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BY EMAIL

9 March 2012

RE: Erlotinib for the first line treatment of EGFR-TK mutation positive mNSCLC

Dear Kate,

Thank you for giving us the opportunity to comment on the ACD for the above technology appraisal. Our response is provided below.

If any further clarification is required in order to aid the Committee's deliberations we would be more than happy to provide it.

Yours Sincerely,

[redacted]

[redacted]

The additional analyses requested

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As requested the economic model has been modified as follows:

1. A PFS HR of 1 has been applied for the indirect comparison of erlotinib and gefitinib
2. The PFS utility value estimated for erlotinib has been applied in both arms
3. Functionality has been added to enable the user to change the proportion of patients receiving erlotinib or gefitinib at day 60 (same proportion applied in both arms)

In order to allow the implementation of this 60 day proportion input within the model an 'IF' statement was placed in the model so that if the proportion of patients yet to cease treatment at day 30 was any lower than that inputted for day 60 the higher day 60 value would be used.

In order to remain consistent with the assumption of equivalent PFS utility values for each treatment it was additionally assumed that the incidence of Rash and Diarrhea in each arm was equivalent. The inclusion of the cost of these adverse would have minimal impact upon the results estimated as both AEs are relatively inexpensive to manage and occur at approximately the same rate for both agents.

The proportion of patients 'activating' the gefitinib PAS and receiving erlotinib on day 60 of the model was varied in the range requested.

These results demonstrate that erlotinib is cost-effective compared to gefitinib so long as more than **91%** of patients 'activate' the gefitinib PAS (i.e. more than 91% of patients are still receiving gefitinib on day 60 of their treatment). Given the evidence currently available (summarized in the bullet points below) this appears highly likely:

- In all four of the gefitinib RCTs the proportion of patients in PFS on day 60 was above 91% (IPASS = **95%**, WJTOG = **96%**, First-SIGNAL = **92%**, NEJSG = **92%**)
- A review of EU patient case records (n=273, Kantar) demonstrates that in EU clinical practice **99**% of patients who receive gefitinib do so for more than 60 days (**100%** in the 51 UK samples)
- This is further supported by a patient case note audit undertaken in 8 English centers which found that 97% of patients 'activated' the gefitinib PAS (n=32) (medeConnect, 2012)
- Clinical experts in the first Committee meeting for this appraisal indicated that *'nearly all'* patients remain on treatment beyond 60 days (a view shared by our own clinical advisors)

Table 1: Additional analyses requested in ACD

Proportion of patients receiving erlotinib or gefitinib on day 60	Gefitinib Drug Costs	Gefitinib PAS Costs	Erlotinib Drug Cost	Incremental Cost (E vs G)	Incremental QALYs (E vs G)	Direct Budget Impact	Indirect Savings	Net Budget Impact of Approval
1	£12,200	£448	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.99	£12,078	£447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.98	£11,956	£447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.97	£11,834	£446	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.96	£11,712	£445	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.95	£11,590	£445	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.94	£11,468	£444	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.93	£11,346	£443	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.92	£11,224	£443	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.91	£11,102	£442	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.9	£10,980	£442	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.89	£10,858	£441	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.88	£10,736	£441	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.87	£10,614	£441	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.86	£10,492	£440	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.85	£10,370	£440	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.84	£10,248	£439	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.83	£10,126	£439	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.82	£10,004	£439	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.81	£9,882	£438	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.8	£9,760	£438	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

The assumption that erlotinib and gefitinib are associated with equal time in PFS

We acknowledge the difficulty in assessing the cost-effectiveness of erlotinib relative to gefitinib (primarily due to the lack of evidence on the efficacy of gefitinib in Caucasian patients and the complexity of the gefitinib patient access scheme); however the assumption that erlotinib and gefitinib are associated with equal time in PFS appears unnecessarily pessimistic towards erlotinib.

The evidence base available indicates that whilst the two treatments may be *similar*, erlotinib is likely to be modestly more effective than gefitinib. Whilst the above analyses demonstrate that approval of erlotinib is a cost-effective use of NHS resources even if it is assumed that erlotinib and gefitinib are associated with equal time in PFS, we believe this assumption is not reflective of the evidence available.

A comparison of erlotinib and gefitinib in comparable patient populations

Whilst a comparison of erlotinib and gefitinib based upon the EURTAC study is subject to clear heterogeneity between the European EURTAC study and the East Asian gefitinib RCTs (an issue raised in the ACD), this is not the case for a comparison of East Asian OPTIMAL and the gefitinib RCTs. Each of these studies were broadly comparable (to the extent that the IPASS and OPTIMAL RCTs were conducted in largely the same centres).

Table 2: Comparison of erlotinib/gefitinib in comparable patients

	PFS HR (Gefitinib or Erlotinib vs Doublet Chemotherapy)	Doublet Chemotherapy Median PFS	Gefitinib Median PFS	Erlotinib Median PFS
OPTIMAL	0.16 {0.11, 0.26}	4.6 months	-	13.7 months
IPASS	0.48 {0.36, 0.64}	6.3 months	9.5 months	-
WJTOG3405	0.49 {0.34, 0.71}	6.3 months	9.2 months	-
NEJSG002	0.30 {0.22, 0.41}	5.4 months	10.8 months	-
First-SIGNAL	0.61 {0.31, 1.22}	6.7 months	8.4 months	-

These results suggest strongly that erlotinib is more effective than gefitinib in the treatment of East Asian patients. Whilst it is not possible to conduct such an analysis in Caucasian patients (as the manufacturer of gefitinib has not completed a study of gefitinib in this patient population) this evidence is highly suggestive of erlotinib having an efficacy advantage over gefitinib when studied in patients with similar characteristics.

The Paz-Ares pooling and resultant conclusion of the EMA

The hypothesis of the superiority of erlotinib is also supported by the pooling of phase 2 data undertaken by Paz-Ares et al (see pages 170 and 171 of our submission). The Paz-Ares analysis formed part of the regulatory package submitted to the EMA in support the application to extend erlotinib's use to the first line use of EGFR M+ patients. The EPAR issued by discusses the Paz-Ares analysis as follows:

"In the analysis of the data provided in the meta-analysis by Paz-Ares et al, and although there appear to be some gaps in the funnel plots, (which could be a chance finding due to the small number of studies or could be indicative of publication bias) the larger studies lie closer to the vertical reference lines (pooled median PFS) in the plots than the smaller studies and these references are in support of an ***increasing trend in median PFS with chemotherapy-gefitinib-erlotinib****. Therefore, even in presence of a publication bias, it appears unlikely that it would affect the conclusion of* ***increasing median PFS with erlotinib compared to chemotherapy or gefitinib****. This is also supported by the forest plots."*

In light of this analysis, the resultant conclusion of the EMA and the comparison of erlotinib and gefitinib based upon the IPASS and OPTIMAL studies it appears unreasonably pessimistic to assume that erlotinib and gefitinib are associated with equivalent time in PFS, even though we accept that in the absence of a head-head study the magnitude of any superiority .of erlotinib over gefitinib remains uncertain

Whilst we have presented the analyses requested in the ACD in which it was assumed PFS is equivalent for both agents we believe the indirect PFS HR of 0.82 (and resultant median PFS gain of four weeks) applied in the base-case is the still the most reasonable value to use in a base-case analysis.

It should be noted that this HR is more conservative than the 0.67 {0.46, 0.96} derived using the indirect comparison suggested by LR*i*G in their ERG report addendum (EURTAC/OPTIMAL vs WJTOG3405/NEJSGS/First-SIGNAL). The ICER estimated using this approach is £16,632.

Conclusions

If more than 91% of patients 'activate' the gefitinib PAS, erlotinib is cost-effective ([redacted]) compared to gefitinib. This appears highly likely given the evidence currently available (be that from the RCT evidence, audit of real-world patient case notes or expert opinion). NICE approval of erlotinib as an option offers the NHS access to another EGFR TKI in a first line setting [redacted].

Approval of erlotinib would grant:

- Clinicians the opportunity to utilize an EGFR TKI with demonstrated efficacy in Caucasian patients
- Pharmacists the ability to reduce the burden associated with dispensing an EGFR TKI (via use of the simple erlotinib PAS rather than the complex gefitinib PAS)
- Clinicians the opportunity to use an EGFR TKI that can be flexibly dosed (something not possible with gefitinib) in response to patient needs
- Patients and clinicians *choice* to determine the treatment *they* believe is most appropriate without an increased burden on the NHS

If the wider impacts of the PAS are considered in light of the advantages highlighted above and the results detailed in Table 1 the case for NICE approval of erlotinib appears strong.