

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Atezolizumab for treating locally advanced or
metastatic non-small-cell lung cancer after
chemotherapy**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using atezolizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using atezolizumab in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 24 August 2017

Second appraisal committee meeting: 13 September 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Atezolizumab is not recommended, within its CHMP opinion, for treating locally advanced or metastatic non-small-cell lung cancer in adults after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]-positive tumour).
- 1.2 This recommendation is not intended to affect treatment with atezolizumab that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for non-small-cell lung cancer after chemotherapy includes docetaxel alone, nintedanib plus docetaxel (for adenocarcinoma histology) or pembrolizumab (for tumours expressing PD-L1). Clinical trial evidence shows that overall survival with atezolizumab is longer than with docetaxel alone. There is no evidence directly comparing atezolizumab with nintedanib plus docetaxel or with pembrolizumab. Indirect analyses show that it was uncertain whether there was a survival benefit for atezolizumab compared with nintedanib plus docetaxel.

The most plausible cost-effectiveness results are higher than those NICE normally considers an acceptable use of NHS resources (£20,000 to £30,000 per quality-adjusted life year gained) for atezolizumab compared with nintedanib plus docetaxel. The estimates were also higher than is normally an acceptable use of NHS resources for end-of-life treatments for atezolizumab compared with docetaxel. Therefore atezolizumab is not recommended.

Atezolizumab, when compared with docetaxel, meets NICE's criteria to be considered a life-extending treatment at the end of life. However it does not meet both of the criteria when compared with nintedanib plus docetaxel. Although life

expectancy for people with locally advanced or metastatic non-small-cell lung cancer is less than 24 months and atezolizumab is likely to extend people's lives by more than 3 months compared with docetaxel. However it did not offer a proven extension to life of more than 3 months when compared with nintedanib plus docetaxel.

The cost effectiveness of atezolizumab was also considered only for the subgroup of people with non-small-cell lung cancer expressing the PD-L1 protein, because it may be more effective in this group than in people who do not express PD-L1. However, no estimates of cost-effectiveness for this population were provided so no recommendations can be made.

2 The technology

Atezolizumab (Tecentriq, Roche)	
Marketing authorisation/anticipated marketing authorisation	On 20th July 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product atezolizumab, intended for the treatment of locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour).
Recommended dose and schedule	1,200 mg every 3 weeks by intravenous infusion. The company submission states that patients should have treatment until loss of clinical benefit or unmanageable toxicity.
Price	The list price for atezolizumab is £3807.69 (company submission). The company has agreed a patient access scheme with the Department of Health. If atezolizumab had been recommended, this scheme would provide a simple discount to the list price of atezolizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

The condition

Atezolizumab is a potentially important option for people with locally advanced or metastatic NSCLC after chemotherapy

- 3.1 Locally advanced or metastatic non-small-cell lung cancer (NSCLC) that has progressed after chemotherapy is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms. The current outlook for patients with NSCLC whose disease has relapsed after chemotherapy is poor. The committee heard from clinical experts that people with this disease have limited treatment options, which are all associated with high toxicity. It noted that improving quality of life and even small extensions in duration of life are of considerable importance to this patient group. The committee concluded that atezolizumab is a potentially important treatment option for people with locally advanced or metastatic NSCLC after chemotherapy.

Current treatments

The options for previously treated disease are docetaxel, nintedanib plus docetaxel (for adenocarcinoma histology) and or pembrolizumab (for tumours expressing PD-L1)

- 3.2 The committee understood that platinum therapy is given as a first treatment for NSCLC in people whose tumours are not epidermal growth factor receptor (EGFR-TK)-positive, followed by docetaxel, or nintedanib plus docetaxel for people with adenocarcinoma. For people with EGFR-TK-positive tumours, treatment starts with a tyrosine kinase inhibitor, followed by platinum therapy. For people with anaplastic lymphoma kinase (ALK)-positive tumours, platinum combination therapy followed by an ALK inhibitor are the standard treatment choices. The committee was aware that NICE technology appraisal guidance now recommends [pembrolizumab](#) for treating PD-L1-positive NSCLC after chemotherapy. It heard from clinical experts that since publication of this guidance the use of pembrolizumab has been increasing and it can now be considered

standard care for this population. The committee understood that most patients would have active treatment such as pembrolizumab, docetaxel or nintedanib plus docetaxel (for adenocarcinoma). But in a small proportion of patients who decline docetaxel, or cannot not tolerate it, best supportive care may be the only option. However, the committee concluded that atezolizumab would be a treatment option for people after previous chemotherapy with or without a targeted therapy and as an alternative to docetaxel, nintedanib plus docetaxel, or pembrolizumab for PD-L1-positive disease.

Comparators

Docetaxel, docetaxel plus nintedanib and pembrolizumab (for adenocarcinoma) and pembrolizumab (for PD-L1 positive disease) are relevant comparators

3.3 The committee understood that for both second- and third-line treatment, the comparators would be docetaxel alone, nintedanib plus docetaxel for people with adenocarcinoma, pembrolizumab for PD-L1-positive disease, and best supportive care when docetaxel is not a suitable option. The committee noted that the company had included both docetaxel and nintedanib plus docetaxel as comparators in the submission, which was appropriate. But the company had not considered pembrolizumab, nivolumab, and best supportive care, which were included in the final scope. The committee considered that excluding best supportive care is reasonable because patients eligible to have atezolizumab would be fit enough to have other treatment, and it noted that nivolumab is being appraised by NICE and has not yet received a positive recommendation. The committee discussed why pembrolizumab was excluded from the company's submission, and it was aware that both pembrolizumab and atezolizumab are monoclonal antibodies targeting PD-1. It considered the company's justification that pembrolizumab has a narrower marketing authorisation (PD-L1-expressing tumours with a tumour proportion score of 1% or more) than the marketing authorisation for atezolizumab, and

that [pembrolizumab](#) may not yet be current clinical practice since publication in January 2017. The committee was disappointed that the company did not consider pembrolizumab as a comparator and would have preferred to see comparisons of atezolizumab with pembrolizumab in people whose tumours express PD-L1. The committee concluded that for the populations under consideration, the relevant comparators for this appraisal were docetaxel, nintedanib plus docetaxel for adenocarcinoma, and pembrolizumab for PD-L1-positive disease.

Clinical evidence

Atezolizumab offers a gain in survival compared with docetaxel

3.4 The key clinical effectiveness evidence for atezolizumab compared with docetaxel came from the OAK trial. This was an open-label, phase III randomised controlled trial in adults with locally advanced or metastatic NSCLC, whose disease had progressed during or after 1 platinum-containing chemotherapy regimen. The committee noted that the analyses were from a primary population (n=850) and that since then the study had recruited more participants (n=1225). The committee noted that the results showed a statistically significant median overall survival gain for atezolizumab (13.8 months; 95% confidence interval [CI] 11.8 to 15.7) compared with docetaxel (9.6 months; 95% CI 8.6 to 11.2). It considered that this was an important extension-to-life benefit for people with advanced NSCLC after chemotherapy. The committee concluded that the data could be considered for decision-making, and that atezolizumab offers a gain in survival compared with docetaxel.

PD-L1 expression

Atezolizumab is more effective than docetaxel regardless of PD-L1 expression

3.5 The committee noted that the opinion of the Committee on Human Medicinal Products for atezolizumab is for people after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor

[EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour), and it does not specify treatment based on PD-L1 expression. However, it heard from the ERG that although the company submission did not include data on all of the PD-L1 subgroups from the OAK trial, the trial results show that the higher the level of PD-L1 expression, the greater the clinical response in people with locally advanced or metastatic NSCLC after prior therapy (see table 1).

Table 1 OAK overall survival results by PD-L1 expression

Population	Number (%)	Median overall survival (months)		Hazard ratio (95% CI)
		Atezolizumab	Docetaxel	
ITT	850 (100)	13.8	9.6	0.73 (0.62, 0.87)
TC3 or IC3	137 (16)	20.5	8.9	0.41 (0.27, 0.64)
TC2/3 or IC2/3	265 (31)	16.3	10.8	0.67 (0.49, 0.90)
TC1/2/3 or IC1/2/3	463 (54)	15.7	10.3	0.74 (0.58, 0.93)
TC0 and IC0	379 (45)	12.6	8.9	0.75 (0.59, 0.96)

Abbreviations: CI, confidence interval; IC, tumour infiltrating immune cell; ITT, intention to treat; TC, tumour cell.

Note: In the OAK trial the PD-L1 expression of tumour cells and tumour infiltrating immune cells was measured using an immunohistochemistry assay. The results were grouped according to the proportion of cells stained at any intensity: TC3: ≥50%; TC2/3: ≥5%; TC1/2/3: ≥1%; TC0: <1%; IC3: ≥10%; IC2/3: ≥5%; IC1/2/3: ≥1%; IC0: <1%

The company noted that for all patients, response to atezolizumab was clinically and statistically significantly better than for docetaxel regardless of PD-L1 expression. Therefore it has positioned atezolizumab as a treatment for the whole population. The clinical experts noted that PD-L1 is not a perfect biomarker and therapies such as atezolizumab have shown benefit in people with PD-L1-positive and negative tumours. Further research is needed to develop tests that can be used alongside PD-L1 testing to determine which patients benefit most from treatments. Nevertheless, in practice there does appear to be a correlation between

PD-L1 expression levels and the degree of clinical benefit gained. The committee concluded that it was disappointed that the company did not present all relevant results by PD-L1 subgroup.

Indirect treatment comparisons

The results of the indirect treatment comparisons are uncertain

3.6 The committee was aware that the ERG had requested estimates of difference in overall survival using a reduced network of studies that contained only the comparators that were relevant to the scope, to reduce 'noise' in the analyses. Analysis of results from the full network estimated a difference in overall survival for atezolizumab (whole population) compared with nintedanib plus docetaxel (adenocarcinoma population) of 5.31 months (95% CI 2.96 to 8.17). From the reduced network the difference was 3.33 months (95% CI -0.16 to 6.74). The committee also heard from the ERG that it preferred a random effects model rather than the company's fixed effects model because it captures the uncertainty in the expected difference of overall survival better than the fixed effects model. The ERG noted that the result from the reduced network was not statistically significant and atezolizumab might not provide an increase in overall survival compared with nintedanib plus docetaxel. It explained that the estimates from the indirect treatment comparison were not robust and were difficult to interpret given the wide variety of factors that could affect the results. This includes model choice and the studies included in the network. The committee agreed to proceed with ERG's preferred network and noted the degree of uncertainty associated with all the indirect analyses.

The trial populations compared are not equivalent

3.7 The committee noted that although the company had provided comparisons for atezolizumab with nintedanib plus docetaxel, the company's base case estimates included patients without adenocarcinoma histology, which is outside nintedanib's marketing

authorisation. The committee was aware that the company had also provided estimates comparing the total trial population for atezolizumab (including people with non-adenocarcinoma histology) with the adenocarcinoma population from the nintedanib plus docetaxel trial. The committee noted that it would have preferred to have seen like-for-like comparisons of atezolizumab and nintedanib plus docetaxel in patients with adenocarcinoma histology, but in its absence, it was prepared to use the analysis that restricted the nintedanib plus docetaxel patients to just those with adenocarcinoma in its decision making.

The company's economic model

The model structure is appropriate

3.8 The committee discussed the company's cost-effectiveness evidence and its critique by the ERG. It accepted the structure of the company's economic model and considered it appropriate for decision-making.

The ERG corrected the errors in the economic model

3.9 The ERG explained that it corrected for 3 errors in the company's economic model:

- applying a different discount rate for the intervention (discount from week 1) than for the comparators (discount from year 2)
- not applying an age-related utility decrement and
- applying an inappropriate half cycle correction.

The committee accepted the corrections made to the company's economic model.

Long-term treatment effect

A lifetime treatment effect for atezolizumab is implausible

3.10 The company's model assumed that benefit from treatment with atezolizumab has a lifetime protective effect. The committee heard from

the ERG that this assumption was not supported by evidence. The ERG preferred to apply a conservative assumption whereby the treatment effect lasted for 3 years after stopping atezolizumab, and after this the effectiveness of atezolizumab is assumed to be the same as the comparators. The committee considered that there is no evidence to support a substantial continued benefit of atezolizumab after stopping treatment and the size of this effect and its duration is unknown for NSCLC. The committee concluded that although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any evidence on which it could agree a single clinically plausible scenario.

Cure rate

The mixed cure rate model and the cure rate applied are not appropriate

3.11 The company applied a 2% cure rate to the economic model, which assumes that 2% of patients in the model regain the general population's mortality rate. The company justified the cure rate using data from the National Lung Cancer Audit (NLCA) registry. However the ERG explained that there was no link between that analysis and the choice of the 2% cure fraction. It noted there is no evidence to support the use of a cure rate model and it was not aware of any NLCA registry data that suggested that there was a subgroup of NSCLC patients with different mortality rates to the whole population. The committee heard from the clinical experts that immunotherapies might be able to create a long-term durable response for a proportion of patients with lung cancer. However, there was no evidence to support this and immunotherapies have not been used long enough for this effect to be observed in clinical practice. The clinical experts also noted that the mortality rate after immunotherapy decreases after about 5 years for a proportion of patients with advanced melanoma. However, the clinical experts noted that melanoma is a different disease and it tends to respond better to immunotherapy than lung cancer. The committee agreed that the use of the cure rate model and the cure rate

applied had not been sufficiently justified and the long-term effect of immunotherapy on NSCLC was largely unknown. The committee concluded that the company's cure rate of 2% was not sufficiently supported by evidence.

Extrapolation of overall survival

Log-logistic curve creates implausibly long survival tail, and an exponential model is preferred

3.12 To estimate overall survival for atezolizumab, the company used data from OAK in which the median duration of survival follow-up was 21.4 months for atezolizumab. The company fitted a log-logistic model to the non-cured proportion (98%) of patients based on best statistical fit for the whole atezolizumab survival curve, rather than part of the curve. The plausibility of the log-logistic model was also assessed by a company advisory board of clinical experts, who stated that it was 'not implausible' for 10% of patients to be alive at 5 years. The ERG explained that the company's model assumptions led to 12% of patients being alive at 5 years, which was higher than the proportion suggested by the company advisory board. The company explained that its advisory board had assessed the suitability of the extrapolation based on the overall outcomes although the log-logistic survival curves were not presented to them. The committee considered that it was unclear how the company had arrived at the choice of a log-logistic model. It heard from the clinical experts that there is considerable uncertainty around the long-term survival benefit for patients with NSCLC after prior therapy before atezolizumab. The ERG explained that the log-logistic distribution was not robust and this is more important than the statistical fit of the model to the data. The ERGs preferred method was to use the Kaplan–Meier curve up to 19 months and then extrapolate using an exponential model, which was the best fit visually for the trial data after 19 months. The committee noted that the approaches used by the company and the ERG to extrapolate overall survival had a major impact on the results of the economic model

(see section 3.14). The committee concluded that using Kaplan–Meier data up to 83 weeks followed by extrapolation using the exponential model was a more appropriate visual fit and was more clinically plausible.

Difference in overall survival for atezolizumab compared with nintedanib plus docetaxel is uncertain

3.13 The ERG recalled its earlier conclusion that atezolizumab may not provide additional clinical benefit when compared with nintedanib plus docetaxel (section 3.6) and explained that its preferred base case assumed that atezolizumab did not provide an increase in overall survival compared with nintedanib plus docetaxel. The committee considered that the result for overall survival was not statistically significant. However it noted that this may have been due to the small sample size associated with the reduced meta-network analysis. It considered additional analyses carried out by the ERG looking at other assumptions for overall survival including:

- using the company's results from the indirect treatment comparison (overall survival gain for atezolizumab 2.86 months) and
- using the hazard ratio from the LUME-LUNG 1 trial for nintedanib plus docetaxel (overall survival gain for atezolizumab 2.16 months).

The ERG explained that these analyses were not robust; the analyses using the company's network meta-analyses were informed by studies outside of the scope and proportional hazards did not hold for the LUME-LUNG 1 trial data. The committee considered that the overall survival gain for patients treated with atezolizumab compared with nintedanib was likely to lie between the ERGs preferred assumption and the ERG additional analyses provided.

Cost-effectiveness estimates

The company's ICERs and the ERG's ICERs are very different

3.14 The incremental cost-effectiveness ratios (ICERs) for atezolizumab compared with docetaxel are reported based on the list price for atezolizumab, the ICERs using the PAS price for atezolizumab are confidential and cannot be reported here. The company's deterministic base-case ICER was £77,569 per quality-adjusted life year (QALY) gained compared with docetaxel (including corrections made by the ERG, see section 3.9), whereas the ERG's preferred deterministic ICER was £170,497 per QALY gained compared with docetaxel. The ICERs for atezolizumab compared with nintedanib plus docetaxel are based on the PAS prices for atezolizumab and nintedanib, these ICERs are confidential and reporting the exact ICERs could allow the company to back-calculate the level of the discount in the nintedanib patient access scheme. The company's deterministic base-case ICER was over £30,000 per QALY gained compared with nintedanib plus docetaxel (including corrections made by the ERG, see section 3.9), whereas the ERG's preferred deterministic ICER was over £600,000 per QALY gained.

The most plausible ICERs using the committee's preferred assumptions are high

3.15 The committee's preferred assumptions were:

- Atezolizumab overall survival estimated from Kaplan–Meier data for atezolizumab up to week 83 followed by extrapolation of trial data using an exponential model (see section 3.12).
- No cure rate assumption (see section 3.11).
- The estimated overall survival gain for atezolizumab compared with nintedanib plus docetaxel lies between 0 and 2.86 months (see section 3.6).

The committee considered the most plausible ICERs for atezolizumab were:

- £170,497 per QALY gained (compared with docetaxel), this ICER is calculated based on the list price for atezolizumab (the ICER using the PAS price for atezolizumab is confidential).
- £100,000 to £150,000 per QALY gained (compared with nintedanib plus docetaxel). The exact ICERs are confidential and cannot be reported here.

End of life

People with NSCLC have a life expectancy of less than 24 months

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The committee discussed whether life expectancy without atezolizumab would be less than 24 months. It noted the evidence presented by the company, which showed that people with NSCLC have an average life expectancy of less than 24 months (median survival was 7.5 months for stage IIIb and 3.4 months for stage IV NSCLC). The committee concluded that the short life expectancy criterion was met.

Atezolizumab compared with docetaxel meets NICE's end-of-life criteria

3.17 The committee discussed whether a survival benefit of over 3 months can be expected for atezolizumab compared with docetaxel. The committee heard that the average number of months of life gained with atezolizumab, as estimated by the company's economic model, is 3.5 months compared with docetaxel. It agreed that there was significant uncertainty in the overall survival gain. However the committee considered it reasonable to assume that the benefit is likely to exceed 3 months and concluded that atezolizumab met the end-of-life criteria for this population.

Atezolizumab compared with nintedanib plus docetaxel does not meet NICE's end-of-life criteria

3.18 The committee discussed whether a survival benefit of over 3 months can be expected for atezolizumab compared with docetaxel plus nintedanib in people with adenocarcinoma histology. The average number of months of life gained with atezolizumab, as estimated by the company's economic model, is 2.7 months compared with nintedanib plus docetaxel. The ERG considered that the size of the survival gain for atezolizumab was uncertain because there was no statistically significant difference in overall survival in the indirect analysis (3.33 months, [95% CI -0.16 to 6.74]), and therefore it assumed that the survival gain was the same for atezolizumab and nintedanib plus docetaxel. The committee considered that the overall survival gain estimated by the company was not objective or robust and concluded that atezolizumab compared with nintedanib plus docetaxel did not offer a proven extension to life of more than 3 months.

Other factors

- 3.19 No equality issues were identified.
- 3.20 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of atezolizumab.
- 3.21 The company did not highlight any additional benefits that had not been captured in the QALY.

Conclusion

Atezolizumab is not recommended

3.22 The committee concluded that the most plausible ICERs (see section 3.15) were higher than those usually considered a cost-effective use of NHS resources, even for end-of-life treatments. The cost-effectiveness evidence was highly uncertain for atezolizumab compared with nintedanib plus docetaxel. The committee was unable to make a judgement on the cost effectiveness of atezolizumab for people who have PD-L1-positive tumours, because cost-effectiveness estimates were not

provided for this subgroup. The committee did not recommend atezolizumab for routine use in the NHS for people with locally advanced or metastatic NSCLC after chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour).

4 Proposed date for review of guidance

- 4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens

Chair, appraisal committee

July 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Jessica Maloney

Technical Lead

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Technical Adviser

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ISBN: [to be added at publication]