National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Durvalumab in combination with platinum-based chemotherapy for untreated extensive stage small-cell lung cancer

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	AstraZeneca UK	As explained below (under "Any additional comments on the draft remit"; page 2–3), AstraZeneca would like to request that appraisal ID1618 be restricted to durvalumab in combination with etoposide and platinum-based chemotherapy (EP) versus EP alone, and that durvalumab + tremelimumab + EP be appraised separately. Our suggested wording (aligned to the anticipated marketing authorisation for durvalumab in this indication) is as follows: [redacted]	Thank you for your comments. The intervention in the scope have been restricted to cover durvalumab in combination with etoposide and platinum-based chemotherapy (EP) only. The remit has also been amended.
	BTOG-NCRI-RCP-ACP-RCR	Accurate reflection of burden of disease from SCLC.	Thank you, your comment has been noted. No changes have been made.
Timing Issues	AstraZeneca UK	Extensive-stage small cell lung cancer (ES-SCLC) is an area of high clinical and patient need, with median OS of just 4 months (Khakwani et al., 2013. Thorax, 68(3)]. The standard-of-care (etoposide-platinum combination chemotherapy) has remained unchanged for several decades,	Thank you, your comment has been noted. No changes have been made.

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		despite >40 clinical trials involving >60 agents. No new innovative treatment options (including immunotherapy) are currently available in routine NHS commissioning in this setting (although atezolizumab with carboplatin and etoposide for untreated ES-SCLC is currently being appraised by NICE; ID1504). Results from a planned interim analysis of the CASPIAN study demonstrated a statistically-significant and clinically meaningful overall survival benefit in favour of durvalumab + EP versus EP alone in previously untreated ES-SCLC patients (further explained in the "Innovation" section). CASPIAN data mark an important advancement in the treatment of a highly aggressive disease and we request this appraisal be prioritised so that a decision can be reached in line with expected timelines for EC Marketing Authorisation ([redacted]).	
	BTOG-NCRI-RCP-ACP-RCR	Atezolizumab undergoing NICE appraisal in October 2019 in same setting. So if approved: no longer area of unmet need for durvalumab	Thank you, your comment has been noted. No changes have been made.
Additional comments on the draft remit	AstraZeneca UK	CASPIAN, the pivotal Phase III clinical trial of durvalumab with or without tremelimumab in combination with EP for the first-line treatment of patients with ES-SCLC, is a three-arm study. Patients who fulfilled the inclusion criteria for the study were randomised in a 1:1:1 ratio to receive treatment with either durvalumab + EP, durvalumab + tremelimumab + EP, or EP alone. The trial met its primary endpoint of overall survival in a planned interim analysis [redacted]), showing a statistically-significant and clinically-meaningful improvement in OS in patients treated with durvalumab + EP versus EP alone. The trial is currently ongoing and will continue to the final analysis of OS for durvalumab + tremelimumab + EP versus EP alone.	Thank you for your comments. The interventions in the scope have been restricted to cover durvalumab in combination with etoposide and platinum-based chemotherapy (EP) only. The remit has also been amended.

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		Regulatory filing for durvalumab in this indication at the present time will focus on the efficacy and safety of durvalumab + EP (without tremelimumab), versus EP alone. Should the durvalumab + tremelimumab + EP arm of the CASPIAN study also read positive at the final OS analysis, then AstraZeneca may separately seek regulatory approval for the use of tremelimumab, in combination with durvalumab and EP, for the first-line treatment of ES-SCLC. Given the distinct regulatory submissions and time-frames for the use of durvalumab + EP versus durvalumab + tremelimumab + EP, in the first-line ES-SCLC setting, and current uncertainty regarding the outcome of the durvalumab + tremelimumab + EP arm of the study, AstraZeneca would like to request that appraisal ID1618 be restricted to durvalumab + EP versus EP alone, and that durvalumab + tremelimumab + EP be appraised separately. This approach is aligned to that adopted by NICE for appraisals relating to other studies with a three-arm study design (e.g. MYSTIC [IDs 1143 and 1331] and DANUBE [IDs 1169 and 1335]).	
	BTOG-NCRI-RCP-ACP-RCR	Caspian data with durvalumab almost identical to that of IMPOWER133 with atezolizumab: Caspain: median OS 13m vs 10m favouring combination of carb/etop/durvalumab over chemotherapy alone. Further comments should be acquired once published data can be analysed in detail.	Thank you, your comment has been noted. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal. No changes have been made.

Comment 2: the draft scope

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Background information	AstraZeneca UK	Paragraph 2: 1. The 5-year survival rate of 10% is not specific to ES-SCLC (from our interpretation of the publication cited). We suggest revising the statement as follows: “The prognosis for patients with extensive-stage SCLC is poor, with a 5-year survival rate of ~2% (in patients treated with standard-of-care etoposide-platinum chemotherapy)”. Refs: Lassen et al., J Clin Oncol 1995;13:1215-1220; Sundstrøm S, et al. J Clin Oncol 2002;20:4665–4672 (note: these are examples from grey literature searching and are not derived from a systematic literature review). 2. More recent analysis from the National Lung Cancer Audit (1/1/2015–31/12/2015) shows that 1,633 of 2,818 or ~58% of patients diagnosed with ES-SCLC received chemotherapy (Jones et al., 2018; presented at the 16th Annual BTOG / Lung Cancer 115S1, S1–S89). Therefore, we suggest revising 66% to 58% for a more-recent snap-shot of treatment landscape. Paragraph 3: 3. Clinical practice: -Irinotecan in combination with cisplatin: NICE guideline 122 does not specify the use of irinotecan in the first-line treatment of ES-SCLC patients. Furthermore, an analysis of first-line chemotherapy regimens used to treat histologically confirmed SCLC in England, did not identify any irinotecan use specifically (Jones et al., 2018; presented at the 16th Annual BTOG / Lung Cancer 115S1, S1–S89; data from the National Lung Cancer Audit; 1/1/2015–31/12/2015). Thus, while the statement referring to irinotecan in combination with cisplatin is aligned to ESMO guidelines, it does not reflect UK clinical practice - Gemcitabine in combination with carboplatin: an analysis of first-line chemotherapy regimens used to treat histologically confirmed SCLC in England showed that just 12 of 2,238 SCLC patients (i.e. <1%) who	Thank you for your comments. The background section is intended to give a brief overview of the disease area. Some changes have been made to improve clarity: 1. The survival time has been amended to a 2-year survival of around 5% 2. The figure of 66% has not changed but this sentence does not specify the type of chemotherapy. The conference abstract is not publicly available therefore this reference has not been used. 3. This section has been amended to make recommendations from the ESMO guideline more explicit. 4. This section is based on previous scopes in the same disease area. However, this section has been removed because this

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		received any chemotherapy were treated with gemcitabine + carboplatin (Jones et al., 2018; presented at the 16th Annual BTOG / Lung Cancer 115S1, S1–S89; data from the National Lung Cancer Audit; 1/1/2015–31/12/2015). Thus, this regimen does not represent a "commonly-used" treatment for ES-SCLC in the UK. Paragraph 4: 4. Data sources supporting figures relating to the proportion of patients who do not respond to first-line platinum-based combination chemotherapy treatment or relapse, as well as the proportion of patients who do not receive second-line treatment is unclear. No references are cited.	scope focuses on untreated disease.
	Roche Products	"The prognosis for patients with extensive-stage SCLC is poor, with a 5-year survival rate of 10%" – this statement is inaccurate. Alvarado-Luna et al 2016 actually states that "only 5% of patients are alive 2 years after diagnosis."	Thank you for your comment. The survival time has been amended to a 2-year survival of around 5%
The technology/ intervention	AstraZeneca UK	Due to the reasons detailed above (under "Any additional comments on the draft remit"; page 2–3), AstraZeneca would like to request that appraisal ID1618 be restricted to "durvalumab in combination with etoposide and either cisplatin or carboplatin" (and that durvalumab + tremelimumab + EP be appraised separately).	Thank you for your comments. The interventions in the scope have been restricted to cover durvalumab in combination with etoposide and platinum-based chemotherapy (EP) only. The remit has also been amended.
Population	AstraZeneca UK	Yes; no further comments	Comment noted.

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Comparators	AstraZeneca UK	The current wording is ambiguous – it is not clear what is referred to by "[treatments] not limited to platinum-based chemotherapy regimens". NICE guidelines on Lung Cancer: Diagnosis and Management (2019; no: 122) state that patients with ES-SCLC who are fit enough for treatment should be offered up to a maximum of 6 cycles of platinum-based combination chemotherapy (depending on response and toxicity). The guidelines state that prophylactic cranial irradiation with or without thoracic radiotherapy should be considered for those patients who have had a partial or complete response to chemotherapy within the thorax and at distant sites. There is no mention of any other treatment options in this setting. Atezolizumab with carboplatin and etoposide for untreated ES-SCLC is currently being appraised by NICE (ID1504). The anticipated publication date for advice (i.e. NICE FAD) is 11 December 2019. The CASPIAN NICE submission (per current timelines) is scheduled for January 2020. There is no way of currently knowing whether a decision on ID1504 will be reached after just one NICE committee meeting and prior to the CASPIAN NICE submission, whether or not it will be a positive recommendation, and whether the recommendation will be for access in routine commissioning or through the Cancer Drugs Fund (in which case, atezolizumab + carboplatin-etoposide will not qualify as an appropriate comparator per NICE's position statement on this topic). Finally, even if the atezolizumab + carboplatin-etoposide combination was to receive a positive FAD in December 2019, it is unlikely that it will have become a commonly-used treatment in the UK and hence, an appropriate comparator, within less than a month. For these reasons and significant uncertainty regarding the timing and outcome of appraisal ID1504, we believe atezolizumab + etoposide-platinum should not be included in the current scope as a comparator.	Thank you for your comments. The comparators listed are examples of treatments that may be used in clinical practice. Atezolizumab [ID1504] is under appraisal for a similar indication to durvalumab, therefore, subject to ongoing NICE guidance, it may be in routine use by the time of appraisal. The appraisal committee will discuss the most appropriate comparator during the development of the appraisal. No changes have been made.

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		Instead, we request that the comparator statement be modified to encompass the current standard-of-care as per NICE guidelines, i.e. “Platinum-based combination chemotherapy”.	
Outcomes	AstraZeneca UK	We agree that the outcomes listed capture important benefits and risks associated with durvalumab + EP treatment. Other outcomes, which we also believe to be relevant include: • Duration of response (in addition to objective response rates), as this outcome provides valuable insight into the proportion of patients who may derive sustained benefit from treatment • Time from randomisation to second progression or death (PFS2), and time from randomisation to first subsequent anticancer therapy or death (TFST) - intermediate clinical endpoints, such as PFS2 and TSST, also provide information about the long-term benefits of a treatment (beyond discontinuation) and reflect real-life treatment decisions and patient experience • EORTC QLQ-C30 and EORTC QLQ-LC13 (subscales and items), and EQ-5D-5L dimensions, as the QALY (derived using EQ-5D-3L) may not adequately capture all health-related quality-of-life benefits that ES-SCLC patients could derive from durvalumab treatment • Post-progression survival (PPS), and time to treatment discontinuation (TTD), both of which may be relevant to health economic modelling	Thank you, your comments have been noted. The outcomes listed in the scope are examples and are not intended to be an exhaustive list. No changes have been made.
Economic analysis	AstraZeneca UK	The economic analysis will follow the NICE reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared.	Comment noted.

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Equality and Diversity	AstraZeneca UK	No equality considerations identified at this stage	Comment noted.
Other considerations	AstraZeneca UK	None that have not been covered elsewhere.	Comment noted.
Innovation	AstraZeneca UK	At present, no immunotherapy treatment options are available in routine baseline commissioning within the NHS. Atezolizumab in combination with carboplatin-etoposide for first-line treatment of ES-SCLC patients is currently being appraised by NICE (STA ID1504); a decision is anticipated in December 2019 (but is subject to confirmation). Results from an interim analysis of the CASPIAN study demonstrated a statistically-significant and clinically meaningful median OS of 13 months for durvalumab + EP versus 10.3 months for EP alone (HR = 0.73; P = 0.0047) (Paz-Ares et al; 2019; presented at the 19th IASLC World Conference on Lung Cancer, September 7–10, Barcelona, Spain). At the landmark assessment of OS at 18 months, 33.9% of patients in the durvalumab + EP arm were still alive versus 24.7% of patients in the EP only arm. In addition to improving OS, durvalumab + EP also extended progression-free survival (PFS), with 17.5% of patients remaining alive and progression-free in the durvalumab + EP arm at12 months (versus 4.7% of patients in the EP arm) (Paz-Ares et al; 2019; presented at the 19th IASLC World Conference on Lung Cancer, September 7–10, Barcelona, Spain). More patients in the durvalumab + EP arm responded to treatment versus the EP arm (confirmed objective response rate [ORR] of 67.9% versus 57.6%). Furthermore, 22.7% of responses were still ongoing in the durvalumab + EP arm at 12 months (versus 6.3% in the	Thank you, your comment has been noted. During the development of the appraisal, the committee will consider the degree to which durvalumab in combination is an innovative technology when making its recommendations. No changes have been made.

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		EP arm), which is remarkable in the context of the highly aggressive nature of ES-SCLC. Importantly, durvalumab + EP treatment provided the aforementioned efficacy benefits in conjunction with an acceptable safety profile (Paz-Ares et al; 2019; presented at the 19th IASLC World Conference on Lung Cancer, September 7–10, Barcelona, Spain) and [redacted] These data mark an important advancement in a disease area where there have been >40 failed clinical trials, involving >60 failed agents / combinations, and should be considered in this context. The significance of these data is also underscored by the fact that they were presented at the Presidential Symposium of the 19th IASLC World Conference in Lung Cancer (Barcelona; 7th–10th September 2019). Both durvalumab and atezolizumab are delivered every three weeks for the first four cycles (in combination with chemotherapy). However, thereafter, durvalumab maintenance treatment is administered every four weeks, while atezolizumab maintenance is delivered every three weeks (Horn et al; N Engl J Med 2018; 379:2220-2229; Paz-Ares et al; 2019; presented at the 19th IASLC World Conference on Lung Cancer, September 7–10, Barcelona, Spain). Fewer treatment administrations have benefits beyond the costs borne by the NHS, such as patient / care-giver benefits due to reduced out-of-pocket expenses for hospital visits, as well as less inconvenience and disruption. Wider societal costs are not captured within the NICE reference case (aside from exceptional circumstances). Patient references towards different treatment	

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		administration regimens are also rarely adequately captured in oncology evaluations. Finally, durvalumab was discovered and developed by MedImmune in the UK and is an important example of UK research extending and improving the lives of cancer patients.	
Questions for consultation	AstraZeneca UK	No further comments.	Comment noted.
Additional comments on the draft scope	AstraZeneca UK	No further comments.	Comment noted.
Matrix	AstraZeneca UK	• We suggest that NICE consider adding the British Oncology Pharmacy Association and the Specialist Pharmacy Service to the list of Consultees. • The UK Health Forum has now ceased trading and therefore, should be removed as a stakeholder. • Specialised Healthcare Alliance is a coalition of patient groups and corporate supporters (Actelion, Amicus Therapeutics, BioMarin etc), with secretariat services provided by a Public Affairs Agency. Therefore, we suggest they are included as a “commentator”, rather than a consultee patient group. Finally, as stated on page 5 (“Comparators” section), we strongly believe that atezolizumab + etoposide-platinum should **not** be included in the current scope as a comparator. Therefore, we suggest that Roche	Comments noted. British Oncology Pharmacy Association and the Specialist Pharmacy Service have been added to the matrix. UK Health Forum has been removed and Specialised Healthcare Alliance have been moved to the commentator section. Atezolizumab is still included as a potential comparator in the scope therefore no changes have been made to the comparator companies.

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		products be removed from the list of Commentators as a “possible comparator company”.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope