National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

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

Comment: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Roche	Yes	Comment noted.
	NCRI-ACP-RCP-RCR	[moved to background information]	See comment on background information
	The Urology Foundation	Yes	Comment noted.
Wording	Roche	The anticipated indication for atezolizumab is: "Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible." As such the remit should be adjusted to include the changes below: "To appraise the clinical and cost effectiveness of atezolizumab within its marketing authorisation for treating locally advanced or metastatic urothelial carcinoma, in people whose disease has progressed after prior chemotherapy, or for whom cisplatin-based chemotherapy is unsuitable".	Comment noted. The scope has been updated to reflect the anticipated marketing authorisation

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	NCRI-ACP-RCP-RCR	The wording is appropriate. One thing to highlight is the poor survival in patients with cisplatin ineligible group in the range of 8-9 months and for patients with progressive disease after cisplatin based regimen in 2nd line setting is in the range of approximately 7-8 months. In view of the poor survival in both these group of patients Atezolizumab is being considered as a game changer as it is well tolerated and patients are deriving significant clinical benefits, in terms of quality of life , improved response rates and prolongation of survival. The other thing to add is to mention vinflunine as it is used in Europe routinely in 2nd line setting and is recommended in ESMO guidelines.	
	The Urology Foundation	Yes	Comment noted.
Timing Issues	Roche	Given the paucity of effective treatment options for patients with locally advanced or metastatic urothelial carcinoma, there is an urgency to provide the NHS with guidance on the use of atezolizumab in this indication immediately following marketing authorisation.	Comment noted. No change to the scope required
	NCRI-ACP-RCP-RCR	Single arm large Phase II trial data from GO29293 has been presented and published with an encouraging efficacy and toxicity profile. In May 2016 FDA has approved the drug in USA in 2nd line setting. This single-arm clinical trial involving 310 patients with locally advanced or metastatic urothelial carcinoma measured the objective response rate. The study also looked at the difference in response rate in based on 'positive' versus 'negative' expression of the PD-L1 protein on patients' tumor-infiltrating immune cells. Overall 14.8 percent of patients experienced at least a partial response, and	Comment noted. No change to the scope required

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		the duration of response ranged from more than 2.1 to more than 13.8 months at the time of the response analysis. In patients who were 'positive' for PD-L1 expression, 26 percent of patients experienced a tumor response (compared to 9.5 percent who were classified as 'negative' for PD-L1 expression). As overall survival is limited in this group of patients there is an urgency from patient and clinician perspective of this proposed appraisal to NHS so that patients meeting the criteria to access this drug are not denied this treatment while waiting for phase III trial data. The phase III international trial data GO29294 comparing Atezolizumab versus standard of care chemotherapy of choice (Vinflunine or Doecetaxel, or weekly paclitaxel) has completed recruitment and will be reported in due course of time and if that meets its primary end point this will change the landscape in bladder cancer.	
	The Urology Foundation	Bladder cancer patients needs access to new treatments now	Comment noted. No change to the scope required

Comment: the draft scope

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Background	Roche	No comment	Comment noted.

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information	NCRI-ACP-RCP-RCR	Over all the summary is well written. However, points made above should be considered for inclusion for completeness. [See below] Patients with relapse following primary treatment, or with advanced disease at presentation, confer a significant challenge, and even among those fit for optimal platinum-based combination chemotherapy the median overall survival does not exceed the range of 12-15 months (Loehrer, 1992, von der Maase, 2000, von der Maase, 2005). The recommended first line chemotherapy for these patients are cisplatin based combinations and either MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin) (Loehrer, 1992, von der Maase, 2000, von der Maase, 2005) although the GC regimen is often preferred due to a milder toxicity profile (von der Maase, 2000). For patients with acceptable performance status and preserved organ functions, and where the relapse occurs later than 12 months following neoadjuvant/adjuvant cisplatinum-based combination chemotherapy, re-challange of platinum based regimen may be a feasible option (Necchi, 2015). In selected cases the addition of paclitaxel to gemcitabine and cisplatin may be considered (Bellmunt, 2012). For patients unfit for cisplatin combinations alternative although potentially less efficient combination regimens have been proposed, either with alternative platinum agents (oxaliplatin [Carles, 2007] or carboplatin [de Santis, 2012]) or a platinum-free combination of paclitaxel and gemcitabine (Calabro, 2009). In patients deemed ineligible for standard cispltin based treatment, combination treatment with Split dose cisplatin and Gemcitabine has reported encouraging results. (Hussain , 2004)	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.

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		Following failure of first line chemotherapy, be it early relapse following platinum based neoadjuvant/adjuvant chemotherapy, or progressive disease during palliative first-line chemotherapy, treatment options have so far been limited. Studies, mostly phase II and retrospective series, have reported activity with taxanes and pemetrexed (Bambury et al, The Oncologist 2015; Ko et al, Lancet Oncol 2014). Vinflunine, a microtubule inhibitor of the vinca-alkaloid family of anticancer agents (Bennouna, 2008), was the first drug to obtain European Medicines Agency (EMA) approval for use in Transitional cell cancer of urothelium (2009) due to evidence of efficacy from Phase II (Culine, 2006, Vaughn, 2009) and Phase III trials (Bellmunt, 2009, Bellmunt, 2013). Considering the multiple challenges in the second-line setting, with declining performance status due to progressive disease, persistent side effects or complications from earlier treatments, and primary or acquired chemoresistance after primary chemotherapy, the safety profile and efficacy data from the vinflunine publications are encouraging. In the phase III trial (Bellmunt, 2009, Bellmunt, 2013) median overall survival was 6.9 months in the vinflunine plus best supportive care compared to 4.3 months in the best supportive care only population. Further empirical studies in real life settings have confirmed vinflunine to be a safe and effective second line approach in Spain (n=66, Castellano, 2014), France (n=134, Medioni, 2013) and Germany (n=77, Hegele, 2013) , UK (n=49, Hussain 2015) with reported overall survival of 7.7 – 10.4 months. Based on the accumulating evidence, the ESMO guidelines suggest vinflunine as the recommended second-line therapy in advanced bladder cancer (Bellmunt, 2014). Vinflunine is currently not recommended by NICE	

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		for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy (NICE technology appraisal 272).	
The technology/ intervention	Roche	Atezolizumab is an anti-programmed cell death ligand-1 (PD-L1), as opposed to an anti-programmed cell death 1 (PD-1). The description should be adjusted to reflect this.	The scope has been updated to reflect this comment.
	NCRI-ACP-RCP-RCR	Yes this is accurate	Comment noted.
Population	Roche	The anticipated indication for atezolizumab is: "*Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible."* As such the population should be adjusted to include the changes below: "*Adults with locally advanced or metastatic urothelial carcinoma:* • *Whose disease has progressed after prior chemotherapy* *For whom cisplatin-based chemotherapy is unsuitable*."	Comment noted. The scope has been updated to reflect the anticipated marketing authorisation
	NCRI-ACP-RCP-RCR	Yes population has been defined appropriately.	Comment noted.
	The Urology Foundation	Believe so but not qualified to comment	Comment noted.

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Comparators	Roche	Clinical advice suggests best supportive care is not an appropriate comparator to include. Patients able and willing to receive treatment after prior chemotherapy will receive paclitaxel or docetaxel. Patients ineligible to receive cisplatin, who are able and willing to receive therapy will be treated with gemcitabine plus carboplatin. It is at this point within the treatment pathway that atezolizumab is proposed to replace these existing therapies of paclitaxel or docetaxel, or gemcitabine plus carboplatin. A patient will only receive best supportive care if they are unable, or unwilling to proceed with therapy. These patients would also not be suitable for treatment with atezolizumab. As such, best supportive care is not an appropriate comparator to include	Comment noted. At the scoping workshop it was noted that there is a proportion of patients who receive best supportive care but would wish to receive an active treatment if they could tolerate it. Therefore it was considered that best supportive care is an appropriate comparator
	NCRI-ACP-RCP-RCR	The comparators described in the scope reflect the standard treatments available through NHS. Vinflunine is licensed in 2nd line setting and is used in Europe but is currently not available through NHS outside of a trial.	Comment noted.
	The Urology Foundation	Not qualified to comment	Comment noted.
Outcomes	Roche	The listed outcomes are appropriate. Clinical advice proposed additional outcomes are of interest and relevance to	Comment noted. No change to the scope is required as these additional outcomes

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		this population in order to capture important health related benefits: • Duration of response • Disease control rate (DCR)	would be covered by the outcome 'response rates', which is already within the scope
	NCRI-ACP-RCP-RCR	Yes they are appropriate outcome measures	Comment noted.
	The Urology Foundation	Yes	Comment noted.
Economic analysis	Roche	The time horizon will be appropriate to capture differences in costs and outcomes	Comment noted.
	NCRI-ACP-RCP-RCR	This seems appropriate.	Comment noted.
Equality and Diversity	Roche	No equality issues identified.	Comment noted.
	NCRI-ACP-RCP-RCR	Not applicable	Comment noted.
Innovation	Roche	Atezolizumab is an innovative treatment option, which offers a step change in the management of metastatic urothelial carcinoma. Atezolizumab is the first medicinal product (humanised monoclonal antibody	Comment noted. No change required to scope

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		immunoglobulin IgG1 [IgG1]) that binds directly and selectively to PD-L1 immune checkpoint protein, thus preventing it from binding to receptors PD-1 and B7.1. This prevents down-regulation of T cell activity, allowing for the priming of new T cells to facilitate anticancer immune responses. In parallel, the PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis. Data available from a phase II study (IMVigor 210, NCT02108652) has demonstrated atezolizumab's clinical benefit, with a favourable toxicity profile. Based on the novel and unique mechanism of action, combined with the paucity of treatment options available for patients with metastatic urothelial carcinoma, atezolizumab offers a new treatment approach for a population with high unmet need, and a step change in the management of the disease	
	NCRI-ACP-RCP-RCR	Bladder cancer is given a Cinderella status. The myth that 2nd line palliative chemotherapy has limited role needs changing. The landscape in bladder cancer management is changing and we need to ensure that best available treatment on the basis of clinical trials are available for our patients. Atezolizumab has been used in a large single arm study of 310 patients in bladder cancer. This is the first drug of its class (PDL-1/ PD-1 inhibitor) to be approved by US food and drug administration to treat patients with urothelial cancer. This technology is innovative and its potential impact on health related benefits with improved efficacy in terms of response rate and durability of response while maintaining an excellent quality of life is key to highlight. This will provide a step change in the management of urothelial cancer. Single arm large Phase II trial data from GO29293 has been	Comment noted. No change required to scope

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		presented and published with an encouraging efficacy and toxicity profile.	
	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	Roche	No additional issues to be considered	Comment noted.
	NCRI-ACP-RCP-RCR	Impact on response rate and survival in PDL-1 positive and PDL-1 negative patients will need to be carefully explored and studied	Comment noted. At the scoping workshop it was agreed that the PDL-1 positive and PDL-1 negative subgroups should be removed from the scope – due to a lack of mature and consistent data.
Questions for consultation	Roche	1. Have all relevant comparators for atezolizumab been included in the scope? All relevant comparators are included for patients after prior chemotherapy or patients who are considered cisplatin ineligible. Clinical advice suggests best supportive care is not an appropriate	Comment noted. At the scoping workshop it was noted that there is a proportion of patients who receive best supportive care but would wish to receive an active treatment if

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		comparator to include. Patients able and willing to receive treatment after prior chemotherapy will receive paclitaxel or docetaxel. Patients ineligible to receive cisplatin, who are able and willing to receive therapy will be treated with gemcitabine plus carboplatin. It is at this point within the treatment pathway that atezolizumab is proposed to replace these existing therapies of paclitaxel or docetaxel, or gemcitabine plus carboplatin. A patient will only receive best supportive care if they are unable, or unwilling to proceed with therapy. These patients would also not be suitable for treatment with atezolizumab. As such, best supportive care is not an appropriate comparator to include 2. Is best supportive care a comparator for the populations described above? If so, how should best supportive care be defined? Best supportive care can be defined as the basket of symptomatic and supportive treatments designed to enhance comfort and quality of life but not delivered with the primary intention or expectation of prolonging life, for example pain relief. Active anti-tumour treatments are excluded by this definition. Clinical advice suggests best supportive care is not an appropriate comparator to include.	they could tolerate it. Therefore it was considered that best supportive care is an appropriate comparator.

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		Patients able and willing to receive treatment after prior chemotherapy will receive paclitaxel or docetaxel. Patients ineligible to receive cisplatin, who are able and willing to receive therapy will be treated with gemcitabine plus carboplatin. It is at this point within the treatment pathway that atezolizumab is proposed to replace these existing therapies of paclitaxel or docetaxel, or gemcitabine plus carboplatin. A patient will only receive best supportive care if they are unable, or unwilling to proceed with therapy. These patients would also not be suitable for treatment with atezolizumab. As such, best supportive care is not an appropriate comparator to include 3. Are PD-L1 positive patients more likely to benefit from this treatment? The anticipated marketing authorisation is for patients with locally advanced, or metastatic urothelial carcinoma, regardless of PD-L1 status. The primary and secondary analyses of the phase II clinical trial will be performed in patients according to PD-L1 expression in tumor tissue as evaluated by IHC. 4. Are the outcomes listed appropriate? Appropriate, with the addition of: • Duration of response	Comment noted. At the scoping workshop it was agreed that the PDL-1 positive and PDL-1 negative subgroups should be removed from the scope – due to a lack of mature and consistent data. Comment noted. No change to the scope is required as these additional outcomes

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		• Disease control rate (DCR) 5. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom atezolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Although subgroups have been defined within the atezolizumab clinical development programme, the base case cost-effectiveness analysis should be conducted in the population as per the anticipated marketing authorisation. 6. Where do you consider atezolizumab will fit into the existing NICE pathway Bladder cancer? Atezolizumab will offer a step change in the treatment of patients with locally advanced, or metastatic urothelial carcinoma, who have had an inadequate response to chemotherapy. In this population it will replace the use of taxane therapies (paclitaxel or docetaxel). Additionally it will offer an alternative first-line treatment option for patients who are cisplatin ineligible.	would be covered by the outcome 'response rates', which is already within the scope Comment noted. No change required to scope
	NCRI-ACP-RCP-RCR	Relevant comparators have been discussed in the scope and in my comments above.	Comments noted. At the scoping workshop it was agreed that the PDL-1 positive and PDL-1 negative

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		Patients who are fit for treatment both in 2nd line setting after cisplatin based treatments and in cisplatin ineligible patients in 1st line settings, the standard chemotherapy discussed in comparator sections are offered to patients. Data available so far points towards higher and durable response rates and improved outcomes in patients treated with Atezolizumab who are PDL-1 positive. Outcomes are listed appropriately. Subgroups suggested in other considerations are appropriate. Atezolizumab will fit in the NICE bladder cancer pathway. Atezolizumab can potentially be the 2nd line treatment of choice for patients progressing post 1st line cisplatin based chemotherapy. Atezolizumab is also likely to be the treatment of choice for patients ineligible for cisplatin based chemotherapy in 1st line setting. Further data on biomarkers to assess the impact of PDL-1 positivity in both these disease settings on response rates, durability of response and over-all	subgroups should be removed from the scope – due to a lack of mature and consistent data .

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		survival will help to refine the recommendations. These drugs are offered to patients based on their performance status and meeting specific criteria stipulated within treatment protocols. They are not likely to lead to any exclusion of patients on any other grounds and therefore equality legislation is not likely to be applicable in this treatment setting. Atezolizumab is innovative and its potential impact on health related benefits with improved efficacy in terms of response rate and durability of response while maintaining an excellent quality of life is key to highlight. This technology is likely to provide a step change in the management of urothelial cancer. Large single arm large Phase II trial data from GO29293 has been presented and published with an encouraging efficacy and toxicity profile. Phase III (GO29294) trial data comparing Atezolizumab versus standard of care chemotherapy (Vinflunine or Docetaxel or paclitaxel) in patients progressing post platinum based therapy is awaited.	
Additional comments on the draft scope	Roche	None	-
	NCRI-ACP-RCP-RCR	None	-

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

Department of Health