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Bosutinib (Bosulif) for Philadelphia positive chronic myeloid leukaemia – first line

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LAY SUMMARY

Chronic myeloid leukaemia (CML) is a rare cancer that affects the bone marrow and is most often seen in adults around 60 to 65 years old. People with CML produce too many white blood cells which gradually crowd the bone marrow and can interfere with healthy blood production. The disease occurs when a gene from one chromosome incorrectly attaches to a gene on another chromosome, and this altered chromosome is referred to as the "Philadelphia chromosome". Over 95% of patients with CML have the Philadelphia chromosome and are so-called "Philadelphia positive".

Bosutinib is a treatment that is already available for those patients who have not responded to previous treatments for CML. It is taken as a once-daily tablet and works by blocking certain signals in abnormal white blood cells and inhibiting cancer cell growth. Ongoing development of bosutinib is testing whether or not this treatment can be offered as a first-line therapy for CML patients.

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TARGET GROUP

Chronic myeloid leukaemia (CML) Philadelphia positive – first line

TECHNOLOGY

DESCRIPTION

Bosutinib (Bosulif; SKI-606; SKI-758) is a second-generation tyrosine kinase inhibitor that inhibits Abl-kinases, including Bcr‑Abl kinase. It also inhibits the Src family kinases, which have been implicated in driving chronic myeloid leukaemia (CML) progression.[1]

It has a UK marketing authorisation for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blastic phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom the tyrosine kinase inhibitors called imatinib, nilotinib and dasatinib are not considered appropriate treatment options.[2]

Bosutinib is administered orally, once daily by 500mg tablet in its currently licensed indication. The dose can be increased up to 600 mg if there has not been a complete haematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12 and if no severe or persistent moderate-adverse reactions have been experienced by the patient.[1]

Common or very common events associated with bosutinib treatment include but are not limited to: abdominal pain; abnormal liver function; acne; arthralgia; biochemical disturbances; cough; decreased appetite; dehydration; diarrhoea; dizziness; dysgeusia; dyspnoea; electrolyte disturbances; gastritis; headache; hepatotoxicity; infection; malaise; myalgia; oedema; pericardial effusion; pleural effusion; pruritus; pyrexia; QT prolongation; rash; renal failure; renal impairment; urticaria.[2]

Bosutinib is currently in clinical trials for CML first-line use as a 400mg, once-daily tablet.[3] Bosutinib is also in phase II development for in use in adult patients with recurrent glioblastoma.[4]

INNOVATION and/or ADVANTAGES

Bosutinib is already licensed for the treatment of patients with CML patients previously treated with one or more tyrosine kinase inhibitors and, if licensed for first-line use, will offer an additional treatment option for patients with Philadelphia positive CML.

DEVELOPER

Avillion LLP and Pfizer Inc.

AVAILABILITY, LAUNCH or MARKETING

Prior to its marketing authorisation in second-line CML treatment, bosutinib was granted an orphan designation (EU/3/10/762) by the European Commission.

PATIENT GROUP

BACKGROUND

CML is one of the most common types of leukaemia in England and Wales. In CML, the bone marrow produces an excessive number of abnormal cells. The abnormal cells may eventually suppress the production of normal white blood cells, which act to protect the body against infection.[1]

Ninety-five percent of people with CML have a chromosomal abnormality caused by a reciprocal translocation between parts of the long arms of chromosome 22 and chromosome 9; this produces what is commonly known as the 'Philadelphia chromosome'. As a consequence of the translocation, a *bcr-abl* fusion gene is produced. The abnormal protein encoded by this fusion gene is a constitutively active tyrosine kinase, which influences cellular processes such as proliferation, differentiation and survival. Cells containing the abnormal gene and protein replicate quickly and may be protected from programmed cell death. They therefore become predominant, initially in the bone marrow and subsequently in the bloodstream.[1]

CML is diagnosed by the presence of a characteristic blood and bone marrow cellular picture, together with cytogenetic and molecular diagnostic techniques (such as fluorescence in situ hybridisation [FISH], Southern and Western blotting techniques, reverse transcriptase polymerase chain reaction [RT-PCR], and CRKL phosphorylation assay).[1]

CML usually has three identifiable phases (the chronic phase, the accelerated phase and the blastic phase) and in an untreated patient, the disease has a predictable pattern of progression through them. Generally, the chronic phase lasts 3 to 5 years following diagnosis and the accelerated phase lasts 2 to 15 months before progression to the blastic phase. The blastic phase lasts 3 to 6 months and inevitably leads to death.[1] As a result of the introduction of tyrosine kinase inhibitors, the transformation from accelerated to blastic phase (and its associated mortality) occurs only in a minority of patients.[5]

CLINICAL NEED and BURDEN OF DISEASE

As of 2014, CML accounts for less than 1% of all new cancer cases in the UK, and 8% of all leukaemia types combined, with approximately 700 new cases registered in the United Kingdom that preceding year; the annual case rates are ~1.0 per 100,000 males and ~<1 per 100,000 females. The peak rate of CML cases in the UK (2012-2014) were seen in people over the age of 85.[9]

According to data for haematological cancers in England (2001-2010), while there were no changes in the incidence of CML over the time period, there were noticeable changes in mortality and survival rates. For patients aged 15 to 64 years, relative survival at five years rose from 59% for individuals diagnosed in 2000-03 to 87% for those diagnosed in 2008-10. For patients aged 65 and over relative survival at five years rose from 22% for individuals diagnosed in 2000-03 to 44% for those diagnosed in 2008-10. The change in survival and mortality rates for CML patients over this time period has been attributed to the introduction of tyrosine-kinase inhibitor treatments.[6]

Hospital Episode Statistics for England indicate that all myeloid leukaemias (ICD C92) accounted for 54,754 finished consultant episodes (FCE), 51,501 admissions and 138,515 FCE bed days.[7]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Bosutinib for previously treated chronic myeloid leukaemia (TA401). August 2016.
- NICE technology appraisal. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (TA426). December 2016.
- NICE technology appraisal. Dasatinib, nilotinib and high-dose imatinib for treating imatinib resistant or intolerant chronic myeloid leukaemia (TA425). December 2016.
- NICE technology appraisal. Guidance on the use of imatinib for chronic myeloid leukaemia (TA70). *Updated* January 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Cancer Drugs Fund list. V1.31. 15th June 2017.
- 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). B12/S/b.

CURRENT TREATMENT OPTIONS

Treatment options for CML depend on a patient's age, relative health, phase of leukaemia and, for some, the availability of a matching stem cell donor.[8,9] These include: [10,11,12]

- Allogeneic stem cell transplant – potentially curative
- Tyrosine kinase inhibitors:
    - Imatinib for the treatment of people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) who initially present in the accelerated or blastic phase; for people who present in the chronic phase and then progress to the accelerated phase or blastic phase if they have not received imatinib previously
    - Dasatinib and nilotinib for untreated chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults; for treating only chronic- or accelerated-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults if they cannot have imatinib or their disease is imatinib-resistant
    - Ponatinib for treating chronic-, accelerated- or blastic-phase chronic myeloid leukaemia in adults
- Interferon-alpha

EFFICACY and SAFETY

Trial	BFORE, NCT02130557; adults aged 18 years or older; bosutinib vs imatinib; phase III
Sponsor	Avillion Development 1 Limited
Status	Ongoing
Source of Information	Trial registry;[13] media release[14]
Location	EU (including UK), USA, Canada and other countries
Design	Randomised, parallel assignment, open label study
Participants	n=536; aged 18 years or older; molecular diagnosis of Philadelphia Chromosome Positive CML of ≤ 6 months from initial diagnosis
Schedule	400mg bosutinib or 400mg imatinib once daily, oral administration. All patients will be treated and/or followed for approximately 5 years (240 weeks)
Follow-up	5 years
Primary Outcomes	Proportion of participants with Major Molecular Response (MMR) at 12 months in the bosutinib arm compared with that of the imatinib arm
Secondary Outcomes	• CCyR by 12 months • MMR by 18 months • Response duration • EFS and OS • MMR at 3, 6,9 moinths • MR4, MR4.5 at 3, 6, 9 and 12 months • Time to response • Time to transformation
Key Results	Demonstrated superiority of bosutinib over imatinib at its primary endpoint of MMR at 12 months; Final study results yet to be published
Adverse effects (AEs)	No new or unexpected safety issues were identified
Expected reporting date	Primary Completion Date: August 2016; Study Completion Date: May 2020

Trial	BELA, NCT00574873; adults aged 18 years or older; bosutinib vs imatinib; phase III
Sponsor	Wyeth (now a wholly owned subsidiary of Pfizer, Inc.)
Status	Completed
Source of Information	Trial registry;[15] publication[16]
Location	EU (including UK), USA, Canada and other countries
Design	Randomised, parallel assignment, open label study
Participants	n=502; aged 18 years or older; cytogenetic diagnosis Philadelphia Chromosome Positive CML of < 6 months from initial diagnosis
Schedule	500mg bosutinib or 400mg imatinib once daily, by mouth with food preferably in the morning. Dose can be adjusted upward to 600mg or downward 300mg. Given daily for up to 8 years until treatment failure, unacceptable toxicity, death or withdrawal

Follow-up	8 years
Primary Outcomes	Percentage of participants with Complete Cytogenetic Response (CCyR) at Year 1
Secondary Outcomes	Percentage of Participants With Major Molecular Response (MMR) at Year 1; Kaplan-Meier Estimate of Probability of Retaining CCyR at 192 Weeks; Kaplan-Meier Estimate of Probability of Retaining Complete Hematologic Response (CHR) at 192 Weeks; Kaplan-Meier Estimate of Probability of Retaining Derived MMR at 144 Weeks; Cumulative Incidence of On-Treatment Transformation to Accelerated Phase (AP) or Blastic Phase (BP) at 192 Weeks
Key Results	Study did not achieve primary endpoint (CCyR rate at 12 months was not different for bosutinib vs imatinib); MMR rate at 12 months was higher with bosutinib vs imatinib; Time to CCyR and MMR was faster with bosutinib vs imatinib; On-treatment transformation to accelerated/blastic phase occurred in 2% of patients on bosutinib vs 4% on imatinib
Adverse effects (AEs)	Three CML-related deaths occurred in bosutinib arm vs eight in imatinib arm; Greater frequency of gastrointestinal and liver-related AEs with bosutinib; Greater frequency of neutropenia, musculoskeletal disorders, and oedema AEs with imatinib
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Bosutinib is already marketed in the UK for the treatment of Philadelphia chromosome-positive CML in those previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not clinically appropriate. The publicly listed acquisition costs are as follows:[2]

Table pack (quantity x dose)	Price per pack
28 x 100mg	£859.17 (hospital only)
28 x 500mg	£3,436.67 (hospital only)

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ 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

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Pfizer, Inc.

UK PharmaScan ID number 645025.

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