Breast Pathway Group – Lapatinib & Capecitabine in Advanced Breast Cancer

Indication: Lapatinib in combination with capecitabine is recommended as a treatment option for advanced or metastatic breast cancer

National Cancer Drug Fund criteria:
- HER2 over-expressed (defined by IHC3+ or IHC2+ with gene amplification or gene amplification alone)
- Previous treatment with anthracyclines or anthracycline contraindicated
- Previous treatment with taxanes
- Previous treatment with trastuzumab in the metastatic setting
- Use in combination with capecitabine

National Cancer Drug Fund application and approval is required prior to starting treatment

Regimen details:
- Lapatinib 1250mg PO Continuous
- Capecitabine 1000mg/m² BD PO Days 1 to 14 followed by 7 day rest period

Administration: Lapatinib is available as a 250mg film coated tablet. The daily dose of lapatinib should not be divided and should be taken either at least one hour before, or at least one hour after food. To minimise variability in the individual patient, administration of lapatinib should be standardised in relation to food intake, for example always to be taken one hour before a meal.

Capecitabine tablets orally twice a day, swallow whole with water within 30 minutes after a meal and approximately 12 hours apart. Capecitabine is available as 500mg and 150mg tablets.
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Frequency:
Lapatinib is continuous
Capecitabine taken from Days 1 to 14 every 21 days, continued until disease progression or unacceptable toxicity

Pre-medicine:
Not applicable

Anti-emetics:
Low emetogenicity
Follow local anti-emetic policy

Supportive medication:
Diarrhoea can be managed with loperamide
Mouthcare as per local policy
Topical emollients / suncare

Extravasation:
Not applicable

Regular investigations:
Prior to Cycle 1:
- FBC Day 1 (within 14 days)
- LFTs Day 1 (within 14 days)
- U&Es Day 1 (within 14 days)
- MUGA/ECHO/ECG See Comments

Prior to Day 1 (all cycles):
- FBC Day 1 (within 72 hours)
- LFTs Day 1 (within 72 hours)
- U&Es Day 1 (within 72 hours)

Toxicities:
Diarrhoea, nausea, vomiting, dyspepsia, stomatitis, constipation, abdominal pain, anorexia, rash, hand-foot syndrome (palmar-plantar erythrodysesthesia), dry skin, pain in extremity and back, fatigue, mucosal inflammation, insomnia, headache, decreased LVEF, interstitial lung disease /pneumonitis, hyperbilirubinaemia and hepatotoxicity

Cardiotoxicity: Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris

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DOSE MODIFICATIONS

Haematological Toxicity

<table>
<thead>
<tr>
<th>Neutrophils (x $10^9$/L)</th>
<th>Platelets (x $10^9$/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 &amp; ≥ 100</td>
<td></td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt;1.5 or &lt;100</td>
<td></td>
<td>Delay for 1 week</td>
</tr>
</tbody>
</table>

Repeat FBC - If recovered to above these levels, resume treatment at 100% doses. Dose reduction should be considered if myelosuppression results in delay of subsequent cycles.

Non-haematological Toxicities

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Capecitabine Dose</th>
<th>Lapatinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>30-50</td>
<td>Give 75%</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>Contra-indicated / omit</td>
<td>Caution is advised in patients with severe renal impairment (&lt;30ml/min)</td>
</tr>
</tbody>
</table>

Hepatic Impairment

<table>
<thead>
<tr>
<th>Capecitabine Dose</th>
<th>Lapatinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Decision</td>
<td>Clinical Decision</td>
</tr>
<tr>
<td>In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.</td>
<td>Use with caution in patients with moderate to severe hepatic impairment due to risk of increased exposure to the medicinal product. Discontinue if changes in liver function are severe; patients should not be retreated</td>
</tr>
</tbody>
</table>
Non-haematological toxicities:

### Lapatinib

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
<th>Dose Modification Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis/interstitial lung disease</td>
<td>Hold and investigate</td>
<td>Discontinue if &gt; Grade 3 confirmed as per CTC</td>
</tr>
<tr>
<td>Ejection Fraction &lt;40% or LVEF lower than institution’s lower limit of normal</td>
<td>Discontinue and monitor patient closely OR Resume after 2 weeks if LVEF ≥ normal and patient asymptomatic</td>
<td>Decrease Lapatinib to 1000mg once daily monitor closely. If recurs, discontinue.</td>
</tr>
<tr>
<td>Grade 2 Diarrhoea (Increase of 4-6 bowel movement/day over baseline)</td>
<td>Start loperamide, hold if required until resolved</td>
<td>No dose change required for lapatinib for the first 2 appearances, decrease to 1000mg once daily if recurs.</td>
</tr>
<tr>
<td>Grade 3 Diarrhoea (Increase of &gt;7 bowel movement/day over baseline)</td>
<td>Hold until symptoms resolve, treat with loperamide</td>
<td>Re-start Lapatinib at 1000mg once daily when symptoms resolve</td>
</tr>
<tr>
<td>Grade 2 Rash</td>
<td>Continue Treatment</td>
<td>If not improved after 2 weeks, interrupt lapatinib treatment for up to 14 days. Re-start at full dose if symptoms resolves</td>
</tr>
<tr>
<td>Grade 3 Rash</td>
<td>Interrupt Treatment</td>
<td>If symptoms resolve within 14 days re start lapatinib at 1250mg daily If symptoms recur, interrupt treatment until resolve and restart lapatinib at 1000mg daily</td>
</tr>
</tbody>
</table>

### Capecitabine

Dose modifications for diarrhoea, nausea, vomiting, stomatitis, and hand-foot syndrome (palmar-plantar erythrodysesthesia):

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>1st Appearance Dose</th>
<th>2nd Appearance Dose</th>
<th>3rd Appearance Dose</th>
<th>4th Appearance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>delay* then 100%</td>
<td>delay* then 75%</td>
<td>delay* then 75%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>delay* then 75%</td>
<td>delay* then 50%</td>
<td>discontinue</td>
<td>discontinue</td>
</tr>
</tbody>
</table>

Version: 1.0 Supersedes: all other versions

Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014

Reason for Update: LCA Protocol Development

Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl

Prepared by: Wendy Ng

Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson

Second check by: Lisa Yuen

Date prepared: November 2014 Review Date: November 2016

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<table>
<thead>
<tr>
<th>4</th>
<th>Discontinue or delay* then 50%</th>
<th>Discontinue</th>
<th>Discontinue</th>
<th>Discontinue</th>
</tr>
</thead>
</table>

*Stop treatment immediately and delay until toxicity resolved to grade 0-1

**Cardiotoxicity:**

**Capecitabine:**
Chest pain typical of myocardial ischaemia requires cessation of capecitabine and should be investigated.

**Lapatinib:**
Lapatinib has been associated with reports of decreases in left ventricular ejection fraction (LVEF) and has not been evaluated in patients with symptomatic cardiac failure. Caution should be taken if lapatinib is to be administered to patients with conditions that could impair left ventricular function (including co-administration with potentially cardiotoxic agents).
Discontinue lapatinib in patients with symptoms associated with decreased left ventricular ejection fraction (LVEF) grade 3 or greater or if their LVEF drops below the institutions lower limit of normal.
Lapatinib may be restarted at a reduced dose of 1000mg/day when administered with capecitabine after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic.

**Prolongation of QT interval with lapatinib:**
Caution should be taken if lapatinib is administered to patients with conditions that could result in prolongation of QTc (including hypokalaemia, hypomagnesemia, congenital long QT syndrome, or co-administration of other medicines known to cause QT prolongation). Hypokalaemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be considered prior to administration of lapatinib and throughout treatment.

**Interstitial lung disease/pneumonitis:**
Lapatinib has been seen to cause interstitial lung disease/pneumonitis. Monitor for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. Fatal cases have been reported.

**Location of regimen**
To be supplied to the patient for oral self-administration.

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**delivery:** Suitable for home delivery

**Comments:** Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of capecitabine. Ensure patient is informed of action to take if signs of toxicity (e.g. severe mucositis, diarrhoea) develop within the first few days of treatment, as this is often an early indication of DPD deficiency.

Capecitabine contains anhydrous lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Drug interactions:** Significant interactions below. For full details consult product literature/reference texts.

Capecitabine:
- Allopurinol: avoid concomitant use (reduced efficacy of capecitabine)
- Warfarin/coumarin anticoagulants: switch to low molecular weight heparin (altered coagulation parameters and/or bleeding, including death)
- Phenytoin: monitor plasma phenytoin levels (increase phenytoin level)

Lapatinib:
- Co administration of lapatinib with strong inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole,itraconazole, voriconazole, posaconazole, nefazodone) should be avoided. Co administration of lapatinib with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored.
- Co administration of lapatinib with known inducers of CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort) should be avoided.
- Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors (ketoconazole, itraconazole, quinidine, verapamil, ciclosporin, erythromycin) and inducers (rifampicin, St John's Wort) of these proteins may alter the exposure and/or distribution of lapatinib.
- Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease.
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- Digoxin: Co-administration of lapatinib resulted in an approximate 80% increase in the AUC of digoxin.
- Food & drink: The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat content in the meal.
  Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with lapatinib

References:
GSK Ltd. Summary of Product Characteristics for Tyverb
Roche, Summary of product characteristics for Xeloda
A guide for Healthcare professionals to assist with the management of patients receiving TYBERB
Micromedex review: Lapatinib
Geyer C. E. et al (2006); NEJM, 255(26):2733-2743
SELCN Lapatinib Capecitabine protocol
NWLH Lapatinib Capecitabine protocol
NWLCN Breast Regimen Version 7 01
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
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