National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for previously treated urothelial cancer

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	Fight Bladder Cancer	Yes.	Comment noted.
	MSD	Please revise in line with proposed indication wording: as monotherapy for treatment of patients with locally advanced and unresectable or metastatic urothelial cancer with disease progression on or after platinum-containing chemotherapy.	Comment noted. The scope has been updated to reflect proposed indication wording.
	NCRI-ACP-RCP-RCR-BUG	To appraise the clinical and cost effectiveness, and side effect profile of pembrolizumab within its marketing authorisation for treating advanced/unresectable or metastatic urothelial cancer after prior platinum-based therapy.	Comment noted. The side effect profile may be considered in the appraisal but is not normally included in the remit/appraisal objective. No change to the scope required

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	Royal Free London Foundation Trust	Yes	Comment noted
Timing Issues	Fight Bladder Cancer	This treatment is potentially ground breaking and thus is urgent to review.	Comment noted.
	MSD	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval.	Comment noted. The topic will be scheduled in line with the expected marketing authorisation dates.
	NCRI-ACP-RCP-RCR-BUG	high	Comment noted.
	The Urology Foundation	Bladder cancer patients needs access to new treatments now.	Comment noted.

Comment: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Fight Bladder Cancer	Accurate as far as we know.	Comment noted.
	MSD	For clarity, we would like to propose a few wording changes in the background section as follows: We suggest that the sentence "Urothelial carcinoma is cancer of the transitional cells (TCC)…" should be amended to "Urothelial carcinoma is cancer of the transitional cells (TCC) and mixed transitional/non-transitional cell histology". We suggest "….and accounts for 90% of bladder cancers." Should be amended to "and accounts for 90% of urothelial cancers." We suggest "TCCs can be split into papillary carcinomas…" should be amended to "Most urothelia cell carcinomas of the bladder are TCCs, which can be split into papillary carcinomas…"	Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS. Where appropriate, the scope has been updated.
	NCRI-ACP-RCP-RCR-BUG	Recommended amendment: vinflunine is not recommended in the UK for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy. However, it is standard of care in other European countries and recommended by the EAU and the ESMO guidelines. Therefore, most of the currently finalized or ongoing randomized phase III trials include vinflunine or a taxane by investigator choice as the comparator arms	Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and

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			alternative treatments currently used in the NHS in England.
	Royal Free London Foundation Trust	In patients that have received neo-adjuvant chemotherapy, if recur greater than 12 months post then standard would be to consider re-challenge of platinum based chemotherapy.	Comment noted. The scope has been updated to reflect this comment.
The technology/ intervention	Fight Bladder Cancer	Yes	Comment noted.
	MSD	Yes	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	yes	Comment noted.
	Royal Free London Foundation Trust	yes	Comment noted.
Population	MSD	Please revise in line with proposed indication wording: for treatment of patients with locally advanced and unresectable or metastatic urothelial cancer with disease progression on or after platinum-containing chemotherapy.	Comment noted. The scope has been updated to reflect proposed indication wording.
	NCRI-ACP-	The group of patients that has received chemotherapy in the perioperative	Comment noted. These

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	RCP-RCR-BUG	setting and relapsing after more than 6 months should be included and considered separately as they might benefit more from the novel technology/intervention than from re-induction of chemotherapy. Also non-urothelial cancers evolving from the urothelium should be evaluated and definitely not excluded. They can also derive a benefit from immunotherapy,	patients are included in those progressing following platinum-based chemotherapy. Non-urothelial cancers are not within the remit of this appraisal.
	Royal Free London Foundation Trust	See background information Patients that progress >12months from neo-adjuvant chemotherapy I understand were excluded and offered re-challenge with platinum based chemotherapy.	Comment noted
Comparators	Fight Bladder Cancer	There is no real “best alternative care” for these patients.	Comment noted.
	MSD	We agree with the proposed comparators. We suggest that best supportive care should be considered as no active treatment.	Comment noted
	NCRI-ACP-RCP-RCR-BUG	There is no best alternative care and either paclitaxel or docetaxel are used as the standard. Best supportive care is no standard treatment unless the patients are in a performance status that precludes active cancer treatment. Formally, the comparators should not include best supportive care alone but rather chemotherapy plus best supportive care, which is considered the standard. The Immunotherapy trials so far have not generated data comparing immunotherapy with best supportive care alone. The randomized phase III trials of immunotherapy, which have yet to report findings, compare	Comment noted.

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		immunotherapy with chemotherapy (investigator's choice). Best supportive care for urothelial cancer patients includes a number of potential supportive treatments that may include pain management including opiates, palliative radiotherapy, bisphosphonates, red blood cell transfusions, platelet transfusions, nutritional supplements, bladder instillations with chemotherapy in case of bleeding despite radiotherapy, tumour embolization to treat bleeding, oral and i.v. antibiotics for urinary tract infections and other sources of bacterial infections, urinary catheters, nephrostomies; urostoma care, cystoscopies to search for source of haematuria;	
	Royal Free London Foundation Trust	Yes – though would still be useful to compare with Vinfluinine as although not NICE approved, it is approved for second line use in Europe and is included in the standard arm in current bladder immunotherapy studies. Phase 3 data awaited from KEYNOTE045 study (currently in follow-up)	Comment noted. Sections 6.2.1–4 of the Guide to the methods of technology appraisal 2013 outline the Committee's approach to the relevance and appropriateness of comparators. In particular section 6.2.2 notes that 'Comparators are included if they are established practice within the NHS in England'.
Outcomes	MSD	MSD agrees with the proposed outcome measures. However, it is known that the response to immunotherapies (immuno-oncology drugs) may be delayed, but once triggered, is likely to be durable, bringing unquantifiable long term	Comment noted. Response rates, including duration of

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		survival benefit for a subset of patients. This benefit is not captured by the proposed outcome measures, thus MSD suggests the inclusion of “Duration of Response” as an additional outcome measure.	response, are listed in the scope.
	NCRI-ACP-RCP-RCR-BUG	Progression free survival by itself might not adequately capture benefit and harms as pseudo-progression has to be taken into account and this can be a bias for PFS. Otherwise, response rate and in particular duration of response as well as disease control rate, the time on treatment and time until change of treatment are important aspects for efficacy. Overall survival, toxicity and quality of life will be the most important measures of interest to clinicians and patients, particularly once phase III data become available	Comment noted. Response rates, including duration of response and disease control rate, are listed in the scope
	Royal Free London Foundation Trust	Yes	Comment noted.
	The Urology Foundation	Yes	Comment noted.
Economic analysis	NCRI-ACP-RCP-RCR-BUG	Long term responses in pretreated patients that go beyond one year need to be taken into account.	Comment noted
Equality and Diversity	NCRI-ACP-RCP-RCR-BUG	No specific concerns	Comment noted

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Innovation	Fight Bladder Cancer	Yes, this would be a step change in treatment possibilities.	Comment noted.
	MSD	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits. Pembrolizumab will be the first anti PD-1 pathway targeting agent to be approved with a companion diagnostic to identify patients whose tumours express PD-L1 as determined by a validated test. Pembrolizumab has the potential to improve outcomes for PD-L1 positive patients, being a step-change in the management of advanced urothelial cancer.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	The introduction of pembrolizumab and other immune checkpoint inhibitors currently under evaluation would represent a 'step change' in this disease where systemic therapy is largely confined to conventional cytotoxic chemotherapy and in which outcomes have not improved for over a decade. The technology translates a novel mechanism of action into active tumour treatment and patient benefit: Immune surveillance of tumorigenic cells is well established in animal models as a mechanism by which organisms fight off cancer. Among the body's efforts to recognize and eradicate cancer cells, the use of exogenous cytokines to boost the immune response, vaccines to activate the immune system against specific tumour-associated antigens, agents that cause generalized local inflammation and more recently targeted antibodies against proteins on the surface of immune cells that downregulate the immune response, the so-called immune checkpoint inhibitors (ICIs). [Hurwitz, Curr Op Urol 2016]. In the healthy body and physiologically, immune checkpoints	Comment noted.

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		(ICs) suppress adaptive immune responses to avoid inappropriate, excessive or prolonged T-cell activation, which may result in tissue destruction and/or autoimmunity. The T cell receptor (TCR) on T cells recognizes foreign antigens presented to it by a protein complex called the major histocompatibility complex (MHC) on the surface of antigen presenting cells (APCs). However, MHC presents self-antigens as well as foreign antigens. T cells distinguish between MHC, those the immune system should attack and those it should not. This depends on secondary factors, costimulatory or inhibitory proteins. When the CD28 protein on T cells binds to CD80 or CD86 (called B7-1 and B7-2 respectively) in the presence of a TCR-MHC interaction, the T cell is stimulated. Alternatively, when CTLA-4 (cytotoxic T-lymphocyte associated antigen 4) binds to CD80/CD86, T cells are inhibited. PD-1 (programmed death 1) protein is also expressed on T cells and when it binds to its ligand (PD-L1) which is located on the surface of APCs or tumours cells and suppresses T cell activity. Multiple other immune checkpoint proteins have been identified, and numerous agents are currently under investigation in clinical trials. So far and for clinical use, mainly the CTLA-4 and PD-1 systems have been shown to be relevant. Urothelial cancer is amongst the most genetically instable tumours. This results in mutant proteins, which, in turn, result in the production of abnormal antigens. They are called neoantigens. The immune system views cancer cells as foreign. The presence of these neoantigens in combination with certain features of the tumour microenvironment probably allow the immune system to attack and destroy tumour cells. Tumour cells may up-regulate the IC pathways to avoid being eliminated by the immune system. Therefore, blocking immune checkpoints, such as CTLA-4 and/or the PD-1/PDL1 pathway may restore the anti-tumour activity of T-cells. This innovative treatment approach is a milestone forward in anticancer treatment and in particular for urothelial cancer, where there has been a lack of new and sensible treatment options for decades. The clinical research in IC inhibitors has shown dramatic and durable responses in a considerable number of	

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		patients. This has been unprecedented in bladder cancer progressing after platinum based chemotherapy. The available studies demonstrating an effect of Pembrolizumab in urothelial cancer are as follows: KEYNOTE-012 (NCT01848834]: The safety, tolerability, and antitumor activity of pembrolizumab were assessed in subjects with recurrent or metastatic urothelial cancer in the phase 1b KEYNOTE-012 (NCT01848834], an open-label non-randomized trial of pembrolizumab 10 mg/kg, intravenously (IV) once every 2 weeks in advanced solid tumours. Archival or newly obtained tumour samples from subjects with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype immunohistochemistry assay. PD-L1 expression in stroma or ≥ 1% of tumour cells was required for trial entry. Subjects received pembrolizumab 10 mg/kg every 2 weeks until complete response, progression, or unacceptable toxicity. Subjects deriving benefit could remain on pembrolizumab beyond initial progression. Response was assessed every 8 weeks per RECIST v1.1 by independent central review (primary efficacy end point). In the KEYNOTE-012 trial, a total of 33 subjects with bladder cancer were enrolled and received pembrolizumab 10 mg/kg Q2W, including 30 subjects with transitional cell histology and 3 subjects with nontransitional cell or mixed histology. Median age was 70 years (range 44-85); 70% of subjects had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 1, 52% received ≥ 2 prior therapies for advanced disease, and 21% had liver metastases. Twenty-nine subjects were evaluable for response with measurable disease by central review at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan. A total of 4 subjects discontinued therapy before the first scan and were classified as 'No assessment'. The 29 evaluable subjects have a median follow-up of 15 months.	

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		Of the 33 subjects who received at least 1 dose of trial treatment, the most common drug-related adverse events (DRAEs) reported (> 10% incidence) included fatigue (18%) and peripheral edema (12%). DRAE ≥ Grade 3 or Grade 4 included aspartate aminotransferase (AST) elevation (3.0%), dehydration (3.0%), hypercalcemia (3.0%), myalgia (3.0%), myositis (3.0%), neuromyopathy (3.0%), maculopapular rash (3.0%), pruritic rash (3.0%), rhabdomyolysis (3.0%), thrombocytopenia (3.0%) and toxic encephalopathy (3.0%), of which 1 case of myositis/ rhabdomyolysis resulted in treatment discontinuation. AEs attributed to immune aetiology occurred in 5 subjects (15.2%). These immune-related AEs included Grade 3 colitis in 1 subject (3.0%), Grade 2 myositis in 1 subject (3.0%), Grade 3 myositis in 1 subject (3.0%), Grade 3 rhabdomyolysis in 1 subject (3.0%), Grade 3 maculopapular rash in 1 subject (3.0%), and Grade 2 uveitis in 1 subject (3.0%). Of 29 evaluable subjects with measurable disease, 3 complete responses (CR) and 5 partial responses (PR) were reported. Another 3 subjects developed stable disease (SD) as best objective response for a 37.9% disease control rate in this heterogeneous population. Median DOR had not been reached with a range of 8.1 to 64.1+ weeks. The results in the trial warranted further research of pembrolizumab in bladder cancer. Ongoing trials with pembrolizumab in urothelial cancer: KEYNOTE-045 (NCT02256436) is a randomized phase 3 trial among 542 subjects of second-line plus pembrolizumab versus investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine in metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy. The primary trial hypothesis is that pembrolizumab will prolong OS and PFS compared with paclitaxel, docetaxel, or vinflunine. The final data are still pending. KEYNOTE-052 (NCT02335424) is an ongoing open-label, phase 2 trial of pembrolizumab for first-line treatment of approximately 350 subjects with	

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		advanced/unresectable (inoperable) or metastatic urothelial cancer who are not fit for cisplatin-based therapy. Subjects in KEYNOTE-052 are considered unfit for cisplatin if they meet at least 1 of the following criteria: a. ECOG performance status of 2 (the proportion of ECOG 2 subjects will be limited to approximately 50% of the total population). b. Creatinine clearance (calculated or measured) < 60 mL/min but >30 mL/min (Note: Subjects with a CrCl [calculated or measured] < 30 mL/min, or on dialysis are excluded from the trial.) c. CTCAE v.4, Grade >2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges). d. CTCAE v.4, Grade >2 peripheral neuropathy or New York Heart Association Class III heart failure. The primary trial hypothesis is that pembrolizumab treatment will result in a clinically meaningful ORR in all participants and in participants with high combined positive score (CPS) (tumour and immune cell PD-L1 expression) biomarker determination. The planned analysis of the first 100 patients enrolled in the trial were recently presented (ESMO 2016 conference). The primary endpoint of overall objective response rate was 24%. The biomarker cut point to identify patients who are most likely to respond to the drug was determined to be a combined PD-L1 expression of 10% or greater in immune cells or tumour cells. Thirty patients had this level of expression of whom 11 (37%) responded to treatment. Median duration of response (DOR) has not been reached (range, 1.4+ - 9.8+ mo). DOR rate ≥6 months was 83% (Kaplan-Meier estimate). Treatment was well tolerated. 67% of patients experienced a drug-related adverse event (DRAE), most commonly fatigue (14%). 16% experienced a grade 3/4 DRAE. 5% discontinued therapy because of a DRAE. KEYNOTE-057 (NCT02625961) is an open-label, phase 2 trial of pembrolizumab for the treatment of approximately 260 subjects with high risk non-muscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guerin (BCG) vaccine. The primary hypotheses of this trial are that treatment	

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		with pembrolizumab will result in complete response for subjects with carcinoma in situ (CIS) at baseline – non-muscle-invasive bladder cancer (Cohort A)--and will result in disease-free survival for 12 months in subjects with focal tumors that are resected but are at high risk for recurrence without adjunctive therapy (Cohort B). KEYNOTE-361 (NCT02853305) is an open-label phase III randomized, trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in approximately 990 subjects with advanced or metastatic urothelial carcinoma. The primary hypotheses of this trial are that pembrolizumab plus chemotherapy is superior to chemotherapy alone with respect to Progression-free Survival (PFS) and Overall Survival (OS) in participants with programmed cell death ligand 1 (PD-L1) positive tumours and in all participants (includes those participants with PD-L1 positive tumours and those with PD-L1 negative tumours).	
	Royal Free London Foundation Trust	Growing evidence that PD1/PD-L1 inhibition immunotherapy is effective in bladder cancer, however phase 3 data remains awaited Appears to be very well tolerated with overall less toxicity than chemotherapy suggested though do need to be mindful of potential immune related adverse effects and the management thereof. Recent phase 2 data (KEYNOTE 052) suggests patients not eligible for platinum based chemotherapy were also able to tolerate well. Other than Vinfluinine which is not NICE approved there have been no other chemotherapy advances in metastatic bladder cancer since Gemcitabine and Cisplatin vs MVAC phase 3 study, von der Masse JCO 2000	Comment noted.

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	The Urology Foundation	Anything that might lead to greater chance of recovery or longer survival rates will be welcomed by bladder cancer patients. There have been few new drugs or treatments for this disease.	Comment noted.
Other considerations	MSD	If the evidence allows, consideration will be given to subgroups based on cancer histology and the PD-L1 biological marker.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	Histological variants in bladder and upper urinary tract.	Comment noted.
	Royal Free London Foundation Trust	Phase 3 data awaited – KEYNOTE 045 (in follow-up) Other similar anti PD-1/PD-L1 antibodies are currently being investigated in this setting	Comment noted.
Questions for consultation	MSD	Question: Have all relevant comparators for pembrolizumab been included in the scope? • What are the relevant comparators for pembrolizumab in patients whose disease has progressed after a platinum-based therapy? • How many platinum-based therapies would likely be tried? Answer: We consider that all relevant comparators for pembrolizumab have been included in this draft scope. We would anticipate pembrolizumab to be used after at least one platinum-based therapy has been tried. Question: How should best supportive care be defined?	Comment noted.

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		Answer: MSD suggests that best supportive care should be defined as no active treatment, i.e. any care given when patients are not eligible to receive any further active treatment (palliative care only). Question: Are people with PD-L1 positive tumours more likely to benefit from this treatment? Answer: This will be confirmed once results from KEYNOTE-045 are available. Question: Are the outcomes listed appropriate? Answer: We consider the outcomes listed are appropriate. We have additionally suggested one further outcome (duration of response) for consideration – please see above. Question: Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Answer: We consider that the suggested subgroups based on cancer histology and the PD-L1 biological marker are appropriate. Question: Where do you consider pembrolizumab will fit into the existing NICE pathway Bladder cancer? Answer: We consider that pembrolizumab will be an alternative second-line	

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		treatment option for patients with advanced or metastatic urothelial cancer. Question: Are the subgroups suggested in 'other considerations' appropriate? Answer: Yes.	
	NCRI-ACP-RCP-RCR-BUG	Multiple biomarkers are associated with response and pharmacodynamics and clinical response to anti PD-L1 and anti PD-1 therapy [G.Manson, Ann Oncol 2016]: Transient increase of CD8+ HLA-DR+ Ki-67+ Lymphocytes; Presence of peri- and intratumoural CD8 T cells associated with higher response rates; Increase of granzyme B lymphocytes in the tumour after anti-PD-1 and anti-PD-L1; Increase in granzyme B CD8+ T cells after antiPD1 Ab is associated with clinical efficacy in melanoma patients; Diversity of T cell repertoire; More clonal (i.e. more restricted, less diverse) TCR repertoire in pre-treatment tumour samples associated with clinical response; Increased clonal expansion of T cells after treatment associated with clinical response; Transcriptomic signature associated with innate anti-PD-1 resistance (IPRES) in melanoma and other types of cancer; Increased IFN-γ genes expression on pre-treatment tumour biopsies associated with response to anti-PDL1 in melanoma patients; In KEYNOTE-102 by inclusion criteria, PD-L1 positive patients defined as tumours staining in the stroma or in ≥1% of tumour cells using a prototype IHC assay and the 22C3 antibody clone. Of note, this was in only 33 patients. In KEYNOTE-052 one endpoint was to determine the cut off of a new biomarker definition, a high combined positive score (CPS) (tumour and immune cell PD-L1 expression). A high, ≥10% CPS score could discriminate	Comment noted.

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		all comers with 24% ORR from those with a high CPS showing 37% response rate. This discriminatory capacity seems to be still too inaccurate and many patient would be excluded who actually could benefit from treatment and derive a long term benefit. In summary, the biomarker development with pembrolizumab seems to be immature. The immune response is a dynamic process and a given staining on the primary tumour might not reflect the immune status at the time of relapse or progression. In particular the current immune biomarkers do not reflect the likelihood of response in first line setting. Treatment in all comer patients should be recommended until better and matured biomarker panels and validated data are available.	
Additional comments on the draft scope	NCRI-ACP-RCP-RCR-BUG	Based on emerging trial data, pembrolizumab will fit well in the NICE pathway as the standard of care for patients progressing after any line of chemotherapy and for patients ineligible for chemotherapy. There are also rapidly emerging data for other immunotherapy agents, and their combinations, that will add complexity for treatment decisions for clinicians. It remains unclear if there are comparative differences in effect for these different agents or approaches. NICE is likely to need to address these multiple new options in the next few years.	Comment noted

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

Department of Health