LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy [ID970]

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1 BACKGROUND

As part of the Single Technology Appraisal (STA) process, the company (Roche) has submitted additional information (January 2018 company submission [CS][1]) in response to the second Appraisal Consultation Document (ACD2[2]) issued by the National Institute for Health and Care Excellence (NICE) for the appraisal of atezolizumab for treating advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy [ID970].

Within the company's original submission (February 2017 CS[3]), the main source of direct efficacy evidence used in the company model was data from the OAK trial[4,5] primary population. The OAK trial is an open-label, multicentre, randomised controlled trial (RCT) designed to investigate the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC whose disease has progressed during or following a platinum-containing regimen. The company carried out fractional polynomial (FP) indirect treatment comparisons (ITCs) to provide estimates of the effectiveness of atezolizumab versus nintedanib+docetaxel and atezolizumab versus pembrolizumab.

The Evidence Review Group (ERG) identified a number of weakness and areas of uncertainty relating to the evidence presented in the February 2017 CS.[3] These concerns were set out in the original ERG report[6] and, for information, are provided in Appendix 1.

The OAK trial data provided in the February 2017 CS[3] relate to the primary population (atezolizumab arm=425 patients, docetaxel arm=425 patients). Following the interim analysis of data from the POPLAR trial[7,8] (an open-label, multi-centre phase II RCT designed to investigate the efficacy and safety of treatment with atezolizumab versus docetaxel), the OAK trial population size was increased to ensure that at least 220 patients with programmed death-ligand 1 (PD-L1) tumour cell/ tumour-infiltrating immune cell (TC/IC) 3 (assuming a 20% prevalence) were enrolled. In total, 1225 patients were randomised (614 to the atezolizumab arm and 611 to the docetaxel arm). The primary population (n=850), plus the additional 375 patients, is known as the secondary population.

2 COST EFFECTIVENESS

The company considers (January 2018 CS[1]) that the data from the primary population (data cut-off date July 2016) are the appropriate data for decision making as these data were used in the pre-specified analysis (that provided sufficient power to test the co-primary end points), were the basis for regulatory approval, and are more robust because the results are less confounded by treatment switching compared with results generated from analyses of data from the secondary population (data cut-off date January 2017). The company has, therefore, continued to use data from the primary population in their economic model. This means that

the cost effectiveness results presented by the company in response to ACD2[2] have been developed using the same OAK trial effectiveness data that were used to generate the cost effectiveness results presented in the February 2017 CS.[3] The ERG also highlights that the only structural changes to the company model provided as part of the company response to ACD2[1,13] have been those required to facilitate a comparison of the cost effectiveness of treatment with atezolizumab versus pembrolizumab (an analysis that was not included in the February 2017 CS[3]). The ERG considers that that the changes made by the company to their model are technically correct.

2.1 The all-comers population

The February 2017 CS[3] base case cost effectiveness results relate to the primary population of the OAK trial and are undifferentiated by tumour histology or level of PD-L1 expression.

Within the January 2018 CS,[1] the company has provided cost effectiveness results for the comparison of atezolizumab versus docetaxel in the all-comers population. The company's incremental cost effectiveness ratios (ICERs) are [redacted] per quality adjusted life year (QALY) gained when overall survival (OS) data have been adjusted for treatment switching and [redacted] per QALY gained when no adjustments for treatment switching have been made. The ERG, however, considers that docetaxel would only be prescribed to patients in the TC/IC 1/2/3 subgroup (54% of the all-comers population) if it was determined that immunotherapy was not an appropriate treatment. Pembrolizumab (TA428[9]) is recommended for the treatment of patients with PD-L1 positive NSCLC who have had at least one prior chemotherapy. The ERG, therefore, considers that the ICER per QALY gained for the comparison of atezolizumab versus docetaxel for the OAK trial all-comers population is not relevant to this appraisal.

The ERG highlights that nintedanib+docetaxel is also a treatment option for a subgroup of patients included in the OAK trial (patients with NSCLC of adenocarcinoma histology [**TA347**[10]]) and that, within the original ERG report:[6]

- the ERG's preferred ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel (using list prices for both treatments) was greater than £1million per QALY gained
- the ERG expressed concerns that, when comparing the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel, it might not be appropriate to consider atezolizumab as an End of Life treatment.

The ERG also highlights that there is uncertainty about the size of the population that currently receives treatment with nintedanib+docetaxel.

Company estimates of atezolizumab versus nintedanib+docetaxel, presented at the third AC meeting and generated using PAS prices can be found in Confidential Appendix 5.

2.2 TC/IC 0 subgroup

The company's ICER for the comparison of the cost effectiveness of atezolizumab versus docetaxel for the TC/IC 0 subgroup is [redacted] per QALY gained. The ERG highlights that the magnitude of this ICER per QALY gained (>£50,000) indicates that, even when calculated using the patient access scheme (PAS) price for atezolizumab and assuming adherence to NICE End of Life criteria,[11] atezolizumab is unlikely to be considered a cost effective option for this subgroup.

2.3 TC/IC 1/2/3 subgroup

The company's estimated ICER, for the TC/IC 1/2/3 subgroup, for the comparison of treatment with atezolizumab versus docetaxel is [redacted] per QALY gained. Within the January 2018 CS[1] (p10), the company states that, since the publication of NICE guidance in January 2017 (TA428[9]), pembrolizumab has become standard of care for patients with PD-L1 positive NSCLC who have received prior chemotherapy. The ERG considers that the ICER per QALY gained for the comparison of the cost effectiveness of atezolizumab versus docetaxel in this subgroup is, therefore, not relevant to the appraisal.

Within the December 2017 CS,[13] the company presented results from FP ITCs undertaken to compare the effectiveness of atezolizumab (TC/IC 1/2/3) versus pembrolizumab (tumour proportion score [TPS] ≥1%) using data from the OAK and KEYNOTE-010[12] trials. Analyses were undertaken with, and without, treatment switching adjustments having been made to docetaxel arm data. Results show, for both PFS and OS, that treatment with atezolizumab is non-inferior to pembrolizumab irrespective of adjusting for treatment switching. The ERG highlights that a range of input parameters could be used in the analyses and that it is difficult to identify the most appropriate combination of factors and, therefore, it is difficult to interpret results from the FP ITCs. In addition, as results from the company's FP ITCs show treatment with atezolizumab to be non-inferior to pembrolizumab (in terms of survival), the ERG was surprised to note that the company's QALY estimates for this comparison generally suggest that, over a patient lifetime, treatment with [redacted].

It is not currently possible to directly (or, with any confidence, indirectly) compare the effectiveness of atezolizumab versus pembrolizumab in patients whose tumours exhibit a level of PD-L1 expression. However, for completeness, the ERG has presented available comparable baseline characteristics, summary adverse event (AE) incidence data and survival results from the OAK and KEYNOTE-010 trials in Section 3 of this report.

Company estimates of atezolizumab versus pembrolizumab, presented at the third AC meeting and generated using PAS prices can be found in Confidential Appendix 5.

2.4 Other issues

The ERG highlights that:

- when compared with pembrolizumab, treatment with atezolizumab may not deliver an extension to life of ≥3 months (and, therefore, may not be considered an End of Life treatment)
- PAS prices are in place for atezolizumab, nintedanib, and pembrolizumab.

3 ATEZOLIZUMAB AND PEMBROLIZUMAB: COMPARATIVE INFORMATION

This section provides structured summaries to facilitate comparison between baseline characteristics and trial results of participants in the OAK trial (the TC/IC 1/2/3 subgroup) and KEYNOTE-010 (TPS ≥1%) trials. The KEYNOTE-010 trial data have been extracted from the ID840 (TA428[9]) CS and relate to two arms of that trial: the docetaxel arm and the pembrolizumab 2 mg/kg Q3W (every 3 weeks) arm. Tables facilitating comparison of baseline characteristics, main trial results and AEs are included in this section. In addition, OS and progression-free survival (PFS) Kaplan-Meier (K-M) data from the two trials are presented in graphs to allow comparison of survival over time.

3.1 Characteristics of patients enrolled in the OAK trial

The key baseline characteristics of patients included in the OAK and KEYNOTE-010 trials are provided in **Error! Reference source not found.**.

The ERG considers that the baseline characteristics of the OAK trial intention-to-treat (ITT) population are generally well balanced across the two treatment arms. In addition, clinical advice to the ERG is that the patients recruited to the OAK trial can be considered to be broadly representative of patients with advanced NSCLC, treated in the NHS, albeit slightly younger and fitter. The company states that the baseline characteristics of the TC/IC 1/2/3 subgroup are generally consistent with those of the primary population and generally balanced between arms. Demographic and baseline characteristics of the TC/IC 1/2/3 subgroup with a difference of ≥5% are shown in Table 2.

Table 1 OAK and KEYNOTE-010 trials: participant demographic and baseline characteristics

	OAK trial primary population)		KEYNOTE-010 trial	
	Atezolizumab (1200 mg Q3W) N=425	**Docetaxel (75 mg/m² Q3W) N=425**	**Pembrolizumab (2 mg/kg Q3W) N=339**	**Docetaxel (75 mg/m² Q3W) N=309**
Male n (%)	261 (61)	259 (61)	212 (61.6)	209 (60.9)
Mean months from initial diagnosis to randomisation (sd)	21.04 (21.45)	20.06 (23.0)		
Age				
Age, years, median (range)	63.0 (33.0 to 82.0)	64.0 (34.0 to 85.0)	62.1 (29 to 82)	61.6 (33.0 to 82.0)
<65 years, n (%)	235 (55)	218 (51)	201 (58.4)	209 (60.9)
≥65 years, n (%)	190 (45)	207 (49)	143 (41.6)	134 (39.1)
ECOG PS, n (%)				
0	155 (36)	160 (38)	112 (32.6)	116 (33.8)
1	270 (64)	265 (62)	22.9 (66.6)	224 (65.3)
Histology				
Non-squamous	313 (74)	315 (74)	240 (69.8)	240 (70.0)
Squamous	112 (26)	110 (26)	76 (22.1)	66 (19.2)
Current disease status (%)				
Locally advanced	29 (7)	19 (5)	21 (6.1)	22 (6.4)
Metastatic*	396 (93)	406 (95)	315 (91.6)	312 (91.0
Number of prior therapies n (%)				
1	320 (75)	320 (75)	243 (70.6)	235 (68.5)
2	105 (25)	105 (25)	66 (19.2)	75 (21.9)
Smoking status n (%)				
Never	84 (20)	72 (17)	63 (18.3)	67 (19.5)
Current/previous	341 (80)	353 (83)	279 (81.1)	269 (78.4)
Missing			2 (0.6)	7 (2.0)
Metastases				
Number of metastatic sites at enrolment, mean (sd)	2.89 (1.43)	2.97 (1.32)		
Confirmed metastases at enrolment n (%)				
Brain	38 (9)	47 (11)	56 (16.3)	48 (14.0)
PD-L1 expression				
TC3 or IC3, n (%)	72 (16.9)	65 (15.3)	-	-
TC2/3 or IC2/3, n (%)	129 (30.4)	136 (32.0)	-	-
TC1/2/3 or IC1/2/3, n (%)	241 (56.7)	222 (52.2)	-	-
TPS 1-49%	-	-	205 (59.6)	191 (55.7%)
TPS ≥50%	-	-	139 (40.4)	152 (44.3)

* KEYNOTE-010 trial: stage IIIb and IV
ECOG PS=Eastern Cooperative Oncology Group performance score; IC=immune cell; PD-L1=programmed death-ligand 1; sd=standard deviation; TC=tumour cell
Source: February 2017 CS, Table 24 and Table 26 and ID840 (TA428) CS, Table 17

Table 2 OAK trial TC/IC 1/2/3 subgroup (primary population): demographic and baseline characteristics with difference of ≥5% between treatment arms

Baseline demographic characteristic	Atezolizumab (n=72)	Docetaxel (n=65)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: OAK trial CSR, Table 17

3.2 Results from the OAK trial (TC/IC 1/2/3 subgroup) and the KEYNOTE-010 trial

Survival results (OS, PFS) and response rates from the OAK (TC/IC 1/2/3 subgroup) and KEYNOTE-010 trials are shown in Table 3, with digitised K-M curves for OS and PFS shown in **Error! Reference source not found.** and **Error! Reference source not found.** respectively. The data seem to suggest better OS in the atezolizumab arm of the OAK trial TC/IC 1/2/3 subgroup) than in the pembrolizumab arm of the KEYNOTE-010 trial, with similar PFS. However, when interpreting these results, survival of patients in the docetaxel arms of the two trials should be taken into account, and the ERG highlights that, compared with results from the OAK trial, median PFS was higher, and median OS was lower, in the docetaxel arm of the KEYNOTE-010 trial.

Table 3 Results from the OAK and KEYNOTE-010 trials

Endpoint	OAK trial (Primary population: TC/IC 1/2/3 subgroup)		KEYNOTE-010 trial	
	Atezolizumab (1200 mg Q3W) [redacted]	Docetaxel (75 mg/m^2 Q3W) [redacted]	Pembrolizumab (2 mg/kg Q3W) N=339	Docetaxel (75 mg/m^2 Q3W) N=309
PFS (BICR/IRC)				
Median, months (95% CI)	[redacted]	[redacted]	3.9 (3.1 to 4.1)	4.0 (3.1 to 4.2)
HR (95% CI)	[redacted]		0.88 (0.73 to 1.04) p=0.06758	
PFS rate at 12 months (%)			18%	9%
OS				
Median, months (95% CI)	[redacted]	[redacted]	10.4 (7.4 to 11.9)	8.5 (7.5 to 9.8)
HR (95% CI)	[redacted]		0.71 (0.58 to 0.88) p=0.00076	
12 month OS rate (%)			43	35
ORR (BICR/IRC)				
Responders, n (%) (95%CI)	[redacted]	[redacted]		
Confirmed ORR (95% CI)			18.0% (14.1 to 22.5)	9.3% (6.5 to 12.9)
Time to response				
Median (range), days			65 (38 to 217)	65 (41 to 250)
Responders	[redacted]	[redacted]		
Response duration (BIRC/IRC)				
Median (range), days			NR (20+ to 610+)	189 (43+ to 268+)
Median, months (95% CI)	[redacted]	[redacted]		
% of responder ongoing among responder			73%	43%

*stratified HR
HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival;
Source: OAK trial CSR, Table 1 and ID840 (TA428) CS, Table 20

[redacted]

[redacted]

3.3 OAK trial OS by level of PD-L1 expression

The OS data from the OAK trial, for PD-L1 subgroups, were published in January 2017.[5] The ERG has reproduced these results for information (Table 4).

Table 4 OAK trial (primary population): OS results

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

CI=confidence interval; HR=hazard ratio; IC=immune cell; ITT=intention to treat; OS=overall survival; TC=tumour cell
Source: Rittmeyer[5]

3.4 Adverse events reported in the OAK and KEYNOTE-010 trials

The ERG highlights that comparison of summary AE incidences from the OAK and KEYNOTE-010 trials suggest that, in general, for the populations of interest, experience of AEs in both trials appears to be broadly similar, with the exception of the incidence of adverse events of special interest (AESI) in the docetaxel arms of the two trials and, but to a lesser extent, the incidence of AESIs in the intervention arms of the two trials.

Table 5 OAK and KEYNOTE-010 trials: summary of adverse events

Adverse event type	OAK trial (safety evaluable population: TC/IC 1/2/3)		KEYNOTE-010 trial (APaT population)	
	Atezolizumab (1200 mg Q3W) n=345	Docetaxel (75 mg/m^2 Q3W) n=319	Pembrolizumab (2 mg/kg Q3W) N=339	Docetaxel (75 mg/m^2 Q3W) N=309
One or more AE, n (%)			331 (97.6)	297 (96.1)
Treatment/drug related AE, n (%)	[redacted]	[redacted]	215 (63.4)	251 (81.2)
Grade 3 to 4 AE (%)	[redacted]	[redacted]		
Grade 3 to 5 AE, n (%)	[redacted]	[redacted]	158 (46.6)	173 (56.0)
Grade 3 to 5 drug-related AE, n (%)	[redacted]	[redacted]	43 (12.7)	109 (35.3)
Treatment-related Grade 3 to 4 AEs, n (%)	[redacted]	[redacted]		
Grade 5 AEs, n (%)	[redacted]	[redacted]		
Treatment-related Grade 5 AEs, n (%)	[redacted]	[redacted]		
SAE, n (%)	[redacted]	[redacted]	115 (33.9)	107 (34.6)
Treatment/drug-related SAE, n (%)	[redacted]	[redacted]	32 (9.4)	42 (13.6)
Death, n (%)	[redacted]	[redacted]	17 (5.0)	15 (4.9)
Death due to drug-related AE, n (%)	[redacted]	[redacted]	3 (0.9)	5 (1.6)
Discontinued due to AE, n (%)	[redacted]	[redacted]	28 (8.3)	42 (13.6)
Discontinued due to drug-related AE, n (%)	[redacted]	[redacted]	15 (4.4)	31 (10.0)
Discontinued due to SAE, n (%)	[redacted]	[redacted]	24 (7.1)	19 (6.1)
Discontinued due to drug-related SAE, n (%)	[redacted]	[redacted]	11 (3.2)	11 (3.6)
AESI, n (%)	[redacted]	[redacted]	69 (20.4)	13 (4.2)
Grade 3 to 4 AESI	[redacted]	[redacted]		
Grade 3 to 5 AESI			19 (5.6)	4 (1.3)

AE=adverse event; APaT=all patients as treated; AESI=adverse events of special interest; SAE=serious adverse event;
Source: OAK trial CSR, Table 90 and ID840 (TA428) CS, Table 53 and Table 57

3.5 Treatment costs

The cost of treatment can be estimated taking into account time on treatment, treatment frequency and cost per dose.

As treatment with both atezolizumab and pembrolizumab is continued until disease progression or unacceptable toxicity, trial PFS K-M data act as a reasonable proxy for time on treatment. Data in **Error! Reference source not found.** suggest that time on treatment for patients treated with these drugs is likely to be similar. Moreover, the frequency with which

patients receive both drugs is the same (Q3W). However, atezolizumab is administered as a 1200 mg flat dose, whilst the pembrolizumab dose is 2 mg/kg of body weight. The list price cost of one dose of atezolizumab is £3,808 and the list price cost of one dose of pembrolizumab (estimated based on the mean weight of patients participating in the OAK trial [72kg]) is £3,787. However, PAS prices are in place for both drugs. Furthermore, treatment with pembrolizumab is only permitted for a period of 2 years; data from the OAK trial TC/IC 1/2/3 subgroup indicate that, at 128 weeks, 11.1% of that subgroup were still receiving atezolizumab. The actual lifetime cost differential between treatment with atezolizumab and treatment with pembrolizumab is, therefore, unclear.

4 OVERALL CONCLUSIONS

Within the February 2017 CS,[3] the company provided cost effectiveness estimates for the comparison of treatment with atezolizumab versus docetaxel for the primary population of the OAK trial. The ERG considers that this approach is inappropriate as there are a number of treatment options available for the population participating in the OAK trial, depending on tumour histology and level of PD-L1 expression.

The company's cost effectiveness estimate for the comparison of treatment with atezolizumab versus docetaxel (one of the options that is relevant for patients whose tumours demonstrate no level of PD-L1 expression), for the TC/IC 0 subgroup is [redacted] per QALY gained (calculated using the PAS price for atezolizumab).

There is no direct evidence available to facilitate a comparison of the effectiveness of atezolizumab versus pembrolizumab (one of the options that is relevant to patients whose tumours demonstrate a level of PD-L1 expression) and the ERG considers that results generated by the company's FP ITCs are difficult to interpret. Simple comparisons of baseline characteristics, incidence of AEs, PFS and OS results from the atezolizumab arm of the OAK trial (TC/IC 1/2/3 subgroup) and the pembrolizumab (2 mg/kg Q3W) arm of the KEYNOTE-010 trial suggest that treatment with atezolizumab and pembrolizumab may be similar. However, the ERG highlights that care needs to be taken when drawing conclusions as the median OS of the docetaxel arm of the KEYNOTE-010 trial is lower than that of the docetaxel arm of the OAK trial (primary population: TC/IC 1/2/3).

The ERG has estimated the cost per dose of treatment with pembrolizumab and compared this with the actual cost per dose of treatment with atezolizumab but considers that the lifetime cost differential between the two treatments is unclear.

5 REFERENCES

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6 APPENDICES

6.1 Appendix 1

6.1.1 Weaknesses and areas of uncertainty

Weaknesses and areas of uncertainty relating to the evidence presented in the February 2017 CS[3] were included in the original ERG report[6] and have been reproduced in this appendix.

Clinical evidence

- the company should have included pembrolizumab as a comparator
- only investigator-assessed PFS results are available from the OAK and POPLAR trials
- the ERG considers that the company should have included full subgroup analyses of effectiveness and cost effectiveness by levels of PD-L1 expression
- the PFS and OS HRs from OAK and POPLAR trial data were calculated using a pre-specified method that relies on an assumption that hazards are proportional. However, as demonstrated by the company, this assumption does not hold and therefore OS and PF HRs must be interpreted with caution
- the company approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) which means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results
- the FP ITC results are difficult to interpret
- the company's criteria for assessing the presence of heterogeneity in the ITC analyses are inappropriate
- clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

Cost effectiveness evidence

- the ERG identified three model construction errors: incorrect application of discounting, absence of age-dependent utility decrements and incorrect use of a half-cycle correction to TTD data
- the company's approach to modelling of OS for patients treated with atezolizumab used a mixed cure-rate model; however, there is insufficient evidence for the application of a cure-rate and the value used for the cure-rate was not justified by the company the company's approach to modelling OS for patients treated with atezolizumab is implausible as it resulted in survival rates that, at some points, were higher than that of the UK general population
- the company assumed a lifetime duration of treatment effect for atezolizumab, an approach that has been criticised by a previous NICE Appraisal Committee when assessing an immunotherapy for the treatment of patients with advanced or metastatic NSCLC
- confidence in modelling OS for patients receiving docetaxel by adjusting the OS atezolizumab model by hazard rates generated by the company's ITC is limited by the

ERGs concerns relating to the company's FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal

- confidence in modelling OS for patients receiving nintedanib+docetaxel by adjusting the OS atezolizumab model by the hazard rates generated by the company's ITC is limited by concerns relating to identifying the most relevant FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal and that the FP ITC was not limited to patients with adenocarcinoma histology.