**STANDARD CARE PLAN**

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>First-line Gefitinib (Iressa ®) Therapy</th>
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<tbody>
<tr>
<td>Document Type:</td>
<td>Clinical Guideline</td>
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<tr>
<td>Subject:</td>
<td>Standard Care Plan</td>
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<td>Review date:</td>
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<td>Author(s):</td>
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**Standard care plan for Gefitinib**

**References**


**Patient group**

EGFR sensitising mutation positive metastatic (stage IV) adenocarcinoma of lung origin.

**Inclusion criteria**

- Stage IV adenocarcinoma of the lung PLUS positive EGFR mutational analysis
- Stage III patients unsuitable for radical treatment eg. combined chemoradiotherapy
- No previous palliative chemotherapy received for NSCLC
- Adequate bone marrow reserve

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<td>Last modified</td>
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<td>Page</td>
<td>1 of 7</td>
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<tr>
<td>Agreed by (on behalf of team)</td>
<td>Fiona Blackhall</td>
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</table>
• WCC >3, Plts > 100 recommended but gefitinib may be prescribed if WCC and or platelets are lower as it is not myelosuppressive
• Hb >10 (consider transfusion if anaemic)
• Adequate renal function – GFR (Cockcroft-Gault) >50 mL/min preferred
• ECOG PS 0 and 1 (selected cases with PS 2 and 3)

Cautions
• Patients with brain metastasis can be considered for gefitinib treatment preferably after procedures or treatments to achieve local control.
• Life expectancy < 8 weeks
• Second malignancy excluding non melanomatous skin cancers in the past 3 years
• Severe hepatic derangement

Anticipated benefit

<table>
<thead>
<tr>
<th>Publication</th>
<th>N</th>
<th>ORR</th>
<th>mTTP</th>
<th>OS</th>
<th>MS</th>
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<tbody>
<tr>
<td>Mok TS et al 2009</td>
<td>1217</td>
<td>71% (mut +ve)</td>
<td>5.7 wks</td>
<td>17.8m</td>
<td>18.6m</td>
</tr>
<tr>
<td>Inoue A et al 2009</td>
<td>30</td>
<td>66%</td>
<td>-</td>
<td>-</td>
<td>17.8m</td>
</tr>
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Expected toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CTC G3 – 4 (%)</th>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>3.8</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>3.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3.7</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0.2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.5</td>
</tr>
<tr>
<td>CINV</td>
<td>0.3/0.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.3</td>
</tr>
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</table>

Additionally, adverse events leading to death in 3.8% of patients treated with gefitinib. There was also reported interstitial lung disease events (ARDS, interstitial lung disease, pneumonitis and radiation pneumonitis) in 2.6% of patients. In an international Phase II trial there was a reported 21% incidence of eye toxicity, including conjunctivitis, blepharitis, keratitis, eye pain and corneal erosions from excessive eyelash growth.

Initial investigations and work up prior to start of treatment

Diagnostic review and work up should usually include:
• Pathology/Cytology confirmed diagnosis of adenocarcinoma of lung origin PLUS EGFR mutational analysis on biopsy or cytology (cell block) sample of tumour.
• Stage of disease determined and documented
CT Abdomen/thorax (+/- PET CT) +/- brain scan
- Bronchoscopy/EBUS - desirable
- Clinical assessment and documentation of current disease related symptoms
- Performance status recorded
- Co-morbidities recorded
- Smoking status and significant asbestos exposure recorded
- FH recorded
- Concomitant medications recorded and stopped if necessary
- Baseline FBC and Christie Profile
- Baseline CXR
- Baseline ECG
- Patient consented for aims, practicalities and toxicity of gefitinib therapy for patients with confirmed EGFR mutation positive tumours. If mutation status pending, it is adequate to counsel patients and provide information leaflet with explanation that treatment can be started upon confirmation of a positive mutation status.
- Plan confirmed with consultant oncologist if 1st seen by junior college

Diagnostic review
Metastatic lung cancer with histologically proven adenocarcinoma of lung origin, PLU as a positive EGFR mutational analysis on biopsy or cytology (cell block) sample from tumour.

Re-Staging
CT thorax/abdomen as baseline, (+/- PET CT scan) followed by a restaging CT scan at 8 weeks. Note: Single Patient Access (SPA) Scheme Payment is triggered if restaging scan shows response at 8-week scan and treatment is to be continued. If there is no clinical / radiological benefit at 8 weeks treatment should be discontinued and pharmacy notified so that SPA scheme payment is not triggered.

MDT meeting
Cases will have been discussed at an appropriate MDT meeting.

Overview of treatment programme

Drugs and Starting Doses
Gefitinib 250mg od

Treatment duration
To be continued until disease progression and clinical opinion that treatment beyond progression will not be of benefit*, or unacceptable toxicity.

Cycle length
Continuous once-daily dosage until decision made to discontinue treatment.
**Stopping criteria**

- Treatment to be discontinued in event of clinical and/or radiological disease progression (by RECIST criteria if applicable) and clinical opinion that treatment beyond progression will not be of benefit, unacceptable and/or potentially life-threatening toxicity or patient’s choice.
- In event of hepatic toxicity, i.e CTC grade 3 increase in liver enzymes, which does not resolve on interruption of treatment, treatment should be discontinued.
- Consider discontinuing treatment if there is significant deterioration in PS or any CTC grade 4 toxicity.
- Occasionally, consideration can be given to continue treatment despite radiological progression if there has been a clear and continuing symptomatic benefit. Furthermore, there is a small chance of tumour flare following discontinuation of gefitinib, more commonly seen in patients with short time to progression on TKI, the presence of pleural or brain metastases. (Chaft et al 2011)

**On treatment assessments and schedule of investigations and suggested supportive medications**

<table>
<thead>
<tr>
<th>Visit number</th>
<th>Appointment</th>
<th>Visit description</th>
</tr>
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</table>
| 1            | OP clinic consultant appointment | CXR  
Christie profile, FBC  
CT chest/abdo  
(CT brain – optional)  
Nurse specialist  
Pathology review – optional  
EGFR test  
Baseline ECG |
| 2 (optional) | OP Appt | Review |
| 3            | OP clinic cycle 1  
Oral treatment | Gefitinib 250mg od 1 month supply  
Trimovate cream topical prn  
Metoclopramide 10mg tds 7 days 1 month  
Loperamide 2mg prn 1 month |
| 4            | OP clinic 2 weeks  
Or telephone call from specialist nurse | Toxicity check  
CXR  
Christie profile, FBC |
| 5            | OP clinic cycle 2 (4 weeks post cycle 1)  
Oral treatment | Gefitinib 250mg od 1 month supply  
Trimovate cream topical prn  
Metoclopramide 10mg tds 7 days 1 month  
Loperamide 2mg prn 1 month  
CXR, Christie profile, FBC |
| 6            | OP clinic cycle 3 (4 weekly cycles)  
Oral treatment | Gefitinib 250mg od 1 month supply  
Trimovate cream topical prn  
Metoclopramide 10mg tds 7 days 1 |
<table>
<thead>
<tr>
<th>Month</th>
<th>OP clinic cycle</th>
<th>Treatment Details</th>
</tr>
</thead>
</table>
| 1     |                | Loperamide 2mg prn 1 month  
          CXR  
          Christie profile, FBC  
          CT prior to review at ~ 8 weeks  
          *Note single patient access scheme payment; drug payment is triggered if patient is benefiting from treatment at 8 week scan* |
| 7     | OP clinic cycle 4 | Gefitinib 250mg od 1 month supply  
          Trimovate cream topical prn  
          Metoclopramide 10mg tds 7 days 1 month  
          Loperamide 2mg prn 1 month  
          CXR  
          Christie profile, FBC |
| 8     | OP clinic cycle 5 | Gefitinib 250mg od 1 month supply  
          Trimovate cream topical prn  
          Metoclopramide 10mg tds 7 days 1 month  
          Loperamide 2mg prn 1 month  
          CXR  
          Christie profile, FBC  
          CT |
| 9     | OP clinic cycle 6 – 8 | Same as 3-5 |

**Management of treatment-related acneiform rash**

Rash frequently improves within weeks of initiation of gefitinib and patients should be encouraged to persevere if possible. Supportive measures include:

- Dermatologist approved cover make-up, e.g. Dermablend ®
- Avoidance of, or minimising sun exposure
- Simple emollients used as soap substitute and moisturiser e.g. Oilatum ®, Diprobase ®
- For grade 2B rash, i.e. interfering with daily life, consider topical therapy – Trimovate ® (clobetasone, oxytetracycline, nystatin) +/- analgesia. If secondary infection suspected, consider oral minocycline 100mg bd for 5-7 days, or topical mupirocin tds if Staphylococcus aureus infection more likely.
- For grade 3-4 rash (erythroderma, generalised eruption, bullous or ulcerative/desquamative dermatitis), discontinue therapy until resolved and consider restarting with prior discussion with consultant.
Management of treatment-related diarrhoea

NCI CTCAE v4.03 grading of treatment related diarrhoea

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Increase of &lt;$4 stools per day over baseline, mild increase on ostomy output compared to baseline</td>
<td>Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of &gt;7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death</td>
</tr>
</tbody>
</table>

- Patients should be provided with a supply of loperamide (Imodium®) with their courses of treatment.
- Patients to be advised to start taking loperamide once they start experiencing loose motions (4mg first dose, followed by 2mg with each loose stools, max dose 16mg/24 hours as per BNF guidance).
- In the event of persisting grade 2 diarrhoea despite use of loperamide, or severe diarrhoea i.e. grades 3-4, treatment can be interrupted for up to 2 weeks until resolution of diarrhoea before consideration can be given to restart treatment, after prior discussion with consultant.

Clinical assessment

- Graded documentation of toxicity
- Assessment of disease related symptoms
- Performance status recorded
- Physical examination/focussed examination performed
- Fitness for continuation of chemotherapy assessed and documented

Laboratory assessment

FBC, Christie Profile.

Tumour response assessment

- Clinical assessment of any palpable masses
- CXR at each 4-week clinic review
- First restaging CT scan at 8 weeks, followed by restaging scan every 12 weeks thereafter.

Dose modifications

If grade 3 toxicity occurs, interrupt treatment until resolution. Any grade 4 toxicity must result in consideration of cessation of treatment.
Interpretation of response

Tumour Assessment
- CXR performed on each monthly visit
- CT abdo/thorax performed 8 weeks following start of treatment, followed by restaging scan every 12 weeks thereafter.

Subsequent active therapy options
Palliative radiotherapy should be considered as an adjunct in event of uncontrolled local symptoms, e.g. painful bone metastasis.

Treatment options at progression
- Consider platinum based combination if good PS
- Approved second line therapy if good PS
- Clinical trial if appropriate.
- Palliative radiotherapy for symptom control
- Best supportive care
- Other regimens/therapies on approval by DMC/Drugs and therapeutics.

Appendices
http://www.mangen.co.uk/media/13174/doc19%20genetics%20labs%20referral%20form.pdf