Dasatinib (Sprycel) for castration-resistant prostate cancer

December 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Dasatinib (Sprycel) for castration-resistant prostate cancer

Target group

- Prostate cancer: castration-resistant – in combination with docetaxel.

Technology description

Dasatinib (Sprycel) is a tyrosine kinase inhibitor that potently inhibits SRC-family kinases (SFKs), and also has activity against focal adhesion kinase (FAK) and other tyrosine kinases, exhibiting both anti-tumour and anti-osteoclastic effects\(^1\). Men with bone metastatic prostate cancer that progresses despite androgen deprivation therapy (castration-resistant prostate cancer [CRPC]) belong to a poor prognosis population that is at high risk for skeletal morbidity\(^2\). Elevated SFK and FAK activity have been linked to resistance to anti-hormonal therapies and poor patient outcome in prostate cancer; and the SRC proto-oncogene, which regulates osteoclast function, has a key role in the pathogenesis of bone metastases\(^3,4\). Increased osteolysis in bone metastases leads to skeletal-related events and osseous spread of bone-forming metastases is associated with mortality\(^3,5\). The company report that dasatinib has the potential to influence the transition from an androgen-dependent to an androgen-independent phenotype, and inhibit osteoclastic activity, favouring osteogenesis, thus exerting a bone-protecting effect\(^4,6\).

Dasatinib is intended for use in combination with docetaxel for the treatment of castration-resistant metastatic prostate cancer. It is administered orally at 100mg once daily combined with docetaxel 75mg/m\(^2\) every 3 weeks and prednisolone 5mg twice a day.

Dasatinib is licensed for the treatment of the following\(^7\):

- Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in the chronic phase.
- CML in those who have resistance to, or intolerance of, previous therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) in those who have resistance to, or intolerance of, previous therapy.

It is in or has completed phase II trials for the treatment of the following:

- Ph+ ALL with Hyper-CVAD\(^8\) chemotherapy.
- Children and adolescents with newly diagnosed CML; Ph+ ALL; and accelerated or blast phase CML who relapse after imatinib, or who are resistant or intolerant to imatinib.
- Chronic lymphocytic leukemia (CLL), relapsed and refractory CLL, or small lymphocytic lymphoma.
- Relapsed or refractory diffuse large B-cell lymphoma.
- Advanced non-small cell lung cancer.
- Advanced melanoma.
- Acral lentiginous, mucosal, or chronic sun-damaged melanoma with c-kit mutation.
- Acute myeloid leukemia harbouring c-kit mutations.
- Squamous cell carcinoma of the head and neck.
- Breast cancer: advanced triple-negative; advanced hormone receptor-positive (HR+); advanced oestrogen receptor-positive (ER+); HR+, HER2 receptor-

\(^8\) Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone; Methotrexate and Ara-C.
negative, post-menopausal unresectable, locally recurrent or metastatic; advanced 
ER+ after disease progression on a non-steroidal aromatase inhibitor; stage IV 
with bone metastases; and metastatic with selected molecular features.

The most common adverse events (AEs) associated with dasatinib when used for its 
licensed indications include infection pancytopenia, anorexia, appetite disturbance, 
depression, insomnia, headache, neuropathy, dizziness, dysgeusia, somnolence, visual 
disorders, dry eye, tinnitus, cardiac dysfunction, haemorrhage, hypertension, flushing, 
pleural effusion, dyspnoea, cough, pulmonary oedema, pulmonary hypertension, lung 
infarction, pneumonitis, diarrhoea, vomiting, nausea, abdominal pain, gastrointestinal 
bleeding, colitis, gastritis, mucosal inflammation, dyspepsia, abdominal distension, 
constipation, oral soft tissue disorder, skin rash, alopecia, dermatitis, pruritus, acne, dry 
skin, urticaria, hyperhidrosis, arthralgia, myalgia, muscle inflammation, muscular 
weakness, fluid retention, fatigue, superficial oedema, pyrexia, asthenia, chest pain, 
generalised oedema, chills, weight change, confusion.

Innovation and/or advantages
The current standard for the treatment of CRPC offers only modest survival benefits (18– 
19 months). If licensed, dasatinib may have the potential to increase the efficacy of 
chemotherapy in this situation co-targeting the tumour, soft tissue and bone micro-
environments.

Developer
Bristol-Myers Squibb Pharmaceuticals Ltd.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011)

Relevant guidance
NICE Technology Appraisals
- In development. Cabazitaxel for the treatment of hormone refractory prostate cancer 
previously treated with docetaxel chemotherapy regimens. Expected February 2012.
- In development. Abiraterone for the treatment of metastatic castration resistant 
prostate cancer following previous cytotoxic therapy. Expected May 2012.
- In development. Dutasteride for reducing the risk of developing prostate cancer in men 
who are considered to be at increased risk of developing the disease. Suspended April 
2011.
- Docetaxel for the treatment of hormone refractory prostate cancer. 2006.

NICE Clinical Guidelines

NICE Intervventional Procedure Guidance
- Cryotherapy as a primary treatment for prostate cancer. 2005.

NICE guidance on cancer services
Clinical need and burden of disease

Prostate cancer is the most common cancer in men in the UK, accounting for 25% of all male cancers\(^22\). The lifetime risk of being diagnosed with prostate cancer is approximately 1 in 9 for men in the UK\(^23\). The main risk factor is increasing age, with more than 50% of cases diagnosed over the age of 70\(^22\). In 2009, there were 34,593 new cases registered in England and 2,406 in Wales, resulting in age standardised rates of 107.6 and 114.0 per 100,000 populations respectively\(^24,25\). In 2008, there were 9,150 deaths from prostate cancer in England and Wales, approximately 12% of all male cancer deaths\(^26\). Although epidemiological data on metastatic CRPC is limited, it is estimated that most prostate cancer deaths occur in patients with metastatic CRPC\(^14\). CRPC cannot be cured and prognosis is poor; survival is not expected to exceed between 15 and 20 months\(^14,b\). Ninety percent of men with metastatic CRPC have radiographically detectable bone metastases\(^2\). These result in pain, fractures, hypercalcemia, spinal cord compression, and bone marrow insufficiency\(^27\). Expert opinion suggests that around 4,000-5,000 men with prostate cancer in the UK receive docetaxel each year\(^b\).

Existing comparators and treatments

Treatments aim to improve symptoms, slow disease progression and prolong life\(^15\). Clinical management may be multimodal or sequential, and patients may receive a combination of palliative treatments which include\(^14,15\):

- Docetaxel (Taxotere) in combination with prednisolone. Licensed for up to 10 cycles in castration refractory disease where Karnofsky performance-status score is $\geq 60\%^{13}$.
- Cabazitaxel (Jevtana) – second line after progression on docetaxel (recently licensed).
- Abiraterone (Zytiga) in combination with prednisolone – second line after progression on docetaxel (recently licensed).
- Mitoxantrone with prednisolone (not licensed for this indication).
- Additional hormonal therapy.
- Supportive care, given in combination with the above, including radiotherapy, bisphosphonates, and/or steroids.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00439270, CA180-086; dasatinib with docetaxel; phase I/II.</th>
<th>READY, NCT00744497, CA180-227, 2008-000701-11; dasatinib or placebo, both with docetaxel and prednisolone; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bristol-Myers Squibb Pharmaceuticals Ltd.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Published(^2), trial registry(^28), manufacturer.</td>
<td>Trial registry(^29), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=66 (planned); adults; prostate cancer; castration-resistant; metastatic. Administered dasatinib 50-150mg orally once daily, and docetaxel 60-75 mg/m(^2)</td>
<td>n=1,500 (planned); adults; prostate cancer; castration-resistant; metastatic; receiving docetaxel and prednisolone. Randomised to dasatinib 100mg or</td>
</tr>
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</table>

\(^b\) Expert opinion.
given by IV infusion every 21 days. Both treatments continued until disease progression. Placebo, both orally once daily until disease progression or withdrawal due to treatment-related toxicity.

### Follow-up

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment period and follow up until progression or treatment-related toxicity.</th>
<th>Active treatment period and follow up until disease progression or death.</th>
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</thead>
</table>

### Primary outcomes

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<tr>
<th>Primary outcomes</th>
<th>Safety; pharmacokinetic data.</th>
<th>Overall survival.</th>
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### Secondary outcome

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<th>Secondary outcome</th>
<th>Safety and tolerability; efficacy (prostate-specific antigen [PSA] response), objective tumour response, progression free survival (PFS), changes on bone scan.</th>
<th>Tumour response by RECIST(^5) criteria for subjects with measurable disease at baseline; time to first skeletal-related event; proportion of subjects with reduction in urinary N-telopeptide; PFS; time to PSA progression; proportion of subjects with reduction in pain intensity; safety and tolerability; Brief Pain Inventory (short form); subjective significance questionnaire; Health Utilities Index.</th>
</tr>
</thead>
</table>

### Key results

| Key results | After median treatment duration of 6.2 months (range 0.1-17.2 months): Treatment group (n=46): grade 3-4 toxicity, 28%; durable 50% PSA decline, 57%. RECIST-evaluable patients only (n=30): partial response (PR), 60%; disappearance of a lesion on bone scan, 30%; decrease in urinary N-telopeptide 87%; decrease in bone-specific alkaline phosphatase levels, 76%; stabilisation of disease for an additional 1 to 12 months with single-agent dasatinib after docetaxel discontinuation, 61%. |
|-------------|--------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
|             | -                                                                                                                                 | -  |

### Adverse effects (AEs)

| Adverse effects (AEs) | AEs in ≥10% of patients: fatigue; alopecia; diarrhoea; nausea; dysgeusia; peripheral oedema; decreased appetite; anaemia; dyspnœa; vomiting; dry skin; nail disorder; headache; hypersensitivity; pleural effusion; constipation; hypokalemia; insomnia; peripheral neuropathy |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
|                       | -                                                                                                                             | -  |

### Expected reporting date

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<th>Expected reporting date</th>
<th>February 2012.</th>
<th>February 2013.</th>
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### Estimated cost and cost impact

The cost of dasatinib has not yet been determined for this indication. A pack of 30 x 100mg tablets of dasatinib for the treatment of chronic phase CML costs £2,205\(^7\). The cost of 10 cycles of docetaxel at a dose of 75mg/m\(^2\) IV every 21 days for metastatic CRPC is around £7,200\(^4,7\).

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\(^5\) Response Evaluation Criteria in Solid Tumors.

\(^4\) Costing based on average surface area 1.7m\(^2\).
Claimed or potential impact – speculative

Patients
- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ None identified

Services
- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements

- ☑ Decreased use
- ☐ Other:
- ☑ None identified

Costs
- ☐ Increased unit cost compared to alternative
- ☐ New costs: Additional to current therapy.

- ☑ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed

- ☐ Savings:
- ☐ Other:

- ☐ None identified

Other issues
- ☐ Clinical uncertainty or other research question identified:
- ☑ None identified

References

8 The electronic Medicines Compendium (eMC). Summary of product characteristics, Sprycel. Bristol-Myers Squibb Pharmaceuticals. October 2011. http://www.medicines.org.uk/EMC/medicine/19219/SPC/Sprycel+20mg%2c+50mg%2c+70mg%2c+80mg%2c+100mg+and+140mg+Film-Coated+Tablets/ Accessed 02 November 2011
13 National Institute for Health and Clinical Excellence. Dutasteride for reducing the risk of developing prostate cancer in men who are considered to be at increased risk of developing the disease. Suspended April 2011.
17 National Institute for Health and Clinical Excellence. Cryotherapy for recurrent prostate cancer. Interventional...

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