

*Urothelial cancer: a narrative review of the role of novel immuno-therapeutic agents with particular reference to the management of non- muscle invasive disease*

## **Introduction**

Bladder cancer is the tenth most common cancer in the UK and the ninth most common cancer worldwide, with 429,800 new cases diagnosed in 2013. In the UK in 2014, there were 10,063 new cases of bladder cancer diagnosed and 5,369 deaths from bladder cancer.<sup>1</sup>

Non-muscle invasive bladder cancer (NMIBC) is a urothelial carcinoma that is confined to the mucosa or invading the lamina propria and is classified as stage Ta or T1 according to the TNM classification of malignant tumours. Carcinoma in situ (CIS/TIS) are flat high-grade tumours confined to the mucosa and also fall under the classification of NMIBC. Approximately 75% of bladder cancers present at the NMIBC stage worldwide<sup>2</sup>, and of all UK bladder cancer diagnoses in 2014, 39% were classified as stage 1 disease.<sup>1</sup> The long term maintenance of response demonstrated in the metastatic setting, with the infrequent appearance of significant toxicity, suggests that systemic immunotherapy may be an attractive option for treatment, especially given the degree of upstaging at time of surgery.

### *Current management – surgery, chemotherapy and established immunotherapy*

Transurethral resection of bladder tumour (TURBT) is the initial standard treatment for all patients with NMIBC. Although TURBT alone can eradicate a Ta or T1 tumour, between 40-80% of tumours will recur in the 12 months following resection and up to 25% will develop muscle invasive, regional, or metastatic disease.<sup>3</sup> Post TURBT, pathology results from the resected tumour are used to risk stratify patients into ‘low risk’, ‘intermediate risk’ and ‘high risk’ groups, according to guidelines produced by various bodies, notably the American Urologic Association (AUA), the EAU, and the International Bladder Cancer Group (IBCG).<sup>4,5,6,7,8</sup>

After an apparently complete initial TURBT, a second TURBT is recommended in patients with high risk NMIBC. Studies have shown that a second TURBT improves staging and reduces recurrence as well as progression rates of high risk NMIBC. There is no international consensus about the strategy and timing of second TURBT, but European Association of Urology (EAU) guidelines recommend that it should be performed 14-42 days after initial

TURBT, with a retrospective analysis by Baltaci S et al showing a significant difference in recurrence and progression free survival rates when repeat TURBT was performed within 42 days compared to 43-90 days.<sup>9</sup>

Risk stratification is also used when providing adjuvant treatment recommendations in NMIBC. The European organization for research and treatment of cancer (EORTC) has developed tables for predicting individual risks of tumour recurrence and progression to muscle invasive disease.<sup>10</sup> In low risk patients, a single immediate postoperative intravesical installation of Mitomycin C chemotherapy is considered standard and complete treatment, with a 39% relative risk reduction resulting in a 15% one-year tumour recurrence rate.<sup>11</sup> Serial installations of intravesical chemotherapy or Bacillus Calmette-Guerin (BCG) may be performed for patients deemed to be at intermediate or high risk. Worldwide, there are slight discrepancies between guidelines for patients with intermediate risk. The UK national institute of clinical excellence (NICE) recommend that all patients with newly diagnosed intermediate risk NMIBC undergo a course of at least six doses of intravesical Mitomycin C, based on the favourable toxicity profile of Mitomycin C compared to BCG. EAU guidance states that patients should be offered either a course of intravesical chemotherapy or BCG, highlighting that there is a higher risk of side effects with BCG. For high risk patients, all guidelines recommend treatment with either a prolonged course of intravesical BCG therapy or radical cystectomy.<sup>12</sup>

Intravesical BCG is a form of immunotherapy and has been used for decades as a treatment for NMIBC. The BCG vaccine was developed in 1908 and the first documented success of the vaccination was in 1921, when it was administered to a baby whose mother had died of mycobacterium tuberculosis (TB) infection. The baby was immunised against TB and survived.<sup>13</sup> In the 1950s it was recognized that BCG had anti-tumour effects, and in 1976, the first human study of intravesical BCG was conducted with promising results.<sup>14</sup> In 1990, intravesical BCG was approved by the US food and drug administration (FDA) for use in patients with intermediate or high grade non-muscle invasive bladder cancer.

The mechanism of action of BCG in suppression of tumour cell proliferation is not fully understood. Such mechanisms are likely to involve both innate<sup>15</sup> and adaptive effector responses, as high frequency of pre-existing T cell responses against BCG has been shown to correlate with increased therapeutic efficacy of BCG.<sup>16</sup> This inflammatory process in turn facilitates the recruitment of activated T-cells to the tumour microenvironment which may stimulate anti- tumour immunity. As stated previously, BCG therapy is not without

significant toxicities. The occurrence of side effects is one of the main reasons why urologists try to avoid the use of BCG, particularly in intermediate-risk patients, for whom chemotherapy agents are often prescribed.

In a report by Sylvester et al. on maintenance BCG, only 16% of patients were able to receive all instillations of the 3-yr treatment, mainly because of side effects including chemical and bacterial cystitis, urinary frequency and incontinence, macroscopic haematuria, fevers, sepsis and fatigue.<sup>17</sup>

BCG immunotherapy treatment is associated with a significant treatment failure rate of up to 40%,<sup>18, 19</sup> defined as patients with recurrent or persistent high grade disease following their first induction therapy (6 weeks duration). BCG unresponsive disease is defined as being one of the following: patients with recurrent high grade T1 disease within 6 months of their primary tumour after at least one course of BCG, or patients who have failed at least 2 courses of BCG with either persistent/recurrent pure papillary (Ta) disease within 6 months, or persistent/recurrent carcinoma in situ (CIS) within 12 months.<sup>20, 21, 22</sup>

Potential factors related to BCG failure include: insufficient or excess BCG, presence of subclinical micro-metastatic disease at time of diagnosis, and inadequate immune response.<sup>23</sup> Detailed accounts of these factors are not within the scope of this review article. Clinical parameters (grade, stage, and presence of carcinoma in situ) are the strongest predictors of response to intravesical immunotherapy with BCG.<sup>24</sup> Patients with BCG failure are unlikely to respond to further BCG therapy and cystectomy is the preferred option at this point.<sup>5</sup> Other bladder preservation strategies such as Valrubicin chemotherapy are available but at present there is insufficient evidence to prove superiority to cystectomy.

Cystectomy is a major surgical and anaesthetic undertaking with significant cost and quality of life implications, and an overall 90 day mortality of 4% (ranging from 2% in those under 70 and 9% in those over 80 years of age).<sup>25</sup> NMIBC is also difficult to stage accurately, with recent studies suggesting that high risk NMIBC invading into the lamina propria is frequently under staged and is associated with a high risk of lymph node metastases and mortality<sup>26</sup>. A substantial proportion of patients who have failed BCG with T1 tumours are upstaged at the time of surgery with up to 10% found to have lymph node metastases.<sup>27</sup>

### Previous interest in alternative immunotherapy as a therapeutic option in BCG failure

Research has been undertaken into the use of intra-cutaneous and intravesical immunotherapy with keyhole limpet hemocyanin (KLH) compared to intravesical mitomycin in a 553 patient phase III randomised trial<sup>28</sup>. KLH was inferior to mitomycin in preventing NMIBC recurrences, however the majority of patients in the study had intermediate or high risk disease, and thus BCG therapy would be recommended as the standard of care. Kalble et al had previously found KLH inferior to BCG in this setting.<sup>29</sup>

More recent research looked at quadruple combination immunotherapy for patients who have progressed despite BCG. A small American study (n=52) aimed to achieve immunostimulation using 4 agents: intravesical BCG, IL2 and interferon in combination with subcutaneous granulocyte macrophage colony-stimulating factor with promising results in a small cohort of patients. 53% of patients were disease free 2 years after induction and maintenance therapy.<sup>30</sup>

### *The need for new treatment strategies*

New strategies are needed to improve recurrence and progression rates, improve treatment tolerance, avoid BCG associated toxicity, and provide further bladder sparing treatment options in high risk disease where BCG has failed. Novel “checkpoint inhibitor” immunotherapy agents are increasingly being used in non-urothelial tumour sites, and for muscle invasive bladder disease. However, there is currently no published data on novel immunotherapy in NMIBC despite the long term understanding that NMIBC responds to immunotherapy (BCG). The aim of this article is *to provide a useful narrative review for both oncologists and urologists on current knowledge of novel immunotherapy agents and speculate on their future role in NMIBC, extrapolating from preliminary trial results, and the more established evidence available in the MIBC literature.*

## Methods

To identify relevant published data, using the PubMed/Medline search engine, an online search of the Pubmed/Medline archives was conducted using the terms “bladder cancer” in combination with “checkpoint inhibitors”, and limited to articles in English from 1966 to September 2017. The authors reviewed the retrieved articles, and the references of the retrieved articles were also used, when relevant, to conduct a manual search of additional studies felt to be of relevance.

To identify ongoing trials of interest but not yet published, a further search of the clinicaltrials.gov search engine was conducted using the term ‘non muscle invasive bladder cancer’. Retrieved studies (n=120) were screened and included if they involved use of a novel checkpoint inhibitor (n=8).

## Results

### Checkpoint Inhibitors - a novel immunotherapy agent

T cells within the body distinguish ‘normal’ healthy cells from pathogens or malignant cells by interactions with antigens on the cell surface. On recognising an abnormal antigen from a malignant cell, cytotoxic T cells may be activated to recognise and kill tumour cells.

A number of ‘checkpoint inhibitor’ ligands exist on the cell surface of healthy cells to help protect healthy tissue from this immune response. These checkpoint inhibitors bind to T cell receptors downregulating the activity and proliferation of cytotoxic T cells and maintaining self-tolerance.<sup>31</sup>

In tumour proliferation, malignant cells hijack these signalling pathways, expressing ligands on the cell surface that react with T cell checkpoint inhibitor receptors, and suppress the immune response to avoid apoptosis.<sup>32</sup> One such specific checkpoint inhibitor ligand called PD-ligand 1 (PD-L1) is expressed minimally by healthy tissue, but in high levels by many cancer types.<sup>33</sup>

In recent years, monoclonal antibodies have been developed which competitively bind either directly to checkpoint inhibitor ligands expressed on the tumour cell surface, or to the checkpoint inhibitor receptors on the T cell, blocking the downregulation of the immune system by the tumour.

The most extensively studied immune checkpoint inhibitors which have become clinically important targets of drug therapy in the treatment of malignancy are the checkpoint inhibitor ligand **PD-ligand 1 (PD-L1)**; and the T cell checkpoint inhibitor receptors **programmed cell death 1 (PD-1)** and **cytotoxic T-lymphocyte associated protein 4 (CTLA-4)**. The mechanism of action of these important mediators of programmed cell death are shown in figure 1 and figure 2. A list of monoclonal antibodies currently in clinical use or undergoing clinical trials in bladder cancer which target the checkpoint inhibitor signalling pathway are shown in table 1.

*What is the current evidence for checkpoint inhibitors in advanced urological malignancy?*

There are currently 5 FDA approved checkpoint inhibitors for advanced urothelial carcinoma as a result of phase 1-3 trial data, with similar objective response rates (ORR) of between 15 and 27% in the second line treatment of metastatic bladder cancer (Table 2). Atezolizumab, nivolumab, durvalumab, and avelumab were all initially approved based on the results of Phase 1/Phase II single arm clinical trials comparing median overall survival (OS) and ORR with historical controls. An overview of the clinical trial results that led to each approval follows <sup>34</sup> and the trial data described below is summarised in table 2.

#### Atezolizumab (PD-L1 inhibitor)

In May 2016 Atezolizumab gained FDA approval for use in advanced urothelial cancer with disease progression despite platinum based chemotherapy following the results of IMvigor 210 trial. <sup>35</sup> An objective response rate (tumour regression demonstrated on computed tomography imaging quantified by RESIST v1.1) was demonstrated in 15% of subjects, compared to a historical control overall response rate of 10%. Interestingly, an objective response rate of 26% was demonstrated when PD-L1 expression was >5% compared to 18% when >1%, consistent with findings of previous studies <sup>35</sup>.

It was subsequently approved for first line use in cisplatin ineligible patients April 2017 following results of IMvigor 211. The study was negative for its primary endpoint (improvement in overall survival compared to chemotherapy in the PD-L1 positive (expression >5%) cohort). This is possibly due to the PD-L1 biomarker selecting the chemotherapy ‘winners’ as well as the immunotherapy ‘winners’, and exploratory secondary analyses of patients regardless of PD-L1 status showed a statistical significant difference favouring atezolizumab. The safety profile was consistent with previous studies and there were no new or unexpected adverse effects <sup>36</sup>. In a separate cohort of IMvigor 210, 119 cisplatin ineligible patients were treated with first line atezolizumab with a response reported in all of the PD-L1 expression groups (overall response rate was 19% and median overall survival 10.6 months). The most common grade 3/4 adverse effects that occurred were pruritus, diarrhoea and fatigue.<sup>37</sup>

Atezolizumab was the first immune checkpoint inhibitor to be licensed in the US for metastatic urothelial carcinomas and though the phase III trial has not shown a survival advantage over standard chemotherapy regime, it has certainly fuelled enthusiasm for further researching the potential role of checkpoint inhibitors in both MIBC and NMIBC. The relevance of PD-L1 expression is unclear and is discussed later in this article.

### Nivolumab (anti-PD1)

In February 2017 nivolumab gained FDA approval for use as a second line agent in metastatic urothelial carcinoma following data from Checkmate 275 trial <sup>38</sup>. The overall objective response rate was 19.9% and median survival 8.74 months, demonstrating benefit irrespective of levels of PD-L1 expression. Grade 3/4 adverse effects were reported in 18% of cases, the most frequent being diarrhoea and fatigue.

### Pembrolizumab (anti-PD1)

The first trial directly comparing immunotherapy with second line chemotherapy regimes in the metastatic bladder setting was KEYNOTE-045 <sup>39</sup> (phase III randomized control trial in locally advanced, metastatic or non resectable disease progressing during, or recurring after 12 months of platinum based chemotherapy, delivering 200mg intravenous pembrolizumab, or paclitaxel, docetaxel or vinflurine chemotherapy, every 14 days for 2 years). Overall response rate was 21.1% for pembrolizumab and 11.4% for chemotherapy, with a median

overall survival of 10.3 months for pembrolizumab versus 7.4 months for chemotherapy. Further, fewer treatment related grade 3-5 adverse effects were demonstrated in the pembrolizumab group (15% vs 49.4%). PD-L1 expression >10% was not associated with longer survival.

Keynote 052 (NCT02335424) studying intravenous pembrolizumab use in patients unsuitable for platinum based chemotherapy has closed but final results are as yet unpublished (due Nov 2018).<sup>40</sup> Preliminary progression free survival and overall survival rates at 6 months were 31% and 67% respectively, with grade 3/4 adverse effects occurred in 16% of patients.

Pembrolizumab gained FDA approval in May 2017, and is due for review by NICE in December 2018, with approval likely.

#### Durvalumab (PD-L1 inhibitor)

A recent phase I/II trial in advanced urothelial cancer comprising 61 patients (40 PD-L1 positive, 21 PD-L1 negative) receiving durvalumab 10mg/kg every 2 weeks, with the majority of patients (93.4%) having previously received at least one systemic treatment, demonstrated an objective response rate of 31% (46.6% in the PD-L1 positive cohort, 0% in the PD-L1 negative cohort)<sup>41</sup>.

#### Avelumab (PD-L1 inhibitor)

JAVELIN studied the effect of 10mg/kg intravenous avelumab every 14 days in 44 patients with metastatic disease progressing despite platinum based therapy (JAVELIN) and demonstrated an objective response rate of 18.6% and median overall survival of 13.7 months.<sup>42</sup>

#### Combination immunotherapy

Studies of combination immunotherapy in metastatic bladder cancer are ongoing<sup>43</sup> with promising preliminary data from the non-randomized CheckMate 032 (NCT01928394) study (combination ipilimumab 3mg/nivolumab 1mg vs nivolumab alone), suggesting that an overall response rate of 38.5% in the combination group vs 25.5% in monotherapy.<sup>44</sup>

Overall, these results show significant promise for the treatment of advanced urothelial carcinoma and the evidence for using specific solo or combination regimes will become clearer as ongoing trials publish. Further, there is sufficient promise to broaden the scope of immune checkpoint blockade to other settings of the disease including early stages, pre operative and adjuvant setting and their efficacy as first line treatment. There is current research exploring the role of immune checkpoint inhibitors in combination with other treatment modalities such as targeting therapies, oncolytic viruses, radiotherapy and chemotherapy in both non muscle invasive and muscle invasive disease.

In the preoperative setting, a current phase II trial is assessing patients with muscle invasive disease with residual disease after TURBT who will receive neoadjuvant pembrolizumab prior to planned cystectomy. (NCT02736266). The role of atezolizumab preoperatively is also being assessed in patients with T2-T4a urothelial cancer. (NCT02662309)<sup>45</sup>

Checkpoint inhibitors are also being investigated as maintenance therapy in patients who have received platinum containing first line therapy. Phase II and III trials using Avelumab and pembrolizumab are currently recruiting. Pembrolizumab is being assessed as maintenance therapy after standard first line chemotherapy in patients with locally advanced or metastatic urothelial cancer (NCT02500121). The phase III JAVELIN Bladder 100 trial (NCT02603432) aims to compare maintenance avelumab plus best supportive care versus BSC alone in patients with metastatic bladder cancer who have not progressed during or following first line systemic therapy.<sup>45</sup>

Oncolytic viruses are modified viruses which selectively replicate and kill cancer cells, acting as immune stimulators. They are currently being investigated in basket trials assessing a number of cancer sites rather than urothelial cancer alone. CA21 and enadenotucirev are currently under evaluation.<sup>45</sup>

Radiotherapy and chemotherapy in combination with immune checkpoint inhibition is currently being explored. Irradiating cells drives an immune response that also leads to the regression of distant and unirradiated disease. This is known as the abscopal effect. There are currently 2 early phase trials assessing the association between pembrolizumab and radiotherapy with or without chemotherapy. (NCT02621151, NCT 02560636)

Immune checkpoint inhibitors in combination with targeted therapies such as angiogenesis inhibitors are currently under investigation in a number of early phase clinical trials.<sup>45, 46</sup>

*What is the current evidence for checkpoint inhibitors in non-metastatic urothelial cancer?*

There are many clinical trials which are currently running specifically looking at the role of checkpoint blockade in NMIBC and these are summarised in Table 3. There is currently no available published data, however all studies are due for a completion date from 2019 onwards.

*Predicting response to novel agents in bladder cancer*

While many patients will benefit from checkpoint inhibitors, there are a significant number of patients who do not respond to checkpoint inhibition, and in these patients novel checkpoint inhibitors come with associated toxicities, and significant expense. Predictive biomarkers may play a role in determining which patients would benefit from them and therefore in which patients they would prove cost effective.

The significant heterogeneity between the clinical outcomes of patients with the same stage of disease suggests that biological subtypes might exist within and between NMIBC and MIBC, and there has been recent research into defining bladder cancer according to transcriptional subtypes. A study by Lund<sup>47</sup> of bladder tumours of all grades and stages in 2012 defined the following five subtypes: urobasal A, genomically unstable, (immune cell) infiltrated, squamous cell carcinoma like and urobasal B. Subsequent studies have shown remarkably consistent evidence supporting the existence of bladder cancer subtypes.<sup>47</sup>

Understanding of the underlying biology of bladder cancer will help to provide opportunity for prognostic application, disease monitoring and personalized therapy<sup>48</sup>. The Cancer Genome Atlas (TCGA) Project has advanced our understanding of the genetic characteristics of muscle invasive bladder cancer and the genetic drivers within the disease which may be targetable. Analysis of 131 urothelial cancers identified statistically significant mutations in 32 genes, including genes involved in cell cycle regulation, chromatin regulation and kinase signalling pathways.<sup>49</sup> Certain bladder cancers express high numbers of somatic mutations, with evidence suggesting a higher mutational load in MIBC compared with NMIBC.

Averages of 169-195 mutations per sample have been reported from exon sequencing of NMIBC compared with 302 in MIBC.<sup>50,51</sup>

Most cases of NMIBC are characterised by activating point mutations in FGFR3. Expression of mutant FGFR3 leads to activation of the RAS-MAPK (mitogen-activating protein kinase). It is estimated that activation of the RAS-MAPK pathway may contribute to development of >80% NMIBC<sup>49</sup>. There is evidence to suggest that the number of predicted immunogenic mutations is associated to responsiveness to PD-L1 inhibitors and increased overall survival.<sup>52,53</sup>

Which there has been much research into the genomic landscape of MIBC and predictive biomarkers in MIBC, research regarding this in the NMIBC setting is limited. Pietzak et al aimed to identify genetic alterations with potential clinical implications in NMIBC. They demonstrated that high rates of DRR gene alterations were identified in high grade NMIBC and were associated with increased mutational load which in turn may have therapeutic implications for treatment with systemic checkpoint inhibitors.<sup>54</sup> There is evidence to suggest that cancers with a high mutational burden, such as bladder cancer gain most benefit from checkpoint blockade because of the greater T-cell-mediated antitumor immune response elicited by these cancers.<sup>14, 55</sup>

#### *PD-L1 expression as a specific predictive biomarker*

Attempts at using PD-L1 expression as a predictive biomarker have been described in many of the aforementioned clinical trials, however results of PD-L1 expression and correlation with response have been inconsistent.<sup>56, 57</sup> It is thought that this conflicting evidence may be due to the lack of sensitivity and reproducibility amongst immunohistochemical assays used to test PD-L1 expression.

In the IMvigor 210 study, the different subtypes of bladder cancer (TCGA molecular subtypes), mutational load and T cell infiltrate level were analysed in an attempt to further predict response. Interestingly, tumours with higher mutational load had better response to atezolizumab. Response to atezolizumab occurred in all TCGA subtypes but was significantly higher in the luminal cluster II subtype than in other subtypes, which demonstrated an objective response rate of 34%.<sup>35</sup>

At this time, it is difficult to justify guiding treatment based on PD-L1 expression alone and it is not clear on what the best strategy is for predicting response. The ideal prediction of response to PD-1/PD-L1 is currently being investigated and likely to involve a combination of disease subtype, mutational load and PD-L1 expression.

#### *Toxicity and tolerability of immune checkpoint inhibitors*

The success of immune checkpoint inhibitors depends not only on anti-tumour immune response and survival outcomes but also on their toxicity profiles and tolerability. Immune checkpoint inhibitors can induce immune-related adverse events (IRAEs) by causing tissue specific inflammation. These effects are mediated by T cell hyper activation against self-antigens. IRAEs have been more frequently reported with anti-CTLA4 blockade compared with PD1/PD-L1 inhibition.<sup>58,59</sup> In the studies involving checkpoint inhibitors in metastatic bladder cancer, IRAEs varied from 12-17%.<sup>34,36,39,40</sup>

Almost every organ can be affected by IRAEs with the use of checkpoint inhibitors. Tissues that are more commonly affected include the skin (rash, pruritus and vitiligo), bowel (diarrhoea and colitis), liver (hepatitis) and endocrine glands (hypophysitis, hypothyroidism, thyroiditis and adrenal insufficiency).<sup>60,61</sup> Immune related adverse effects do not routinely follow a cyclical pattern as with traditional cytotoxic drugs. The majority of IRAEs occur within 3–6 months of therapy<sup>62,63</sup>, however there have been reported toxicities up to a year after the start of anti PD-1 treatment<sup>64</sup>. It is important to note that even though there are a number of adverse effects cited in the literature, the majority of immune checkpoint inhibitors are tolerated well with less than 10% of patients experiencing significant adverse events (Grade 3-5). (Table 4)<sup>65</sup>

Combination immunotherapy may result in a more severe toxicity profile.<sup>66,67</sup> The combination of ipilimumab with nivolumab in patients with melanoma has demonstrated significant severe toxicities amongst patients<sup>68</sup>. In a phase 3 trial of patients with advanced melanoma receiving combination immunotherapy, the rate of grade 3 and 4 toxicities (as per Common Toxicity Criteria) with combination immunotherapy was 55%, in contrast to monotherapies with nivolumab or ipilimumab, which had frequencies of 16.3 and 27.3%, respectively<sup>61</sup>.

Importantly, the majority of IRAE's are self-limiting. Some patients require short course immunosuppression with agents such as corticosteroids. Persistent adverse effects that don't

respond to corticosteroids can be treated with TNF alpha receptor antagonists such as infliximab, or mycophenolate.<sup>60</sup>

### *Intravenous versus intra-vesical delivery?*

Most current checkpoint inhibitors are administered intravenously. Interestingly, a recently opened trial (NCT02808143) is assessing the safety of intravesical pembrolizumab. There have been previous studies of intravesical injection of radiolabelled antibodies directed against tumour-associated antigens which have successfully showed retention of antibodies within the tumour mass, suggesting that this route of delivery is a feasible option in the treatment of NMIBC.<sup>69</sup> Furthermore, the PEMBLA study (NCT03167151), is currently recruiting patients to compare intravesical pembrolizumab and intravenous pembrolizumab in intermediate risk recurrent NMIBC. The primary outcome of this clinical trial is to assess the safety, tolerability and toxicities of intravesical pembrolizumab. One of the secondary outcomes is to assess complete response rate of the marker lesion (all but one lesion will be resected at the time of TURBT; the marker lesion will be left in order to assess response). The results of this trial will aim to answer potential questions such as whether intravesical pembrolizumab could potentially improve delivery of anti PD-1 directly to the tumour site, leading to better clinical responses whilst reducing systemic toxicity.

We must, however, also realise the potential disadvantages of using another intravesical treatment in bladder cancer. As discussed in previous sections, there is evidence that a substantial proportion of patients who have failed BCG with T1 tumours are actually upstaged at the time of surgery, with up to 10% having lymph node metastases. It is not clear if this is a failure of diagnostic imaging or current intravesical therapies. Systemic therapy in the form of intravenous pembrolizumab may therefore be a more effective treatment, and the results of future phase 3 trials will inform us on this matter.

### *Could checkpoint inhibitors be the future in patients who have recurrent NMIBC?*

There is currently no published trial data available to answer this question however we can speculate. Checkpoint inhibitors may be an attractive alternative to cystectomy for patients

who are unwilling or unfit for surgery, and have recurrent NMIBC despite conventional treatment.

Systemic checkpoint inhibition is not without serious side effects, with a minority of patients experiencing autoimmune toxicities resulting in a chronic autoimmune condition, however studies in the metastatic setting have shown that Grade 3/4 adverse immune toxicities only occurred in less than 10% of patients.<sup>60</sup> We are currently unable to predict which patients will experience these toxicities, and there appears to be no correlation with history of autoimmunity. This still, however, represents a comparable safety profile to standard chemotherapy regimes.

The risks of checkpoint inhibition immunotherapy versus the risks of a surgical procedure would need to be discussed on an individual patient basis, and publication of results from the plethora of ongoing trials will better inform these discussions. The major potential pitfall for these drugs is their cost. A single dose of atezolizumab has been proposed to cost approximately 3800 pounds sterling. Dosing schedules and regimes vary however, one trial arm of an ongoing atezolizumab trial in NMIBC delivers a 3 weekly dose for a total of 96 weeks. (NCT02792192) There has as yet been no formal cost analysis for immune checkpoint inhibition in NMIBC but widespread use will certainly be threatened by lack of funding.

Furthermore, in the treatment of NMIBC, it is unclear how long patients would need to be treated for. In the metastatic setting, the current standard is to administer treatment on a continuous basis until progression or toxicity. Evidence of long term remission using immune checkpoint inhibitors in the metastatic setting is starting to emerge. The updated data for the nivolumab only arm of the Checkmate 032 trial shows that objective response rate at 2 years is 25.6%, with 65% of patients who initially responded still enjoying a durable response at 2 years. Analysing the Kaplan Meier progression and survival curves, there appear to be very few progression events after 1 year of therapy. This is mirrored by overall survival data also. At 1 year, overall survival of 46% and at 2 years, overall survival of 37% was reported.<sup>70</sup> This data correlates with patterns of response in patients with melanoma who are treated with checkpoint inhibitors. In patients receiving ipilimumab who had unresectable or metastatic melanoma, a plateau in the overall survival curve began at approximately 3 years.<sup>71</sup> Objective response rate therefore, may underestimate the treatment effect of immunotherapy and overall survival remains the best end point. Further studies in different tumour sites have proven that duration of disease control is sustained much longer in patients

treated with immune checkpoint inhibitors rather than conventional chemotherapy regimens.<sup>72</sup>

This highlights the fact that it seems that those patients who respond to checkpoint inhibitors tend to maintain response by 2 year follow up. The phase 2 OMNIVORE study (Optimized Management of Nivolumab Based on Response in Patients With Advanced Renal Cell Carcinoma) (NCT NCT03203473) is currently evaluating nivolumab treatment strategies based on each patient's individual response to treatment. In participants who have a response to treatment, nivolumab will be stopped and participants will be closely monitored. In participants who do not have a response to treatment, the investigators will investigate whether the addition of ipilimumab improves a participant response to treatment, with an estimated study completion date in 2024. Further studies similar to this will help guide checkpoint inhibition in the adjuvant setting.

### *Summary*

There has been little advance in available adjuvant therapy for NMIBC treated with TURBT. Current intravesical therapies are associated with a high recurrence rate and significant side effect profile, but the cost, mortality risk, and post-operative quality of life impact associated with cystectomy makes this an unattractive option in the first line.

Inevitably checkpoint inhibition will have a role in the treatment of NMIBC. The impending publication of the wealth of ongoing trials, both into the delivery, and efficacy, of this exciting new NMIBC treatment avenue should answer many of the questions posed in this article, and clarify exactly how the treatment of NMIBC will change.

Further, the long term maintenance of response demonstrated in the metastatic setting and the possibility of combination therapy is promising.

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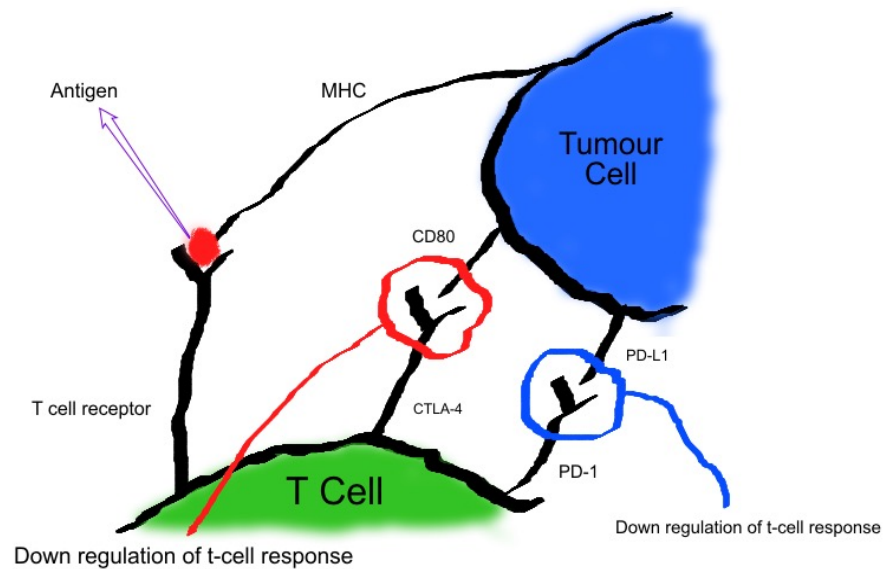
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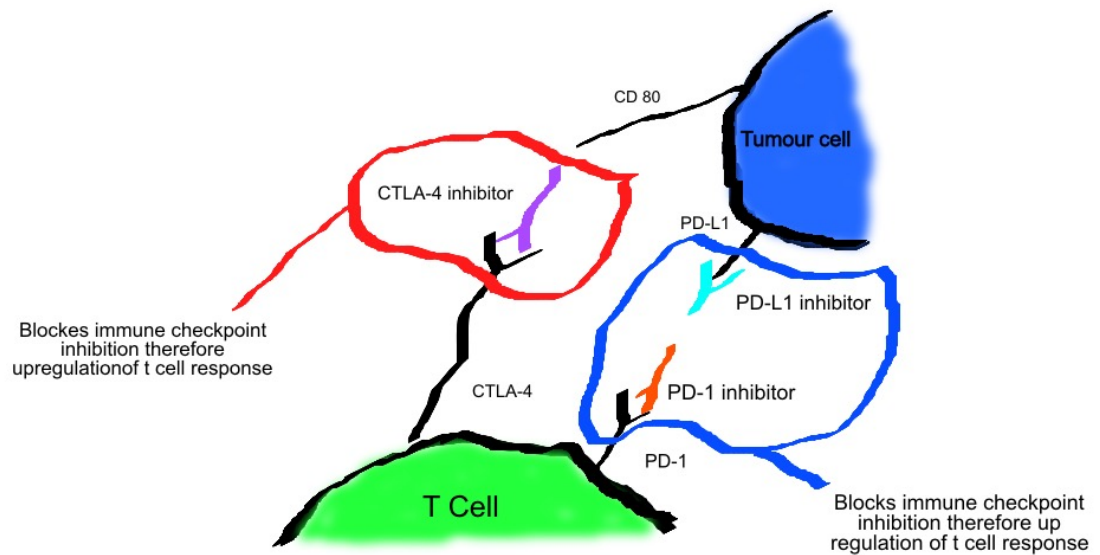
Figure 1



*Basic illustration of activation of the checkpoint inhibition pathway.*

*The major histocompatibility complex (MHC) binds with the T-cell receptor (TCR) and the cell is recognised as “self” or “non-self”. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death receptor-1 (PD-1) are checkpoint inhibitor receptors expressed on the surface of T cells. When bound by cell surface ligands CD-80 or programmed death receptor ligand 1 (PD-L1) respectively, cytokines which suppress the activity and proliferation of cytotoxic T cells are released, thus dampening the immune response. Tumour cells which are able to express these ligands as shown above are able to escape destruction despite being recognised as “non-self”.*

Figure 2:



*Illustration of the blockade of the checkpoint inhibitor ligands CD-80 and PD-L1 from binding the T cell checkpoint inhibitor receptors CTLA-4 and PD-1 by the presence of CTLA-4 inhibitor, PD-L1 inhibitor and PD-1 inhibitor drugs. This prevents the tumour high jacking the checkpoint inhibitor signalling pathway to escape apoptosis.*

Table 1

<b>Checkpoint Inhibitor</b>	<b>Administration</b>	<b>Mechanism of Action</b>
Atezolizumab	Intravenously every 3 weeks	IgG monoclonal antibody directed against PD-L1
Nivolumab	Intravenously every 2 weeks	IgG monoclonal antibody directed against PD-1
Pembrolizumab	Intravenously every 2 weeks	IgG monoclonal antibody directed against PD-1
Ipilimumab	Intravenously every 3 weeks	IgG monoclonal antibody directed against CTLA-4
Durvalumab	Intravenously every 2 weeks	IgG monoclonal antibody directed against PD-L1
Avelumab	Intravenously every 2 weeks	IgG monoclonal antibody directed against PD-L1

*Current immunotherapy agents that are being used clinical trials and clinical practice and their mechanism of action.*

**Table 2. Studies involving checkpoint blockade agents in locally advanced/metastatic bladder cancer**

Clinical Trial	Study Phase	Agent	Number of patients	Population	Results
IMvigor 210 Cohort 1	Phase II	Atezolizumab	119	Treatment naïve, platinum chemotherapy ineligible	ORR 23% Median OS 10.6 months
IMvigor 210 Cohort 2	Phase II	Atezolizumab	310	Previous treatment with platinum Chemotherapy	ORR 15% Median OS 11.4 months
IMvigor 211	Phase III	Atezolizumab versus chemotherapy (vinflunine, docetaxel or paclitaxel)	931	Previous treatment with platinum chemotherapy	No difference in overall survival between the two arms of the trial.
Checkmate 275	Phase II	Nivolumab	265	Previous treatment with platinum chemotherapy	ORR 19.9% Median OS 8.7 months
KEYNOTE 045	Phase III	Pembrolizumab versus chemotherapy (paclitaxel, docetaxel, or vinflurine)	542	Previous treatment with platinum chemotherapy	ORR pembrolizumab vs chemo 21.1% vs 11.4%. (p=0.001) Median OS 10.7 vs 7.4 months. (p=0.002)
KEYNOTE 052	Phase II	Pembrolizumab	370	Treatment naïve, platinum chemotherapy ineligible.	ORR 27% PFS 31% @ 6 months OS 67% @ 6 months
Durvalumab	Phase 1/II	Durvalumab	191	Previous treatment with chemo/ ineligible for chemo	ORR 17.8% OS 18.2 months
JAVELIN	Phase 1/II	Avelumab	44	Previous treatment with cisplatin chemo	ORR 18.6% Median overall survival 13.6 months

**Table 3: Current human studies involving checkpoint blockade agents in bladder cancer. Adapted using information from clinicaltrials.gov. (Last accessed Sept 2018)**

Clinical Trials.gov number	Phase	Treatment	Population	Planned patients	Start date	Planned completion date
NCT02792192	1b/2	Atezolizumab +BCG vs BCG	High risk NMIBC	70	June 2016	November 2021
NCT02844816	2	Atezolizumab	Recurrent BCG unresponsive NMIBC	143	Feb 2017	Feb 2019
NCT02451423	2	Atezolizumab	BCG-refractory NMIBC or muscle invasive TCC appropriate for cystectomy and refusing /ineligible for neoadjuvant chemotherapy	42	April 2016	December 2019
NCT02324582	1	Pembrolizumab and BCG	High risk NMIBC post surgery	15	June 2015	Nov 2020
NCT02808143	1	Pembrolizumab and BCG (intravesical)	High risk, BCG refractory NMIBC	27	Feb 2017	Feb 2020
NCT02625961	2	Pembrolizumab	High risk NMIBC unresponsive to BCG	260	Feb 2016	Dec 2021
NCT03167151	1/2	Pembrolizumab (intravesical)	Intermediate risk recurrent non-muscle-invasive bladder cancer	Phase 1: 6 Phase 2: 20	May 2017	April 2021
NCT03528694	3	Durvalumab and BCG vs BCG alone	High risk non muscle invasive bladder cancer	975	May 2018	Nov 2024

Table 4: Immune related adverse toxicities extracted and adapted from Khoja L et al<sup>60</sup> systematic review.

ICI Agent	Anti-PD-1 (n=4077)		Anti-PDL1 (n=275)		Anti-CTLA-4 (n=2520)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
<b>Endocrine</b>						
Hypothyroidism	5.1%	0.1%	2.2%	0.0%	1.2%	0.0%
Hyperthyroidism	1.6%	0.1%	0.0%	0.0%	0.5%	0.0%
Thyroiditis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Hypophysitis	0.2%	0.1%	0.0%	0.0%	1.2%	0.8%
Pituitary insufficiency	0.0%	0.0%	0.0%	0.0%	0.3%	0.2%
Pan hypopituitarism	0.0%	0.0%	0.0%	0.0%	0.2%	0.0%
Adrenal insufficiency	0.0%	0.0%	0.7%	0.4%	0.4%	0.2%
Type 1 diabetes	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%
<b>Gastrointestinal</b>						
Nausea	10.5%	0.3%	7.7%	0.0%	17.3%	1.2%
Vomiting	3.1%	0.3%	1.1%	0.4%	9.8%	1.0%
Diarrhea	12.1%	1.0%	7.3%	0.0%	30.2%	7.4%
Colitis	0.7%	0.4%	0.0%	0.0%	5.7%	4.1%
Hepatitis	0.4%	0.3%	0.0%	0.0%	0.4%	0.2%
<b>Musculoskeletal</b>						
Arthralgia	7.0%	0.2%	6.2%	0.0%	2.1%	0.2%
Arthritis	0.2%	0.0%	0.0%	0.0%	0.2%	0.0%
Myalgia	3.0%	0.2%	2.9%	0.0%	0.6%	0.0%
<b>Skin</b>						
Pruritus	14.0%	0.1%	5.1%	0.0%	21.8%	0.4%
Rash	12.2%	0.3%	5.5%	0.0%	21.4%	1.1%
Vitiligo	4.0%	0.0%	0.0%	0.0%	1.1%	0.0%
<b>Lung</b>						
Cough	2.8%	0.0%	0.0%	0.0%	3.3%	0.1%
Dyspnoea	2.8%	0.6%	0.0%	0.0%	3.3%	0.6%
Pneumonitis	2.4%	0.7%	0.0%	0.0%	0.4%	0.1%
<b>Constitutional symptoms</b>						
Fatigue	25.2%	1.0%	14.9%	1.1%	21.9%	2.2%
Pyrexia	3.2%	0.1%	4.4%	0.0%	6.0%	0.2%

Decreased appetite (anorexia)	8.5%	0.3%	5.1%	0.0%	9.8%	0.9%
<b>Blood and lymphatic disorders</b>						
Anaemia	4.8%	0.7%	0.7%	0.0%	1.6%	0.3%
Lymphopenia	1.0%	0.4%	2.6%	0.4%	0.9%	0.1%