first-line treatment for patients with non-small cell lung cancer harboring *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations[17]

Figure 1. Afatinib mechanism of action



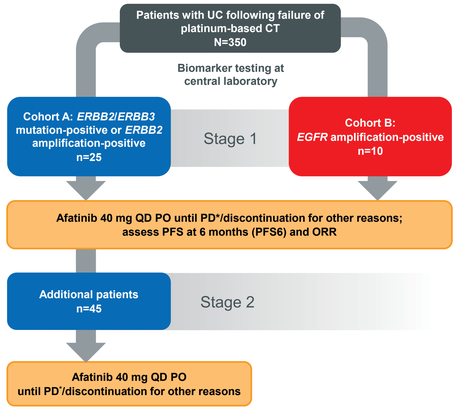
Targeting the whole ERBB family enhances the effect on important signalling pathways

- Afatinib demonstrated prolonged time to progression in six patients with UC harboring *ERBB3* mutations and/or *ERBB2* gene amplifications, compared with 15 patients without *ERBB* alterations (6.6 vs 1.4 months)[18]

AKT, protein kinase B; ERK, extracellular signal-regulated kinase; 2; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase

Study design

- LUX-Bladder 1 trial (NCT02780687) is a Phase II, single-arm, open-label, multicenter trial



ORR, overall response rate; PD, progressive disease; PO, orally; QD, once daily; RECIST version 1.1, Response Evaluation Criteria in Solid Tumors version 1.1
*Response will be determined throughout according to RECIST version 1.1

Patient eligibility criteria

Key inclusion criteria

All cohorts

- Aged ≥18 years
- Not amenable to surgical treatment
- Locally advanced/metastatic UC
- Measurable disease (RECIST version 1.1)
- Progressed on/after platinum-based CT
- Adequate organ function
- ECOG PS 0 or 1
- Archival tissue biopsies (blocks) available for biomarker testing

Cohort A

ERBB2 or *ERBB3* mutation(s) or *ERBB2* amplification

Cohort B

EGFR amplification

ECOG PS, Eastern Cooperative Oncology Group performance status

Patient eligibility criteria (Cont'd)

Key exclusion criteria

Patients with:

- Brain metastases
- Other malignancy
- Interstitial lung disease
- Hypersensitivity to afatinib
- Cardiovascular abnormalities
- Concomitant condition that would interfere with efficacy/safety

Treatment within 4 weeks prior to start of study treatment

- Chemotherapy
- Investigational drug
- Biological therapy
- Radiotherapy
- Major surgery

Previous targeted treatment

- EGFR
- ERBB2
- ERBB3

Previous immunotherapy is allowed

Endpoints and other assessments

Primary	PFS6 (Cohort A)
Key secondary	ORR (Cohort A)
Other secondary	PFS; OS; DCR; DOR; tumor shrinkage (Cohort A)
Further endpoints	PFS6; PFS; ORR; OS; DCR; DOR (Cohort B)
Safety	Incidence and intensity of AEs*
Biomarker analysis	Tumor samples assessed for: (i) *ERBB2*/*ERBB3* mutations or *ERBB2*/*EGFR* amplifications for inclusion; and (ii) additional, specified genomic and protein biomarkers to increase understanding of responses to EGFR tyrosine kinase inhibitors in metastatic UC Archival tumor tissue, serum and urine samples are required (laboratory tests include custom designed NGS panel for *ERBB* family and FISH for *ERBB2* and *EGFR*)

AE, adverse event; DCR, disease control rate; DOR, duration of objective response; FISH, fluorescence in situ hybridisation; NGS, next generation sequencing
*According to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

Trial initiation

- 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
- As of January 8, 2018, 24 patients have received study drug:
  - 17 patients have received study treatment in Cohort A and 7 in Cohort B
- Recruitment is currently ongoing in Spain, France, and Italy

Summary

Objective

- To assess the efficacy and safety of afatinib in patients with UC harboring *ERBB2*/*ERBB3* mutations or *ERBB2*/*EGFR* amplification, who have progressed after platinum-based CT

Study design

- Open-label Phase II trial using a two-stage design
  - Patients are assigned to Cohort A (*ERBB2*/*ERBB3* genetic alterations) or Cohort B (*EGFR* amplification) based on screening biomarkers

Endpoints and assessments

- Primary endpoint: PFS6 (Cohort A only)
- Secondary endpoints: PFS; OS; ORR; DCR; DOR; tumor shrinkage (Cohort A)
  - Safety assessments and biomarker analysis will also be performed

Trial initiation

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