ERLOTINIB (TARCEVA®) FOR NSCLC

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Cycle length</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 to 28</td>
<td>Continuous</td>
<td>Erlotinib</td>
<td>150 mg</td>
<td>Oral</td>
<td>ONCE daily</td>
</tr>
</tbody>
</table>

DOSE FORM
Presented as 25mg, 100mg and 150mg Tablets

CYCLE LENGTH AND NUMBER OF DAYS
One 150mg dose orally, taken ONCE daily until disease progression.

APPROVED INDICATION(S)
As an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) who have been tested positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation

As an option for second-line therapy for non-small-cell lung cancer treated with non-targeted chemotherapy;
- because of delayed confirmation of a positive epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation status or
- if it is not known if the cancer is EGFR-TK mutation-positive because of problems with the test, and the cancer is very likely to be EGFR-TK mutation-positive and
- it responds to the first 2 cycles of treatment with erlotinib.

ELIGIBILITY CRITERIA
- PS 0, 1, 2.
- Radiologically or clinically evaluable disease
- Able to take oral medication
- Using effective contraception if of reproductive potential

EXCLUSION CRITERIA
- Pregnant or lactating women
- Concurrent uncontrolled medical illness
- Severe renal impairment
- Severe hepatic impairment (Bilirubin > 2 x ULN, ALT 2 x ULN or ALT 5 x ULN with liver mets)

PREMEDICATION
None

RECOMMENDED TAKE HOME MEDICATION
Metoclopramide 10 three times daily as required (not usually needed).
Loperamide 2mg pm (max 16mg in 24 hours) for diarrhoea as required.
Emollients (for skin rash) e.g. Diprobase, Epaderm, E45, Neutrogena (encourage patients to use regularly to prevent skin dryness).
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INVESTIGATIONS / MONITORING REQUIRED
Baseline chest X-ray/ CT scan, FBC, U&E, LFT's & tumour markers as appropriate prior to starting treatment and at appropriate intervals during treatment.

ASSESSMENT OF RESPONSE
Radiological and clinical assessment will be performed at baseline and then 8 weeks (2 cycles) following commencement of erlotinib. Erlotinib will only be continued if response is documented. Assessment will thereafter be at 3 to 4 monthly intervals.

REVIEW BY CLINICIAN
Assessment of response at 8 weeks and then at 3 to 4 monthly intervals or sooner as appropriate to individual patient.

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local practice.

ADMINISTRATION NOTES
- Taken with water 1 hour prior to or 2 hours after food
- Avoid strong sunlight or use a good sunscreen SPF 15 or higher
- Hepatic cytochromes CYP3A4 and CYP1A2 are involved in the metabolism of erlotinib. Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 and CYP1A2 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided.
- Patients are advised to avoid grapefruit or grapefruit juice, because it inhibits CYP3A4, leading to increased plasma levels of erlotinib.
- Drugs that are CYP3A4 inhibitors include systemic anti-fungals e.g. ketoconazole, itraconazole, voriconazole; ciprofloxacin, protease inhibitors, erythromycin, clarithromycin and SSRI's e.g. fluoxetine, fluvoxamine. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.
- Drugs that are CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, rifampin, phenobarbital or Hypericum perforatum (St John’s wort) may increase metabolism and decrease erlotinib plasma concentrations and hence potentially decrease efficacy.
- As bleeding events were observed in the BR21 study when patients were taking concurrent warfarin it has been suggested that there may be a possibility of an interaction, however no formal interaction studies with warfarin have been performed. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.
- Cigarette smoking increases erlotinib clearance, reducing erlotinib exposure by 50-60%. Efficacy and long-term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes (and so is not recommended). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced.
- Erlotinib solubility is altered by acidity of the upper GI tract, therefore drugs affecting pH, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for the loss of exposure. If an H2 antagonist (or proton pump inhibitor) is required they should be taken 10 hours before or 2 hours after erlotinib.
- The effects of concomitant administration of erlotinib with antacids are unknown, however, reduced bioavailability is likely. Administration of antacids and erlotinib should be avoided - if the combination is considered necessary the antacid should be taken at least 4 hours before or 2 hours after erlotinib.
- Erlotinib in combination with NSAIDs or steroids increases the risk of gastric perforation, and so should be avoided where possible.
- Around 1 in 100 patients taking erlotinib develops Interstitial Lung Disease like events (which can be fatal). Patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, should have their erlotinib interrupted pending diagnostic evaluation.

TOXICITIES
- Skin Reactions (see under dose modification below)
- Diarrhoea (see under dose modification below)
- Fatigue
- Nausea & vomiting (Note: if the patient vomits after taking an erlotinib tablet, the patient should NOT take another tablet, until the next dose is due.)
- Gastrointestinal perforation (rare)
- Interstitial Lung Disease

DOSE MODIFICATION / TREATMENT DELAYS
All dose modifications must be made by an oncology specialist following the recommended dose reduction strategy below.

<table>
<thead>
<tr>
<th>Level</th>
<th>Erlotinib dose</th>
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<tbody>
<tr>
<td>Starting</td>
<td>150mg daily</td>
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<tr>
<td>1st reduction</td>
<td>100mg daily</td>
</tr>
<tr>
<td>2nd reduction</td>
<td>50mg daily</td>
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All toxic events will be graded according to NCI CTCAE v3.0 criteria plus the following scale for describing rash.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>asymptomatic, macular or papular erythematous eruption in acneiform distribution;</td>
</tr>
<tr>
<td>Grade 2</td>
<td>like grade 1 but with symptoms such as pruritus;</td>
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<tr>
<td>Grade 3</td>
<td>extension of the eruption beyond the aceniciform distribution of head, chest and back or the development of confluent lesions, painful lesions, or minor ulceration;</td>
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<tr>
<td>Grade 4</td>
<td>exfoliative or ulcerating dermatitis.</td>
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</table>

In the event of any grade 3 or 4 toxicity that is not controlled by optimal supportive care (see below for guidelines) then dose reduce to the next dose level. Toxicity must improve by at least 1 NCI CTCAE grade within 2 weeks or further dose reduction by 1 level will be required. Once a patient has had a dose reduction the dose will not be re-escalated except after resolution of the skin rash.

DOSE ADJUSTMENT FOR SKIN RASH
Typical erlotinib rash has the following appearance:
- Pustular/papular appearance and usually involves the face, head and upper torso.

Erlotinib rash may be secondarily infected as diagnosed by:
- A tan/brown crust overlying inflammatory lesions, with significant oozing of fluid
- And/or an abrupt change in the appearance of lesions (particularly if they differ from those in other areas).
## Toxicity | Symptoms | Dose modification | Management
--- | --- | --- | ---
1 to 2 | Generally localised Minimally Symptomatic No sign of infection | None | Topical hydrocortisone 1% and/or topical clindamycin 1% lotion/gel (non-alcoholic based),

3 | Generalised moderate symptoms No sign of infection | Interrupt treatment for 7 to 14 days | Topical hydrocortisone 1% or short course of oral prednisolone and/or topical clindamycin 1% lotion/gel (non-alcoholic basis) plus oral minocycline or doxycycline 100mg BD for 10 to 14 days

4 | Generalised Severe symptoms Potential for infection Significant impact on daily life. | Dose interruption for 7 to 14 days as for Grade 3 or discontinue | Topical Eumovate (clobetasol butyrate 0.05%) or short course of oral Prednisolone and/or topical clindamycin 1% lotion/gel (non-alcoholic basis) plus oral minocycline or doxycycline 100mg BD for 10 to 14 days

### Steroid regimen
Start with prednisolone 25 mg for 1 week; reduce by 5 mg/day over 4 days. Assess patient response and need for ongoing steroid treatment.

- Consider adding in antihistamines e.g. chlorphenamine/ hydroxyzine and painkillers, paracetamol/ibuprofen if itching and or painful.
- Topical retinoids and other acne medications (e.g. benzyl peroxide) are NOT recommended since rash is not acne. Their skin drying effects may exacerbate rash.

### DOSE ADJUSTMENT FOR DIARRHOEA
Diarrhoea has occurred in 50% of patients on erlotinib.

| Toxicity | Dose modification | Management |
--- | --- | --- |
1 or 2 | None | Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day))

3 | If unresponsive to antidiarrhoeal medication for 24 hours then stop drug until resolution to grade <1 and then restart at next dose level down | Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day))

4 | If unresponsive to antidiarrhoeal agent for >24 hours then discontinue drug | Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day))

**Note:** In more severe or persistent cases of diarrhoea leading to dehydration erlotinib treatment must be stopped and appropriate measures should be taken to intensively rehydrate the patients intravenously.

### TREATMENT LOCATION
Cancer Centre and Cancer Units
ERLOTINIB (TARCEVA®) FOR NSCLC

REFERENCES:
6. NICE Guidance TA258 Available at https://www.nice.org.uk/guidance/ta258
7. NICE Guidance TA374 Available at https://www.nice.org.uk/guidance/ta374

Document Control

<table>
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<tr>
<td>Document No:</td>
<td>CRP-07-L018</td>
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<tr>
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<tr>
<td>Reviewer:</td>
<td>Chris Beck Chemotherapy Pharmacist Northern Cancer Alliance</td>
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<tr>
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<td>Steve Williamson Consultant Pharmacist Northern Cancer Alliance</td>
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<tr>
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Summary of Changes

1.2 Changed format titles to reflect new style; Added extra detail
1.3 Changed topical steroid recommendations
2.0a Document number updated. A number of drug interactions and additional administration notes added.
3.0 Document number updated to reflect latest guidance on cutaneous toxicity (reference 6) and CDF approval for 3rd line.
3.1 Protocol reviewed and reissued.
4.0 Updated indications following NICE TA374
4.1 Minor spelling/formatting updates & reissued.