BLADDER CANCER

NICE's rejection of pembrolizumab for platinum-refractory urothelial carcinoma: is there a greater good?

Shilpa Gupta and Ashish M. Kamat

Anti-PD1 and anti-PDL1 immunotherapy has transformed urothelial carcinoma treatment. Pembrolizumab is the only immunotherapy agent shown to have survival benefit compared with standard chemotherapy after progression on platinum-containing chemotherapy. Initial National Institute for Health and Care Excellence (NICE) approval was based on efficacy data, but the final appraisal report rejected use of pembrolizumab owing to treatment cost.

Refers to National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]. *NICE* https://www.nice.org.uk/guidance/indevelopment/gid-ta10466 (2020).

Pembrolizumab in mUC

Urothelial cancer has the eleventh-highest incidence and ninth-highest mortality of all cancers in the UK, with >10,000 cases and >5,000 deaths each year. The duration of response is short lived after first-line platinum-based chemotherapy, and median survival is poor at around 9 months with carboplatin-based regimens and 12–15 months with cisplatin-based regimens[1]. Before the development of immunotherapy, standard treatment was not available. Vinflunine — which had demonstrated a modest survival benefit of only 2 months — was approved by the EMA and no standard drugs were approved in the USA, where taxanes were most widely used without a demonstrable survival benefit. Regardless of the choice of subsequent chemotherapy, median overall survival (OS) remained dismally low — ~6 months — for over four decades[2]. Immunotherapy with anti-PD1 and anti-PDL1 inhibitors has revolutionized the therapeutic landscape in platinum-refractory metastatic urothelial carcinoma (mUC): improved response rates, durable responses and OS higher than with retrospective controls of subsequent chemotherapy have been observed[3,4]. In the USA, five anti-PD1 and anti-PDL1 inhibitors are approved by the FDA for patients with mUC who have previously received platinum-containing regimens: pembrolizumab, atezolizumab, durvalumab, avelumab and nivolumab (TABLE 1). These drugs received initial approval based on single-arm phase I/II trials[3].

In the KEYNOTE-045 study[5], 542 participants with advanced urothelial cancer were randomly allocated (1:1) to pembrolizumab or single-agent chemotherapy (docetaxel, paclitaxel or vinflunine). The co-primary end points were OS and progression-free survival (PFS). Median OS was 10.3 months with pembrolizumab versus 7.4 months in the chemotherapy group (HR for death 0.73; $P = 0.002$), with a median follow-up duration of 14.1 months. Median PFS was 2.1 months and did not differ between the two groups. On the basis of this evidence, pembrolizumab is the preferred category recommendation for mUC patients who have progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PDL1 expression levels, in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines for bladder cancer[6,7]. Pembrolizumab and atezolizumab are also recommended for first-line treatment for patients with mUC who are ineligible for cisplatin-based therapy and whose tumours express PDL1, or for patients who are not eligible for any platinum-containing chemotherapy regardless of PDL1 status[6,7].

NICE guidance

In April 2018, the National Institute for Health and Care Excellence (NICE) recommended pembrolizumab for use within the Cancer Drugs Fund for treating patients with platinum-refractory mUC, on the condition that treatment stopped after 2 years of uninterrupted treatment, or earlier in the event of

Table 1 | **Comparison of costs and approvals of checkpoint inhibitors in the USA and UK**[3,8,10]

Drug	Dose	Cost in USA ($)	Cost in UK (£)	Approval for platinum-refractory mUC	
				FDA	NICE
Pembrolizumab	200 mg IV every 3 weeks	5,580 per 100 mg	2,630 per 100 mg	Yes, Category 1	Initial approval based on cost per QALY <£50,000
					Later rejected based on cost per QALY >£50,000
Atezolizumab	1,200 mg IV every 3 weeks	10,344 per 1,200 mg	3,807 per 1,200 mg	Yes, Category 2	Yes; recommended only if Roche supplies atezolizumab with a discount agreed in the patient access scheme, and if treatment is stopped at 2 years or earlier in the event of disease progression
Nivolumab	480 mg IV every 4 weeks	13,760 per 240 mg	NA	Yes, Category 2	No
Avelumab	10 mg/kg IV every 2 weeks	1,859 per 200 mg	NA	Yes, Category 2	No
Durvalumab	1,200 mg IV every 4 weeks	4,174 per 500 mg	NA	Yes, Category 2	No

IV, intravenous; mUC, metastatic urothelial carcinoma; NA, not applicable; NICE, National Institute for Health and Care Excellence; QALY, quality of adjusted life year.

disease progression[8]. However, in the final appraisal review in March 2020, NICE recommended against the use of pembrolizumab for patients with platinum-refractory mUC, withdrawing it from the Cancer Drugs Fund for this indication[8].

NICE used the KEYNOTE-045 post-hoc subgroup results for decision-making[5,8]. Vinflunine is not used in the UK, and the post-hoc subgroup analysis included the 188 participants who received pembrolizumab and 182 participants who received investigator's choice of paclitaxel or docetaxel (UK standard of care), excluding vinflunine. Median OS was longer with pembrolizumab than with chemotherapy, and pembrolizumab was better tolerated. Rejection of pembrolizumab for this indication was not based on concerns of efficacy or safety but rather on cost-effectiveness estimates. The current list price of pembrolizumab in the UK is £2,630 per 100-mg vial, amounting to £5,260 per 3-weekly dose[8]. NICE uses quality of adjusted life year (QALY) as a measure to make an argument for a treatment's approval. NICE assigns greater weight to QALYs achieved in the later stages of terminal diseases with a life expectancy of less than 2 years if the treatment extends life by at least an additional 3 months and permits a threshold of £50,000 per QALY for 'end-of-life' treatments[9]. Use of pembrolizumab was projected to cost over £50,000 per QALY gained, resulting in rejection of pembrolizumab at its current price. Although new patients cannot start treatment with pembrolizumab, NICE's updated recommendation will not affect the treatment of patients already taking pembrolizumab before the change in guidance.

NICE's rejection of pembrolizumab will have huge implications for patients with mUC in the UK who have progressed on platinum-containing therapies. This is a substantial setback for patients with mUC who will be denied a life-prolonging therapy with robust category 1 recommendation by the NCCN and ESMO. Pembrolizumab is the only therapy that has shown an improvement in OS of 3 months or more compared with subsequent chemotherapies, including vinflunine, and is approved by the EMA for patients who progress on first-line platinum-containing chemotherapy[2,5]. The absence of this option after progressing on a platinum-containing regimen is unfair for patients in the UK, who face a dismal prognosis and will be in essence returning to the pre-immunotherapy era. NICE has received three appeals against their rejection of pembrolizumab from bladder cancer advocacy groups and Merck Sharp & Dohme. A decision on the appeal was originally scheduled for June 2020, but owing to the COVID-19 pandemic this appraisal has been paused as it was not judged to be therapeutically critical[8].

NICE's decision to withdraw approval for pembrolizumab also raises questions about the social obligations of pharmaceutical companies and how the cost of treatments and patient access schemes can be reduced to meet NICE's cost-effectiveness criteria. Responsibility is now with Merck Sharp & Dohme to reduce the cost of pembrolizumab to make it affordable and accessible as a standard treatment in the UK. From a global perspective, this might be a wake-up call especially for policymakers in countries such as the USA, which spends more per capita on medication than anywhere else in the world. The current disparity between checkpoint inhibitors approved and available in the USA compared with in the UK for the same indication raises several thought-provoking questions. Foremost among these questions is the use of arbitrary cut-off values for cost per QALY gained. In particular, when applying such thresholds denies certain patients access to any further treatment options when proven life-prolonging therapies exist. The rejection of pembrolizumab for mUC is one such example.

In contrast with NICE, the USA lacks any policy to assess cost-effectiveness of a drug before approval, which leads to multiple approvals of similar agents — with outrageous costs — for the same indication (TABLE 1). A fine balance must be found between cost-effectiveness and providing patients with life-saving therapies for terminal illnesses, especially when other options are inferior. For now, the pharmaceutical industry is reaping profits with high prices justified by life-saving innovation, but this may not be sustainable in the long run, especially as the world now faces the immense implications of COVID-19 for global health care and the economy. Rational policies around life-prolonging drug approvals must be developed to increase their availability to patients.

Shilpa Gupta[1] *and Ashish M. Kamat*[2]✉

[1]*Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA.*

[2]*The University of Texas MD Anderson Cancer Center, Houston, TX, USA.*

✉*e-mail: akamat@mdanderson.org*

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1. Richters, A., Aben, K. K. H. & Kiemeney, L. A. L. M. The global burden of urinary bladder cancer: an update. *World J. Urol.* https://doi.org/10.1007/s00345-019-02984-4 (2019).
2. Bellmunt, J. et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J. Clin. Oncol.* **27**, 4454–4461 (2009).
3. Stenehjem, D. D. et al. PD1/PDL1 inhibitors for the treatment of advanced urothelial bladder cancer. *Onco. Targets Ther.* **11**, 5973–5989 (2018).
4. Kamat, A. M. et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. *J. Immunother. Cancer* **5**, 68 (2017).
5. Bellmunt, J. et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N. Engl. J. Med.* **376**, 1015–1026 (2017).
6. Flaig, T. W. et al. Bladder cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J. Natl Compr. Canc. Netw.* **18**, 329–354 (2020).
7. Bellmunt, J. et al. Bladder cancer: ESMO clinical practice guidelines. *Ann. Oncol.* **25** (Suppl. 3), ii40–ii48 (2014).
8. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]. *NICE* https://www.nice.org.uk/guidance/indevelopment/gid-ta10466 (2020).
9. Paulden, M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable? *Expert Rev. Pharmacoecon. Outcomes Res.* **17**, 239–242 (2017).
10. Centers for Medicare & Medicaid Services. 2018 ASP drug pricing files. *CMS.gov* https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles (2020).

Competing interests

A.M.K. is a consultant or advisory board member for Abbott Molecular, Arquer Diagnostics, ArTara Therapeutics, Asieris Pharmaceuticals, AstraZeneca, BioClin Therapeutics, Bristol-Myers Squibb, Cepheid, Cold Genesys, Eisai, Engene, Ferring Pharmaceuticals, FerGene, Imagine Pharma, Janssen, MDxHealth, Medac, Merck, Pfizer, Photocure, ProTara Therapeutics, Roviant Sciences, Seattle Genetics, Sessen Bio, Theralase Technologies, TMC Innovation and US Biotest. A.M.K. has received grants and/or research support from Adolor Corporation, Bristol-Myers Squibb, FKD Industries, Heat Biologics, Merck, Photocure, SWOG/NIH, Specialized Programs of Research Excellence (SPORE) and AIBCCR. A.M.K. also holds the patent for Cytokine Predictors of Response to Intravesical Therapy (CyPRIT) joint with UT MD Anderson Cancer Center. S.G. is an advisory board member for Merck.

RELATED LINKS

Atezolizumab guidance: https://www.nice.org.uk/guidance/ta525
Cancer Drugs Fund: https://www.england.nhs.uk/cancer/cdf/
Cancer Research UK bladder cancer statistics: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer