National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Durvalumab for maintenance treatment of locally advanced unresectable non-small cell lung cancer that has not progressed after platinum-based chemoradiation therapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	AstraZenca	Please consider the addition in red font: Durvalumab for maintenance treatment of locally advanced unresectable non-small-cell lung cancer ~~after platinum-based chemoradiation therapy.~~ whose disease has not progressed following platinum-based chemoradiation therapy	Comment noted. The scope has been updated to reflect this wording
	Eli Lilly	No comment	-
	RCPath	yes	Comment noted.
Timing Issues	AstraZenca	There are no other maintenance treatment options for this patient population and therefore the urgency for this appraisal is high.	Comment noted.
	Eli Lilly	No comment	-
	RCPath	Urgent	Comment noted.

Comment: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	AstraZenca	Please amend this section to the following wording which more closely reflects the clinical setting for this appraisal: Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small cell lung cancers. NSCLC can be further classified into 3 histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes (stage III) or to other parts of the body (metastatic disease; stage IV). In 2014 approximately 37,453 people were diagnosed with NSCLC in England and there were 28,849 NSCLC deaths.[1] Approximately 30% of men and 35% of women survive lung cancer for at least one year after diagnosis.[1] Approximately 19% of patients present with Stage III disease in England (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Three). The aim of treatments depends on many factors but mostly important by cancer stage. For stage IV and a small subset of stage IIIb disease (the majority of people with NSCLC), the aims of treatment are to prolong survival and improve quality of life. In contrast, the aim of treatments for stage III patients are to cure cancer, expect for a small subset of patients with pleural effusion (this subset is considered non-curative and is clinically managed as metastatic NSCLC). Approximately 23% to 41% of newly diagnosed NSCLC patients have locally	Comment noted. Pemetrexed has been removed as a comparator. The wording of this section has been updated to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS in England.

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		advanced stage III NSCLC at the time of diagnosis{Carrato et al, 2014}. Locally advanced NSCLC is a heterogeneous, pre-metastatic group consisting of both stage IIIA (largely resectable) and stage IIIB (unresectable) disease. Locally advanced, unresectable NSCLC comprises of mostly stage IIIB patients, but also some with stage IIIA where multiple tumors are limited to the lung but due to their size, number and/or location cannot be surgically removed. The proportion of stage III patients that are likely to be unresectable varies from 41% to 79%, although these estimates were based on a patient population that included those at stage IV.{Fan et al, 2015 } Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy administered with curative intent. National clinical guidelines (NICE, NCCN and ESMO) recommend platinum-based chemoradiation (CRT) for unresectable stage III patients. No maintenance therapy is recommended by clinical guidance for patients with stage III unresectable NSCLC patients who have completed CRT and whose disease is under control (partial response or stable disease). There were several clinical studies comparing active post-CRT consolidation/maintenance treatment with best supportive care, but none of the studies have conclusively demonstrated clinical benefits. The rationale for combining chemotherapy and radiotherapy is to combine the benefits of radiotherapy in terms of local regional control with the benefits of chemotherapy in terms of reducing the risks of metastatic disease. With CRT there is the potential for chemotherapy, given during a course of radiotherapy, to enhance the effectiveness of radiotherapy (ie, radiosensitisation) (O'Rourke et al 2010). For patients with unresectable Stage IIIA or Stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone and concurrent CRT (cCRT) is	

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		superior to sequential therapy (NCCN Guidelines 2014). The setting post CRT may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient immune system to eliminate cancer cells. Tumours that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell. Potential priming agents for immunotherapy agents include chemotherapy and radiotherapy.	
	Eli Lilly	The 'Background' section refers to the following NICE recommendation: *NICE clinical guideline 121 (CG121): recommends platinum-based chemotherapy as an option for people with previously untreated stage III or IV NSCLC and good performance status*. The above recommendation appears to be based upon the NICE CG121 recommendations 1.4.40 and 1.4.41, i.e. **Chemotherapy for non-small-cell lung cancer** • 1.4.40 Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. [2005] • 1.4.41 Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [2005] However, the above recommendations refer specifically to the palliative chemotherapy setting, i.e. chemotherapy alone, not with concurrent radiation therapy, rather than the chemoradiation setting relevant for the appraisal of	Comment noted. Pemetrexed has been removed as a comparator. The wording of this section has been updated to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS in England.

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		durvalumab. Thus, it would be more appropriate to refer to the following NG121 recommendations that relate to the chemoradiation setting. **Combination treatment for non-small-cell lung cancer** • 1.4.31 Offer patients with stage I–III NSCLC who are not suitable for surgery an assessment by a clinical oncologist specialising in thoracic oncology for radiotherapy with curative intent. [new 2011] • 1.4.32 Consider chemoradiotherapy for patients with stage II or III NSCLC who are not suitable for surgery. Balance potential benefit in survival with the risk of additional toxicities. [new 2011] https://www.nice.org.uk/guidance/cg121/chapter/1-Guidance#treatment	
	Eli Lilly	The 'Background' section refers to two NICE technology appraisals of pemetrexed: *TA190, which recommends pemetrexed as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.* *TA402: recommends pemetrexed as an option for the maintenance treatment of locally advanced or metastatic non‑squamous non‑small‑cell lung cancer in adults when their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment.* Since both of these appraisals are for maintenance treatment in the palliative chemotherapy setting rather than the chemoradiation setting relevant to durvalumab, Lilly suggests deleting reference to these appraisals from this section.	Comment noted. Pemetrexed has been removed as a comparator. The wording of this section has been updated to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS in England.

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The technology/ intervention	Eli Lilly	No comment	-
Population	AstraZenca	Please amend this section to the following wording which more closely reflects the likely marketing authorisation proposed wording: Adults with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed after platinum-based ~~chemotherapy with concurrent~~ chemoradiation therapy	Comment noted. The wording of this section has been updated.
	RCPath	No comment	-
Comparators	AstraZenca	Please remove Pemetrexed, as is not approved or commonly used in UK clinical practice for treating stage III NSCLC patients after they have completed CRT and have disease control (partial response or stable disease). National clinical guidelines (NCCN, ESMO or NICE do not recommend any maintenance therapy for patients with stage III unresectable NSCLC patients who have completed CRT and whose disease is under control (partial response or stable disease)	Comment noted. Pemetrexed has been removed as a comparator.
	Eli Lilly	Pemetrexed is **not** indicated in the chemo-radiation setting. Thus, pemetrexed is not a standard treatment used in the NHS in this patient population (patients whose disease has not progressed after platinum-based chemotherapy with concurrent radiation therapy) and durvalumab should not be compared to pemetrexed in this setting.	Comment noted. Pemetrexed has been removed as a comparator.

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		Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. (Ref: Alimta SmPC http://www.medicines.org.uk/emc/medicine/15513) I.e. pemetrexed is **not** licensed for maintenance treatment following chemotherapy *with concurrent radiation therapy*. Lilly therefore suggests deleting pemetrexed from the list of comparators.	
	RCPath	The draft scope does not seem to mention other immune therapies such as pembrolizumab and nivolumab	Comment noted. Comparators are included if they are established practice within the NHS in England. Pembrolizumab and nivolumab are new technologies and are not yet established practice within the NHS in England.
Outcomes	AstraZenca	Please consider adding the following outcomes measured in the clinical trial: - Time to first or subsequent therapy or death - Time to death or distant metastasis	Comment noted. The outcomes suggested can be captured within the progression-free survival and overall

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			survival outcomes. The health economic model can also take these into account if appropriate. No changes to the scope required.
	Eli Lilly	No comment	-
Economic analysis	AstraZenca	As per 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.
Equality and Diversity	AstraZenca	To ensure NICE is promoting equality of opportunity, the population within the scope of this appraisal needs to reflect the proposed licensed indication	Comment noted.
Innovation	AstraZenca	Durvalumab is a step change in treatment for patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based CRT, as there are no other maintenance therapy options recommended by clinical guidance. In addition, durvalumab will be the first available human monoclonal antibody directed against PD-L1 in this specific clinical setting Durvalumab represents a novel therapeutic strategy to boost anti-tumor immune responses by targeting PD-L1, a regulator of T-cell function, allowing T-cells to recognize and kill tumor cells. Cancer cells exploit the PD-1/PD-L1 pathway to protect themselves from tumor-specific T-cells and escape immune elimination. The binding of PD-L1 on tumor cells to PD-1 and CD80 on tumor-infiltrating T-cells delivers an inhibitory signal to these T-cells and	Comment noted.

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		blocks the production of cytotoxic mediators required for cancer cell killing. Durvalumab prevents PD-L1 interaction with PD-1 and CD80 receptors, thereby reinvigorating the T-cell function. The utilisation of durvalumab therapy directly after chemoradiation is supported by the immune system priming effects of both chemotherapy and radiotherapy, which have been reported in preclinical studies to enhance the effectiveness of immuno-oncology therapies.{Drake et al. 2012; Deng et al. 2014]}	
Other considerations		The main issue for pathologists in relation to treatment with this kind of drug is the probable need for an associated diagnostic test that may decide whether the patient is eligible for treatment. From reported evidence to date, data suggest that those with greater immunostaining of the tumour for PD-L1 have a better response, although I am not sure whether this is the same for this particular drug. If this is the case, pathologists will have to be trained in interpretation and systems for validaton will need to be put in place, as well as the cost of the test (and possible rebiopsy) taken into account. Impact on biomedical scientists workloads/staff will also need to be taken into account.	Comment noted.
Questions for consultation	-	-	-

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Additional comments on the draft scope	AstraZenca	Please remove the Pemetrexed appraisals (TA402 and TA190) from the "Related NICE recommendations" section as they are not relevant in this specific clinical setting. Please include the following organisations: - British Oncology Pharmacy Association (BOPA) - International Thoracic Oncology Nurses Forum (ITONF) - Royal college of surgeons	Comment noted. Pemetrexed has been removed as a comparator. Comment noted. The organisations have been added to the matrix

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

Department of Health