Bladder cancer is the most common cancer of the urinary tract, with ~350,000 new cases and ~156,000 deaths per year worldwide. ~15–20% of bladder cancers are UC2,3

**Background**

**Trial objectives**

To assess the efficacy and safety of afatinib monotherapy in patients with platinum-refractory UC, whether harboring EGFR mutations or EGFR amplification, who have progressed after platinum-based chemotherapy (CT) for UC.

**Rationale**

The EGFR pathway is a potential target for patients with various UC subtypes, which frequently harbor EGFR receptor alterations including EGFR mutation and amplification. EGFR mutated, over-expression, or amplification, and KRAS mutations14,15. Therefore, inhibition of this pathway is considered to be attractive therapeutic targets in UC.

**Trial design**

- Open-label Phase II trial using a two-stage design
- Goal to determine PFS6 in a registration-enabling cohort
- Phases of the trial:
  - Stage 1: used to determine the PFS in an exploratory cohort (Stage 1A) and to determine the cut-off for PFS6 (Stage 1B)
  - Stage 2: used to determine the PFS6 in a confirmatory cohort (Stage 2A) and to determine the cut-off for PFS6 (Stage 2B)
- The trial is based on current clinical guidelines16,17.

**Endpoints and other assessments**

- **Primary endpoints:** PFS (Cohort A)
  - OS (Cohort A)
  - DOR (Cohort A)

**Safety**

- **Incidence and intensity of AEs**

**Patient eligibility criteria**

**Key inclusion criteria**

- Aged ≥18 years
- Prior to study treatment, had progressed on previous CT for UC, or had relapsed within 12 months after the completion of previous CT for UC, with measurable progressive disease according to RECIST v.1.1
- Aged ≥18 years
- Performance status (ECOG PS) 0–2
- Adequate organ function = ECOG PS ≤ 1

**Key exclusion criteria**

- Resistant to platinum-based CT

**Trial initiation**

- Trial commenced in June 2016
- As of January 8, 2018, tumor samples from 267 patients have been analyzed, with 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
- Recruitment is currently ongoing in Spain, France, and Italy

**Summary**

- In the current trial, afatinib demonstrated prolonged time to progression in patients with UC harboring EGFR mutations and/or EGFR gene amplifications, compared with patients without EGFR alterations (6.8 vs. 4.9 months).8

**References**

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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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\(^4\)

CT, chemotherapy; UC, urothelial carcinoma
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 \(^4\text{-}^9\).

OS, overall survival; PFS, progression-free survival
Background (cont’d)

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.

- 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;\textsuperscript{10-13} including a significant OS benefit with pembrolizumab versus second-line CT\textsuperscript{11}

- However, no other targeted therapies have shown significant clinical activity to-date
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$^{17}$
Rationale

Figure 1. Afatinib mechanism of action

AKT, protein kinase B; ERK, extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase
Rationale (cont’d)

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

- Afatinib demonstrated prolonged time to progression in six patients with UC harboring \textit{ERBB3} mutations and/or \textit{ERBB2} gene amplifications, compared with 15 patients without \textit{ERBB} alterations (6.6 vs 1.4 months)\textsuperscript{18}
Study design

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

**Diagram**

- Patients with UC following failure of platinum-based CT N=350
  - Blomarker testing at central laboratory
  - Stage 1
    - Cohort A: ERBB2/ERBB3 mutation-positive or ERBB2 amplification-positive n=25
    - Cohort B: EGFR amplification-positive n=10
    - Afatinib 40 mg QD PO until PD*/discontinuation for other reasons; assess PFS at 6 months (PFS6) and ORR
    - Additional patients n=45
    - Stage 2
      - Afatinib 40 mg QD PO until PD*/discontinuation for other reasons

*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

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>Treatment within 4 weeks prior to start of study treatment</th>
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<tbody>
<tr>
<td>Brain metastases</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Other malignancy</td>
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<td>Interstitial lung disease</td>
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<td>Hypersensitivity to afatinib</td>
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<tr>
<td>Cardiovascular abnormalities</td>
<td>Major surgery</td>
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<tr>
<td>Concomitant condition that would interfere with efficacy/safety</td>
<td>Previous targeted treatment</td>
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<td></td>
<td>EGFR</td>
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<td>ERBB2</td>
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<td>ERBB3</td>
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Previous targeted treatment is allowed
Endpoints and other assessments

<table>
<thead>
<tr>
<th>Primary</th>
<th>PFS6 (Cohort A)</th>
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<tbody>
<tr>
<td>Key secondary</td>
<td>ORR (Cohort A)</td>
</tr>
<tr>
<td>Other secondary</td>
<td>PFS; OS; DCR; DOR; tumor shrinkage (Cohort A)</td>
</tr>
<tr>
<td>Further endpoints</td>
<td>PFS6; PFS; ORR; OS; DCR; DOR (Cohort B)</td>
</tr>
<tr>
<td>Safety</td>
<td>Incidence and intensity of AEs*</td>
</tr>
</tbody>
</table>

**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
Summary

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

17. EMA. 2017. Giotrif SmPC.

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Data were originally presented: Font, et al. ESMO 2017; poster #920TiP. *Corresponding author email address: afont@iconcologia.net

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