NICE National Institute for Health and Care Excellence

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Chair's presentation

2nd appraisal committee meeting

Committee D, 20th March 2019 (previous meeting 17th January 2019)

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ERG: Southampton Health Technology Assessments Centre

NICE technical team: Emily Eaton Turner, Caron Jones

Company: Roche

Preview of key issues

- Does the committee agree with the company's new base case with respect to:
  - range of 46.6% to 60% of people receiving subsequent therapy
  - proportion of people receiving subsequent therapy being the same after treatment with atezolizumab combination and pemetrexed combination
  - 69% of people receiving pembrolizumab and 31% of people receiving atezolizumab as a subsequent therapy following pemetrexed combination
- Effect of updated PAS for bevacizumab on ICER
  - What is the most plausible ICER?

[redacted]

Recommendation in Appraisal Consultation Document (ACD)

‘Atezolizumab plus bevacizumab, carboplatin and paclitaxel is **not recommended**, within its anticipated marketing authorisation, for untreated metastatic non-squamous non-small-cell lung cancer (NSCLC) or for previously treated (with targeted therapy) epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC in adults.’

[redacted]

Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel *Tecentriq, Roche*

Marketing authorisation	Indicated in adults for treating untreated metastatic non-squamous non-small cell lung cancer or after targeted therapies in people with EGFR mutant or ALK-positive non-small cell lung cancer	
Administration & dose	**Atezolizumab**: 1,200 mg	**Bevacizumab:** 15 mg/kg
	Carboplatin: area under curve of 6 mg/mL/min*	**Paclitaxel:** 200 mg/m^2*
	*during induction phase, 4 or 6 cycles lasting 21-day only all by intravenous infusion every 3 weeks **for 2 years maximum in economic model**	
Mechanism of action	**Atezolizumab**: directly & selectively binds to PD-L1 **Bevacizumab:** binds to VEGF **Carboplatin:** alkylating chemotherapy **Paclitaxel:** taxane chemotherapy	

Committee's considerations in the appraisal consultation document (1)

Issue	Committee's consideration	ACD
Relevant comparator	Pemetrexed plus carboplatin or cisplatin, with pemetrexed maintenance	3.2
ECOG performance status	Atezolizumab combination is only a treatment option for people who are well enough (ECOG PS 0 or 1)	3.4
Clinical evidence	IMpower150 trial is generalisable to UK practice	3.7
Clinical effectiveness (compared with pemetrexed with platinum drug with pemetrexed maintenance)	• Atezolizumab combination improves OS and PFS in ITT population • EGFR- or ALK-positive subgroup in IMpower150 is small, no biological reason for combining the groups & survival data are immature	3.8 3.9
Indirect treatment comparison	• IMpower150 does not include any comparator treatments used in clinical practice • Company's approach was appropriate	3.10 3.11
Network meta-analysis	PARAMOUNT should not be included in network	3.12

[redacted]

Committee's considerations in the appraisal consultation document (2)

Issue	Committee's consideration	ACD
Model structure	Acceptable for decision making	3.13
Clinical data in economic model	Results for the ITT network meta-analysis that excludes PARAMOUNT are appropriate to include in the model for all populations	3.14
Extrapolation of OS	Exponential and Weibull are both acceptable	3.15
Long-term overall survival estimates for EGFR- or ALK-positive subgroup	• 5-year OS estimates are not credible • Only 13 events in the atezolizumab combination arm	3.16
Stopping rule	Including a 2-year stopping rule is acceptable	3.17
Duration of treatment benefit	A 3-year treatment effect from when treatment is stopped is acceptable for decision making	3.18
Proportion receiving subsequent therapy	• Assumption that 100% is not appropriate • Estimate 30% to 60% is more appropriate	3.20 3.21

*

[redacted] * Company amended its approach in response to the ACD

Committee's considerations in the appraisal consultation document (3)

Issue	Committee's consideration	ACD
Types of subsequent therapy	• Docetaxel after atezolizumab combination • Immunotherapy after pemetrexed combination • Nivolumab (in CDF) and docetaxel are not appropriate to include as options after pemetrexed combination	3.5 3.6 3.21 *
Disutility for treatment-related AEs	Reasonable to include	3.22
End of life criteria	Met; life expectancy with standard care less than 24 months & extension to life >3 months	3.26 3.27
Innovation	May be innovative but no additional evidence of benefits that had not been captured	3.29
Cancer Drugs Fund	Did not acknowledge any possibility that clinical uncertainty could be addressed through data collection	3.31
Incremental cost-effectiveness ratio (ICER)	Most plausible ICER above £50,000 per QALY gained	3.25

[redacted] * Company amended its approach in response to the ACD

ACD Consultation

ACD consultation responses

- Consultee comments from:
  - Roche Products Ltd (the company)
  - Department of Health and Social Care – no comment response

- No commentator or web comments

[redacted]

Responses to consultation – company (Roche)

- **NICE committee focus should be on the ITT comparison** of atezolizumab combination versus pemetrexed plus a platinum drug with pemetrexed maintenance
- Agree, EGFR- or ALK-positive NSCLC **subgroup in IMpower150 is small** (~8% EGFR-positive and ~3% ALK-positive) but note **aligned with rates seen in UK clinical practice**
- **Realistic to combine EGFR- and ALK- positive groups** into one subgroup
- Atezolizumab combination is a treatment option for people with brain metastases → IMpower150 did not exclude them but few were included in the trial
- Company used **most conservative approach when extrapolating the survival data** for the EGFR- or ALK-positive subgroup → not noted in ACD
- Agree with ERG approach to **use relative effect from the ITT NMA to model long-term survival for the subgroups**
- OS estimates in ERG base case for EGFR- or ALK-positive subgroup are conservative and credible
- Agree **100% of people receiving subsequent therapies does not reflect clinical practice**
- Agree with NICE-preferred assumptions for appropriate subsequent therapies
- **Updated patient access scheme discount submitted for bevacizumab**

(see later slides for further details)

[redacted]

Committee preference and company response (1)

Committee preference	Company response
ERG's corrections for discrepancies in company model	**Accepted –** company also updated for another inconsistency
Exclusion of PARAMOUNT from the network meta-analysis	**Accepted**
Using the hazard ratio from the ITT network meta-analysis for all groups	**Accepted** - effectively represents an even more conservative way to model survival for EGFR/ALK positive patients → more modest relative treatment effect from the ITT population
Including disutility for treatment-related AEs of grade 3 or higher	**Accepted**

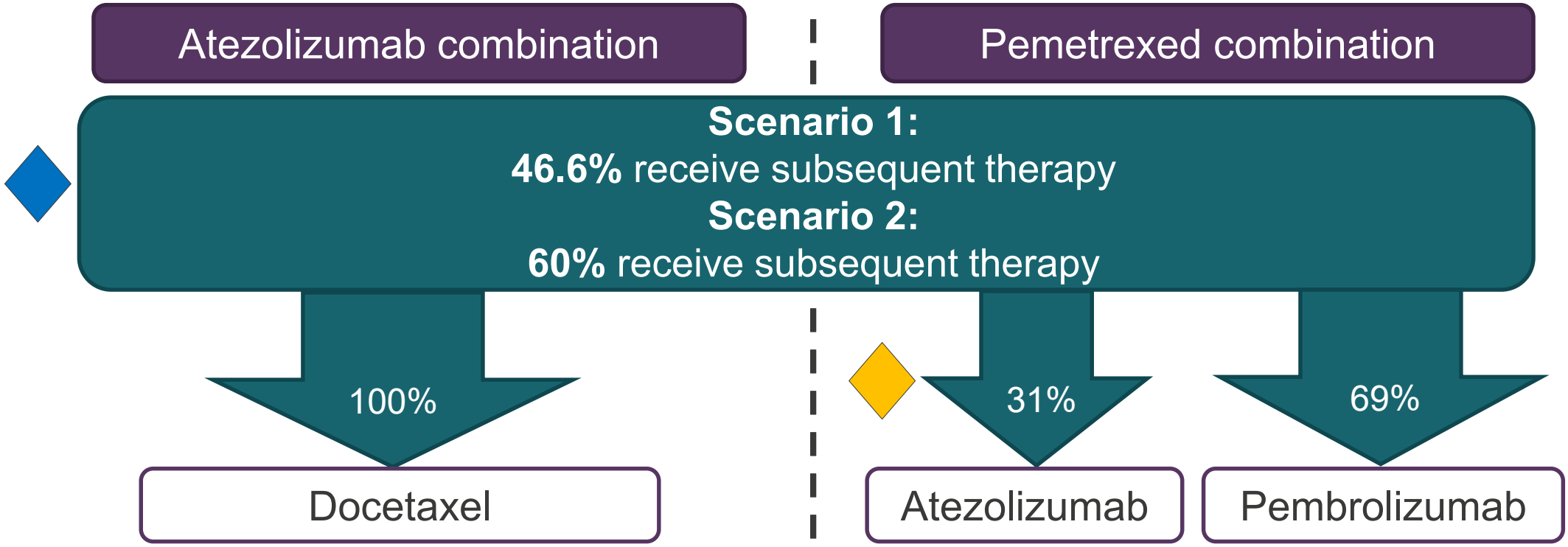
[redacted]

Committee preference and company response (2)

Committee preference	Company response
Assuming between 30% and 60% of people have subsequent therapy	Accepted that 100% of people receiving subsequent therapies not reflective of clinical practice. **Revised model includes two scenarios: 46.6%* and 60% receiving subsequent therapy** • *46.6% of patients in the standard-of-care arm of the KEYNOTE-189 trial received any subsequent treatment (data used in TA557 appraisal) • 55% of people were assumed to receive subsequent therapy from NICE budget impact for this appraisal • estimate of subsequent treatment based on UK market research data was 53%
Only immunotherapies are subsequent therapies after treatment with pemetrexed combination	**Accepted** - proportion of people receiving each therapy informed by UK market share data (pembrolizumab 69%, atezolizumab 31%)

[redacted]

Company's revised approach to subsequent therapies (ITT population)



- What proportion of people would receive subsequent therapies after:
  - atezolizumab combination?
  - pemetrexed plus platinum chemotherapy with pemetrexed maintenance?
    - Or would these proportions be the same?
- Is it reasonable to assume that 69% of people would receive pembrolizumab and 31% of people would receive atezolizumab as a subsequent therapy following pemetrexed combination?

Company's updated deterministic base case:

Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

Population & proportion of people receiving subsequent therapies	Fully incremental ICER (£/QALY)
46.6% of people treated with subsequent therapy	
ITT	£13,410
PD-L1 low/negative	£10,885
EGFR/ALK positive*	£19,931*
60% of people treated with subsequent therapy	
ITT	£1,282
PD-L1 low/negative	Dominant
EGFR/ALK positive*	£11,549*

- *PAS discounts exist for treatments received 2nd line, the estimates for cost-effectiveness which include these will be presented in the closed part 2 of this meeting*

* ERG noted an error in the company's model. ERG's corrected results shown

[redacted]

ERG critique of company's updated base case

- Checked and verified company's updated base case
- ERG included the NICE-preferred lower range of 30% subsequent treatment uptake and the uptake in the IMpower150 trial, XXX[1], in their additional analyses
- Note that adjusting the proportions of people receiving subsequent therapies only adjusts the costs, not the effects on overall survival
  - Not possible to adjust for effects of subsequent treatments in the company's model
- Scenario analyses:
  - explored the impact of changing the proportion of people receiving pembrolizumab and atezolizumab following pemetrexed with platinum drug and pemetrexed maintenance
    - company used market share data stating 69% receive pembrolizumab and 31% receive atezolizumab
  - applied trial-specific proportions for subsequent treatment uptake in IMpower150 and included the actual subsequent treatments included in the trial arms → this includes consistent assumptions about costs and survival effects of subsequent treatments
    - however, this does not reflect actual NHS practice in England as some of the subsequent treatments are not used or available

ERG's updated deterministic analyses (ITT population): Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

Proportion of people treated with subsequent therapy	Atezolizumab combination		Pemetrexed combination		ICER (£/QALY)
	Total QALYs	Total costs	Total QALYs	Total costs	
100% (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
60%	[redacted]	[redacted]	[redacted]	[redacted]	£1,282
46.60%	[redacted]	[redacted]	[redacted]	[redacted]	£13,410
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	£28,434

[redacted]

ERG's scenario analysis (1) (ITT population):

Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

- **50%** of people receiving **pembrolizumab** and **50%** receiving **atezolizumab** as subsequent therapy following pemetrexed, platinum drug and pemetrexed maintenance

Proportion of people treated with subsequent therapy	Atezolizumab combination		Pemetrexed combination		ICER (£/QALY)
	Total QALYs	Total costs	Total QALYs	Total costs	
100% (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
60%	[redacted]	[redacted]	[redacted]	[redacted]	£6,976
46.60%	[redacted]	[redacted]	[redacted]	[redacted]	£17,833
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	£31,282

[redacted]

ERG's scenario analysis (2) (ITT population):

Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

- Apply **trial arm-specific proportions for subsequent treatment uptake** and **include actual subsequent treatments included in the trial arms in IMpower150**

Proportion of people treated with subsequent therapy		Atezolizumab combination		Pemetrexed combination		ICER (£/ QALY)
Atezolizumab combination	Pemetrexed combination	Total QALYs	Total costs	Total QALYs	Total costs	
XXX	46.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Proportion receiving each treatment:
- pemetrexed plus platinum 63%
- docetaxel 17%
- nivolumab 11%
- bevacizumab 9%

Proportion receiving each treatment:
- pemetrexed plus platinum 2.4%
- single chemotherapy (docetaxel) 2.4%
- immunotherapy 41.8%
  - atezolizumab 1.5%
  - nivolumab 6.8%
  - pembrolizumab 33.5%

[redacted]

ERG's exploratory analysis: EGFR- or ALK-positive survival extrapolation

- **EGFR- or ALK-positive subgroup** in IMpower150 was **small** and **only 13 deaths** occurred in the atezolizumab combination arm over the median follow-up of 18 months
- **5-year overall survival estimates** using committee's preferred functions for extrapolating overall survival, exponential or Weibull, yielded very similar estimates, **27% or 26%**, respectively for the **atezolizumab combination** compared with **18%** (both functions) if treated with **pemetrexed combination**
- **Committee concluded** that these estimates were **too high** → more plausible estimates were in the range of **5% to 10% 5-year survival** with the **pemetrexed combination**, and an **additional 8% to 10% with the atezolizumab combination** (ACD 3.16)
- ERG exploratory analysis → exponential function for OS in atezolizumab combination arm and **vary the assumed hazard rate** to obtain projected estimates of survival in the expected range (5% to 10%)*

Hazard	Atezolizumab combination	Pemetrexed combination	Gain in 5-year survival
0.028	18.7%	9.9%	8.8%
0.036	11.6%	5.1%	6.5%

[redacted]

**Other committee preferred assumptions are applied, including use of the ITT NMA excluding PARAMOUNT and persistence of relative treatment effects for atezolizumab versus pemetrexed combinations for 5 years (3 years beyond the maximum treatment duration of 2 years) (ACD 3.25)*

ERG's exploratory analysis results: EGFR- or ALK-positive survival extrapolation (1)*

	Atezolizumab combination		Pemetrexed combination		ICER (£ per QALY gained)
	Total QALYs	Total costs	Total QALYs	Total costs	
Proportion of patients receiving subsequent treatment: 20%					
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]	£36,569
Weibull[b]	[redacted]	[redacted]	[redacted]	[redacted]	£36,963
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	£40,386
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	£46,180
Proportion of patients receiving subsequent treatment: 30%					
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]	£30,314
Weibull[b]	[redacted]	[redacted]	[redacted]	[redacted]	£30,617
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	£33,270
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	£37,788

[redacted] *Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

[a] = company base case [b] = ERG base case

ERG's exploratory analysis results: EGFR- or ALK-positive survival extrapolation (2)*

	Atezolizumab combination		Pemetrexed combination		ICER (£ per QALY gained)
	Total QALYs	Total costs	Total QALYs	Total costs	
Proportion of patients receiving subsequent treatment: [redacted]					
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]	£24,685
Weibull[b]	[redacted]	[redacted]	[redacted]	[redacted]	£24,905
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	£26,866
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	£30,234
Proportion of patients receiving subsequent treatment: 46.6%					
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]	£19,931
Weibull[b]	[redacted]	[redacted]	[redacted]	[redacted]	£20,082
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	£21,458
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	£23,856

[redacted] *Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

[a] = company base case [b] = ERG base case

ERG's exploratory analysis results: EGFR- or ALK-positive survival extrapolation (3)*

	Atezolizumab combination		Pemetrexed combination		ICER (£ per QALY gained)
	Total QALYs	Total costs	Total QALYs	Total costs	
Proportion of patients receiving subsequent treatment: 60%					
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]	£11,549
Weibull[b]	[redacted]	[redacted]	[redacted]	[redacted]	£11,578
Scenario: hazard 0.028	[redacted]	[redacted]	[redacted]	[redacted]	£11,922
Scenario: hazard 0.036	[redacted]	[redacted]	[redacted]	[redacted]	£12,610

[redacted] *Atezolizumab combination (with PAS) vs. pemetrexed combination (list price)

[a] = company base case [b] = ERG base case

Key issues

- Does the committee agree with the company's new base case with respect to:
  - A range of 46.6% to 60% of people receiving subsequent therapy
  - Proportion of people receiving subsequent therapy being the same after treatment with atezolizumab combination and pemetrexed combination
  - 69% of people receiving pembrolizumab and 31% of people receiving atezolizumab as a subsequent therapy following pemetrexed combination
- Effect of updated PAS for bevacizumab on ICER
  - What is the most plausible ICER?

[redacted]