Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Addendum to the main ERG report

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Date completed 04 October 2019

Following submission of the ERG report for this appraisal, the NICE technical team asked the ERG to clarify where possible its preferred modelling assumptions with respect to the further exploratory scenarios it had undertaken and presented in the original report. In addition, NICE were informed by a clinical expert in ALK+ NSCLC, that for those patients who progress from lorlatinib to another active treatment (60% in the company y model), the assumption that 40% would receive pemetrexed monotherapy is incorrect. The expert stated that pemetrexed is not very relevant here, and that patients would now (since TA584) progress from lorlatinib onto either PDC (50-60%) or ABCP. Since ABCP was not included as a subsequent treatment for this population in the company model, NICE asked the ERG to conduct further sensitivity analysis which varied the percentage of progressed and subsequently treated patients who receive this combination therapy upon progression. These additional scenarios are caveated by the fact that it has only been possible to incorporate the costs of this regimen and not any potential improvement in efficacy associated with it. All analyses presented in this addendum take account of the PAS for lorlatinib but assume 30% discounts for atezolizumab, pembrolizumab, and bevacizumab. Results with the actual available discounts for atezolizumab, pembrolizumab, and bevacizumab are provided in a confidential PAS appendix to this addendum.

ERG reflection on uncertain modelling assumptions

ERG preferred modelling assumptions

Following further reflection, and at the request of NICE, the ERG clarify that they prefer the following modelling assumptions:

1. Pembrolizumab as subsequent therapy should be applied at a fixed dose of 200 mg every 3 weeks in line with clinical practice. This is on the advice of the ERGs own clinical expert, corroborated by another clinical expert consulted by NICE.
2. The utility value applied for progressed disease should be either 0.59 or 0.46, lower than the value applied in the company base case. This is because the value applied in the company base case (0.65) appears to reflect health status around the time of progression on an ALK TKI, when patients may still be on treatment (Labbe et al).[1] Thus, the ERG believe it may not be suitable for reflecting average health related quality of life throughout time spent in the progressed state where patients will continue to deteriorate over time. Therefore, the ERG tends to prefer the lower values reported by Chouaid et al. for progressive disease after 2nd line or 3rd/4th line treatment; 0.59 and 0.46 respectively.[2] On balance, 0.59 represents a reasonable compromise between the company value and the lower value of 0.46 following progression on 3rd/4th line treatments.
3. No more than 50% receive subsequent therapy following PDC. This is in line with discussion in the ACD for TA584, which suggested 60% would be the upper limit for subsequent treatment following PDC, and 50% may be more appropriate.[3] We assume 60% may still be reasonable for patients treated with lorlatinib because they will have more treatment options still available.
4. No more than 40% receive docetaxel following progression on ABCP. This is also in line with committee discussions recorded in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer).[3]

The results with these assumptions all selected are provided in Table 1 below. The combined changes have a modest effect on the company ICER.

Table 1: Cost-effectiveness results with ERG preferred assumptions selected

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
ERG base case: Lorlatinib versus PDC (progressed utility value = 0.59)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,051
ERG base case: Lorlatinib versus PDC (progressed utility value = 0.46)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,289
ERG base case: Lorlatinib versus ABCP (progressed utility value = 0.59)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,892
ERG base case: Lorlatinib versus ABCP (progressed utility value = 0.46)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,268

Assumptions that the ERG remain uncertain about

1. The ERG remains concerned that the comparative efficacy (both PFS and OS) of PDC is underestimated because it is based on data from patients treated with single agent chemotherapies rather than PDC. There is evidence that PDC performs significantly better than pemetrexed monotherapy in NSCLC (see Zukin et al. 2013),[4] although not specifically in ALK+ population. Ascertaining the extent of any bias is complicated by the fact that patients in ASCEND-5, ALUR and PROFILE 1001/1005,[5-7] may have had fewer previous treatments than some in Study 1001. Patients in ASCEND-5,[5] ALUR[6] and PROFILE 1001/1005[7] had progressed after one ALK TKI (crizotinib) but had also had prior platinum-based chemotherapy. Those in Study 1001 EXP-3B:5 cohort (see company submission) had progressed following treatment with at least one second generation ALK TKI, but some had up to three or more ALK TKIs, with or without previous chemotherapy. The company claim it is possible that the single agent chemotherapy data from ALUR, ASEND-5 and PROFILE could also overestimate the comparative efficacy of PDC at the point in the pathway where lorlatinib will be used; i.e. with a previous treatment history matching that of Study1001 (EXP-3B to 5).

The trade-off between the above two arguments could benefit from wider input from clinical experts. On balance, the ERG believes that the efficacy of PDC is more likely to be underestimated than overestimated. It is of note that the PFS and OS data for single agent chemotherapy that the company used matches quite closely with PFS and OS reported by Zukin et al. for pemetrexed monotherapy as first line treatment in people with advanced NSCLC (primarily adenocarcinoma) and ECOG status 2. Further, in the RCT reported by Zukin, patients randomised to PDC had significantly improved PFS (HR = 0.46; 95%CI, 0.35-0.63) and OS (HR = 0.62; 95%CI = 0.46-0.83) compared to pemetrexed monotherapy.

2. The preferred methodological approach for comparative efficacy of PDC; independent curves with no population adjustment (due to non-proportional hazards) versus the MAIC using the EXP-3B;5 cohort. On balance the ERG prefers the company's base case approach of applying independently fitted curves (due to proportional hazards not holding), and as indicated above the ERG is more concerned about the source data used to represent PDC rather than the assumptions of the methodological approach for assessing comparative efficacy.

3. The comparative efficacy of ABCP is another major uncertainty. The company case here relies heavily on a population adjustment for ALK+ versus EGFR+ patients. However, the population adjustment hazard ratios come from comparing OS and PFS for ALK+ patients treated with single agent chemotherapy (again from ALUR, ASCEND-5 and PROFILE 1001/1005), with an EGFR+ population treated with PDC as first line treatment (IMPRESS).[8] Therefore, there is a question as to what extent the adjustment HRs reflect the inferior efficacy of the monotherapies at second or third line versus PDC at first line, rather than the different mutation status of the cohorts.

4. Time on treatment with lorlatinib, and the approach for estimating it, remain uncertain. Based on expert clinical advice, the ERG believe that patients may remain on lorlatinib for longer following progression than the average [redacted] applied in the company base case (the difference in restricted mean ToT and restricted mean PFS in Study 1001 up to [redacted] months). In the absence of more complete data to inform mean post progression ToT, the ERG tends towards favouring a fitted

parametric curve to model ToT. When considering consistency with the company's preferred lorlatinib PFS curve, the ERG further believe that the generalised gamma provides the most plausible projection of ToT out of those assessed by the company.

[redacted]Taken together, the above issues lead to substantial uncertainty surrounding the cost-effectiveness of lorlatinib versus PDC and ABCP, as demonstrated through the exploratory scenario analyses in the main ERG report.

Further sensitivity analysis surrounding the comparative efficacy of PDC versus lorlatinib

In the company's base case, there is a slight problem with the selected curves for PFS (log-logistic) and OS (log-normal) in the PDC arm [redacted]. [redacted]. This is exacerbated if the curves are adjusted upwards using hazard ratios reflecting possible improved effects of PDC versus pemetrexed monotherapy (as per the scenarios in Table 17 of the main ERG report); [redacted] The proportional hazards assumption of these scenarios may also result in implausible long-term survival in the PDC arms. The problem is worse if the second-best fitting curves are selected for PFS (Gompertz) and OS (log logistic). However, if exponential curves are selected for both PFS and OS, it becomes possible to uplift these proportionally whilst generating less implausible long-term extrapolations for PDC survival. Table 2 below shows the impact of several scenarios that do this. It indicates that the potential underestimation of PDC efficacy may be less important if PFS is underestimated to a greater relative extent than OS. This is because if PFS increases by a proportionally greater amount than OS, there is a greater proportional drop in the incremental cost than the incremental QALY for lorlatinib versus PDC. This is driven by patients spending proportionally longer in the progression free state on pemetrexed maintenance therapy.

Figure 1: Fitted PFS and OS for PDC using the log-logistic and log-normal curves respectively

Figure 2: Fitted PFS and OS for PDC using the exponential curves for both

Table 2: Cost-effectiveness scenarios with upward adjustment of the fitted exponential curves for PFS and OS on PDC

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER	% surviving at 5 years
Company base case								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,152	[redacted]
Exponential curves for PFS and OS on PDC								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,440	[redacted]
Adjustment HR for PDC PFS = 0.9; Adjustment HR for PDC OS = 0.9								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,863	[redacted]
Adjustment HR for PDC PFS = 0.8; Adjustment HR for PDC OS = 0.8								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,814	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.7								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,655	[redacted]
Adjustment HR for PDC PFS = 0.8; Adjustment HR for PDC OS = 0.9								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,076	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.8								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,755	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.9								

Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,066	[redacted]
Adjustment HR for PDC PFS = 0.46; Adjustment HR for PDC OS = 0.62 (Zukin et al. 2013)								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,263	[redacted]

Sensitivity analysis on subsequent therapy following progression on lorlatinib

This section presents a set of exploratory sensitivity analyses that varies the percentage of subsequently treated patients who receive ABCP following progression on lorlatinib. The percentage of progressed patients who receive subsequent treatment remains at 60% throughout. In addition, at the request of NICE, and based on advice from a clinical expert, pemetrexed monotherapy is replaced with PDC in the proportional distribution of subsequent treatments.

To implement the ABCP costs, the ERG used the same drug acquisition and administration costs per treatment cycle as applied in the ABCP arm of the model and multiplied these by the proportion assumed to receive this treatment and the average number of treatment cycles. These average treatment costs are then applied as one of costs in the same manner as all other subsequent treatment costs in the company's model. This required an assumption about the mean duration of treatment with ABCP following progression on lorlatinib, and to inform this the ERG assessed the mean time on ABCP in the ABCP arm of the model [redacted]). However, since it may be reasonable to expect a shorter time on ABCP as a subsequent treatment (i.e. at a later line), the mean time on treatment applied to atezolizumab monotherapy as subsequent therapy in the PDC arm (35.8 weeks) was used instead.

These analyses are all caveated by the fact that changes are only made to the costs of subsequent treatment; i.e. the selection of subsequent treatment does not influence OS. The validity of these analyses must therefore be carefully considered in terms of whether the revised subsequent treatment distributions would be expected to affect the OS curves derived from Study 1001. This depends on the relative efficacy of the modelled subsequent treatments compared to actual subsequent treatments received in Study 1001. However, the same caveats also apply to the modelling of subsequent treatments following PDC (these also do not affect the fitted OS curves for PDC) and it is uncertain if they are consistent with subsequent treatments available to participants in PROFILE 1001/1005. Results are presented in Table 3 (PDC comparison) and Table 4 (ABCP comparison) below.

Table 3: Cost-effectiveness scenarios exploring the impact of applying costs of ABCP as a subsequent therapy following lorlatinib (lorlatinib versus PDC)

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
Company base case: 60% PDC, 40% pemetrexed in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,152
100% PDC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,290
60% PDC, 40% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,591
50% PDC, 50% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,666
40% PDC, 60% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,741
50% receive subsequent treatment with 50% PDC, 50% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,555

Table 4: Cost-effectiveness scenarios exploring the impact of applying costs of ABCP as a subsequent therapy following lorlatinib (lorlatinib versus ABCP)

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
Company base case: 60% PDC, 40% pemetrexed in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,369
100% PDC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,520
60% PDC, 40% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,588
50% PDC, 50% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,855
40% PDC, 60% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,122
50% receive subsequent treatment with 50% PDC, 50% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,548

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