National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: August 2017

Erdafitinib capsules for metastatic or surgically unresectable urothelial cancer with FGFR gene aberrations – second line therapy

NIHRIO (HSRIC) ID: 11254 NICE ID: 8748

LAY SUMMARY

Urothelial cancer (UC), is a type of cancer of the urinary system (which includes the bladder and surrounding space). Bladder cancer is the most common type of UC, making up the majority of UC cases. Your risk of getting UC can be increased by smoking, damage to the urinary system (like kidney stones or infections) and having a family history of UC. Changes to a certain gene, the FGFR gene, has been found in one to two thirds of people with UC.

Erdafitinib capsules are a new drug which work by killing cancer cells which have changes to the FGFR gene. It is currently being tested in clinical trials for a range of different cancers, including cancers of the urinary system. If Erdafitinib was licenced for use in the UK it would provide a treatment option for people with late stage or difficult to treat urinary tract cancer with abnormal FGFR gene.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Urothelial cancer for patients with FGFR mutation (metastatic or surgically unresectable) - second line.

TECHNOLOGY

DESCRIPTION

Erdafitinib (JNJ-42756493) is a selective fibroblast growth factor receptor (FGFR) inhibitor intended for use in patients with solid tumours with genetic mutations in the FGFR pathway (up-regulated in many tumour cell types and essential to tumour cell proliferation, differentiation and survival), including urothelial carcinoma. It works by binding to and inhibiting FGFR, resulting in the inhibition of FGFR induced signal transduction pathways leading to tumour cell death in FGFR-overexpressing tumour cells.[1]

Erdafitinib is currently being studied in a phase II clinical trial in urothelial carcinoma. Erdafitinib is administered orally at a dose of 8mg once daily for 28 days, on a 28 day cycle that will continue until disease progression or unacceptable toxicity occurs.[2]

Erdafitinib does not currently have Market Authorisation in the EU for any indication.

The drug is currently in phase II clinical trials for the treatment of:

- advanced hepatocellular carcinoma – second line
- cholangiocarcinoma (bile duct cancer) – second line
- gastric cancer – second line
- non-small cell lung cancer – second line
- oesophageal cancer – second line

INNOVATION and/or ADVANTAGES

Despite the fact urothelial cancer (UC) is the fourth most common tumour type worldwide, it is associated with poor disease outcomes (e.g. overall survival) and there are few effective treatment options available for those with metastatic UC following disease progression after first line platinum containing chemotherapy regimens. There are also currently no standard treatments to target specific genetic mutations or pathways in UC.[3] If licensed, erdafitinib will offer a targeted treatment option for patients with metastatic urothelial cancer with FGFR aberrations who currently have few effective therapies available.

DEVELOPER

Janssen-Cilag Ltd

AVAILABILITY, LAUNCH or MARKETING

No information available.

PATIENT GROUP

BACKGROUND

Urothelial (or transitional cell) cancers are the fourth most common tumours worldwide after prostate (or breast), lung and colorectal cancer. Urothelial cancers originate in the transitional epithelium (or urothelium), a membrane covering the renal pelvis to the ureter, bladder and proximal two thirds of the urethra. Bladder cancers account for 90-95% of urothelial cancers with the remaining 5-10% being upper tract urothelial cancers (UTUCs), involving the renal pelvis and ureter.[3] Urothelial bladder cancer (UBC) may be superficial (not having invaded the deeper bladder layers) or invasive (having invaded the bladder deeper layers). There are several different types of superficial UBCs including papillary (which grow out of the urothelium and can be surgically removed), CIS (which grow flat and quickly and more likely to reoccur) and High grade T1 tumours (which grow into the lamina propria, the tissue layer beneath the urothelium, and have a 30-40% chance of reoccurring).[4]

UBCs and UTUCs are usually diagnosed using several different tests, including:[5,6]

- Physical examination and identification of symptoms, including; haematuria (blood in the urine), back pain, fatigue, weight loss and painful or frequent urination.
- Uranalysis: checking for sugars, protein, blood and bacteria in the urine).
- Urine Cytology: checking for cancer cells shed in the urine.
- Ureterscopy: where an ureteroscope (thin tube with a lens at the end) is inserted through the urethra into the bladder, ureter and renal pelvis.
- Intravenous pyelogram (IVP): a contrast dye is injected into the bloodstream and a series of x-rays of the kidneys, ureters and bladder are taken to check for cancer (appearing as 'blockages').
- CT (Computed tomography), Ultrasound or MR (Magnetic Resonance) Imaging techniques to visualise any tumours.
- Biopsy: a sample of tissue taken for examination (during ureterscopy or surgery) to check for cancer cells.

Risk factors for the development of urothelial cancers include tobacco smoking (accounting for 50% cases), occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons (accounting for about 10% of cases), exposure to ionising radiation, numerous bladder infections or stones, schistosomiasis infection and chronic miss use of over-the-counter painkillers.[5, 6, 7]

Genetic mutations or changes have also been implicated in the pathogenesis of urothelial cancer, including changes to the all four FGFR (fibroblast growth factor receptor) (FGFR1, FGFR2 and FGFR3) genes. Changes to the FGFR genes are thought to promote cell proliferation, migration, angiogenesis and anti-apoptosis in many cancers including urothelial cancer.[3]

Prognosis of urothelial cancer is generally poor and even with extensive resection surgery, the cancer will recur in approximately 50% patients within 5 years, who will then require systemic chemotherapy. If the cancer progresses after first line chemotherapy there are few effective treatment options available for metastatic urothelial cancer.[3]

CLINICAL NEED and BURDEN OF DISEASE

UTUC is generally rare and is more common in men than women with incidence rates of 1.7 per 100,000 in men and 0.8 per 100,000 in women (according to data from England).[8] Data from 2015-16 Hospital Episode statistics for England showing 1,065, 1, 934 and 452 admissions and 1,216, 2,229 and 527 finished consultant episodes for malignant neoplasm of the renal pelvis (ICD10 C65), malignant neoplasm of the ureter (ICD10 C66) and malignant neoplasm of other and unspecified urinary organs (ICD10 C68) respectively.[9]

Conversely, bladder cancer (which accounts for 90-95% of urothelial cancers) is the 10th most common cancer in the UK, accounting for 3% all new cancer cases in the UK in 2014.[10] Bladder cancer incidence rates for England in 2014 were 15.7 per 100,000 (equating to 8,514). Data from 2015-16 Hospital Episode statistics for England showed 67,422 admissions and 71,702 finished consultant episodes for malignant neoplasm of the bladder (ICD10 C67).[9]

Mortality from UTUC in 2010 in England was n=175. Mortality rates for UTUCs generally increase with age with mortality rate of 3.2 per 100,000 in people >80 years in England (calculated from data collected 2007-2009).[8] Mortality from bladder cancer is the 7th most common cause of cancer death in males and the 12th most common cause of cancer deaths in females in the UK. In 2014, there were 4,504 bladder cancer deaths, equating to a mortality rate of 8.3 per 100,000.[11]

Urothelial cancers often have poor outcomes, with a ten year overall survival rate of 20-60% for UBCs and 25% for UTUCs after radical surgical resection.[3] One year survival rates for UTUC for England in 2007-2009 were 71% and five year survival rates for UTUC for England for 2003-2005 were 48%.[8] One, five and ten year survival rates for bladder cancer in England in 2014 were 72.4%, 53.7% and 50.2% respectively.[12]

The prevalence of FGFR1, FGFR2 and FGFR3 gene amplifications in urothelial cancers are estimated at 9-10%, 0.8% and 3-5% respectively. Activating mutations in the FGFR3 gene have been shown in 38-66% of superficial urothelial cancers and in 15-20% of invasive urothelial cancers.[3]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for urothelial cancer (ID1019). Expected publication date November 2017.
- NICE technology appraisal in development. Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy (ID 995). Expected publication date February 2018.
- NICE technology appraisal in development. Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy (ID939). Expected date of issue to be confirmed.
- NICE technology appraisal. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). January 2013.
- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Quality standard for bladder cancer (QS106). December 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised kidney, bladder and prostate cancer services (Adult). B14/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. 16033/P. July 2016.

OTHER GUIDANCE

- Royal College of Surgeons. From Innovation to Adoption 2014

CURRENT TREATMENT OPTIONS

Treatment of urothelial cancer depends on the exact location of the cancer, UTUC or UBC, and the grade of the cancer. Standard treatment options for upper tract urothelial cancer (ureter or renal pelvis) include:

- BCG: Attenuated Mycobacterium tuberculosis – can be curative in those with superficial cancer and is usually reserved for non-surgical candidates. However cancer recurrence rates are high (50%).[13]
- Chemotherapy:[13]
    - Gemcitabine and cisplatin combination – first line therapy for muscle invasive/locally advanced and metastatic cancer.
    - MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) combination – used for muscle invasive/locally advanced cancer.
    - Methotrexate, carboplatin and vinblastine – used in metastatic cancer
    - Gemcitabine and cisplatin every 2 weeks (split dose) – used in metastatic cancer
- Surgery:[14, 15]
    - Endoscopic therapy: tumours removed, usually by laser, during endoscopy procedure – used for superficial tumours.
    - Ureteroureterstomy: surgery to remove tumours of the proximal/mid-ureter – used for superficial tumours.
    - Radical nephroureterectomy: surgery to remove the entire kidney, ureter and bladder cuff (tissues connecting the ureter and bladder) – used for local advanced tumours of the UTUC. Performed laparoscopically or as open surgery.
    - Segmental resection of the ureter: surgery to remove cancerous ureter tissue – only used in superficial cancers of the bottom third of the ureter.
    - Lymph node dissection: extensive regional lymphadenectomy during open nephroureterectomy – for locally advanced UTUC.

Standard treatment options for UBC (urothelial cancer of the bladder) vary according to cancer stage and invasiveness as follows:[16, 17, 18, 5]

- Low risk superficial bladder cancer:
    - White light guided TURBT (transurethral resection of bladder tumour) to remove cancerous tissue from the bladder lining. Further TURBT procedures should be considered within 6 weeks if the results sample does not contain detrusor muscle.
    - Single dose of intravesical mitomycin C given at the time of first TURBT.
- Intermediate risk superficial bladder cancer:
    - Course of minimum 6 doses of mitomycin C chemotherapy into the bladder.
- High risk superficial bladder cancer:
    - If TURBT shows high risk superficial cancer, offer another TURBT as soon as possible.
    - Intravesical (into the bladder) BCG vaccine – induction and maintenance doses.
    - Radical cystectomy (bladder removal) – with a urinary stoma or continent urinary diversion (bladder substitution or catherterisable reservoir).
- Recurrent superficial bladder cancer:
    - Fulguration (removal of malignant tissue using high frequency electrical current by electrode) without biopsy.
- Muscle invasive bladder cancer:
    - Neoadjuvant chemotherapy: cisplatin combination chemotherapy regime before radical cystectomy or radical radiotherapy.
    - Radical cystectomy (bladder removal) - with a urinary stoma or continent urinary diversion (bladder substitution or catherterisable reservoir).
    - Adjuvant chemotherapy after radical cystectomy – adjuvant cisplatin combination chemotherapy after radical cystectomy for muscle invasive or lymph node positive urothelial bladder cancer for those who are not eligible for neoadjuvant chemotherapy.
    - Radical radiotherapy - radiosensitiser (e.g. mitomycin in combination with fluorouracil [5-FU] or carbogen in combination with nicotinamide) when giving radical radiotherapy (for example, 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks).

EFFICACY and SAFETY

Trial	NCT02365597, CR105065, 42756493BLC2001, 2014-002408-26, CDR769515, NCI-2015-00818, EudraCT-2014-002408-26, DRKS00009448, IRAS-177346, WCMC-IRB-1507016367, GDCT00233571; adults with metastatic or surgically unresectable urothelial cancer; Erdafitinib alone; phase II trial
Sponsor	Janssen-Cilag
Status	Ongoing, recruiting
Source of Information	Trial registry.[2]
Location	EU including UK, USA, Middle East and Asia
Design	Uncontrolled / Single Group Assignment / Open label
Participants	n=210 (planned); aged 18 and older; metastatic unresectable urothelial cancer that harbour specific FGFR genomic alterations; second line therapy

Schedule	Single group assignment, open label, uncontrolled. Prior to interim analysis 1 (IA1), there were 2 treatment regimens: Regimen 1 (10 milligram [mg] once daily, 7 days on/7 days off); and Regimen 2 (6 mg once daily for 28 days). Following IA1, Regimen 1 is closed for further enrolment and starting dose of Regimen 2 is increased to 8 mg once daily for 28 days on a 28-day cycle (referred to as Regimen 3).[2]
Follow-up	A post treatment follow-up phase will extend from the end of treatment visit until the subject has died, withdraws consent, is lost to follow, or the end of the study, whichever comes first.
Primary Outcomes	Percentage of participants with Best Overall Response after 1 year
Secondary Outcomes	Progression-free survival (baseline to progression or death, duration of response (baseline to disease progression or death), overall survival (baseline to death), number Adverse Events (AEs) and Serious Adverse Events (SAEs) (baseline to end of study), presence of circulating biomarkers (DNA, RNA, or proteins) associated with FGFR aberrations (baseline up to end of study), plasma concentration, clearance and volume of distribution of erdafitinib (baseline up to end of study).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion estimated Aug 2018

ESTIMATED COST and IMPACT

COST

The cost of erdafitinib is not yet known and is not currently marketed in the EU for any indication.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☒ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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