

Nivolumab in treating advanced melanoma

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Malignant melanoma incidence rates are increasing worldwide and the UK is no exception. The majority of cases are diagnosed at an early stage where surgery may be curative. However, there are more than 2000 melanoma deaths every year (Cancer Research UK, 2016). While the incidence increases with age, melanoma is the second most common cause of cancer death in the 18–35 year age group (Cancer Research UK, 2016).

Prior to 2010, we had made no progress in the treatment of advanced melanoma in living memory; since then, there have been huge advances. These have come from understanding the molecular basis of melanoma, the role of the immune system in combating cancer and the mechanisms controlling this (immune checkpoints). The immune system has huge potential as a treatment; it can recognise tumour-specific antigens, allowing it to specifically target the cancer and minimise damage to normal cells. It adapts as the cancer evolves and mutates—one of the ways cancer becomes resistant to treatments. There is also the potential for ‘memory’; once the cancer is recognised, the immune system remains primed and active, resulting in long-term control. Due to the power of the immune system, it is under complex control to prevent autoimmunity.

Cancer can subvert these control mechanisms, preventing the immune

system from recognising or attacking it. The major advances have come from the development of monoclonal antibodies that can block these regulatory immune checkpoints and allow the immune system to attack the tumour cells.

The National Institute for Health and Care Excellence (NICE) approved the first checkpoint inhibitor, ipilimumab an anti-CTLA-4 monoclonal antibody as second-line therapy in 2012 and first line in 2014 (*TA268* and *TA319*) (NICE, 2012; 2014). While the response rates to ipilimumab are low, approximately 15–20% of patients went on to be long-term survivors—a major advance in melanoma treatment (Hodi et al, 2010; Schadendorf et al, 2015).

More recently, NICE has approved a new class of checkpoint inhibitors, the anti-PD-1 monoclonal antibodies. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor found on T-cells. After binding with its ligands PD-L1 and PD-L2, which are frequently expressed in the tumour microenvironment, PD-1 switches off the T-cell responses. Antibodies blocking this interaction release the cytotoxic potential of tumour-specific T-cells, allowing the cancer to be destroyed by the immune system.

Pembrolizumab received accelerated approval in the UK as part of the early access medicine scheme (EAMS) based on early phase results on previously

treated melanoma patients (Ribas et al, 2015). A subsequent phase 3 trial, comparing two different schedules of pembrolizumab with ipilimumab, confirmed its significantly higher response rate and survival, with a better toxicity profile (Robert et al, 2015b). Pembrolizumab was then approved by NICE in 2015 (*TA357* and *TA366*) (NICE, 2015a; 2015b) and is now a standard of care for patients with advanced melanoma.

Nivolumab is the most recent approval by the NICE (*TA384*) (NICE, 2016). When compared with chemotherapy in previously treated patients (Checkmate 037), it showed a higher response rate (32% *vs* 11%) (Weber et al, 2015). In the first-line setting it was tested in two randomised phase 3 trials. Checkmate 066 (Robert et al, 2015a) compared nivolumab with dacarbazine chemotherapy, and showed a significant improvement in overall survival (HR for death, 0.42; 99.79% CI, 0.25 to 0.73; $P < 0.001$) with a better toxicity profile (12% *vs* 18% of grade 3–4 toxicity). Checkmate 067 (Larkin et al, 2015) compared combination therapy, nivolumab or ipilimumab.

The results showed a significantly higher response rate (57.6%, 43.7%, 19%, respectively; $P < 0.001$) and median progression-free survival (11.5, 6.9, 2.9 months, respectively; $P < 0.001$). The toxicity seen with combination therapy was significant,

with 55% of patients experiencing grade 3–4 toxicity, compared to 16% for nivolumab alone. Survival data for this study are awaited.

The toxicity profile of immunotherapy is distinct to that previously encountered with other anti-neoplastic agents. The result of the activation of the immune system against auto-antigens can lead to immune-related adverse events (irAEs). When they occur with single PD-1 inhibitors, they are typically low-grade and manageable, with fatigue, rash, itching, diarrhoea and nausea the most common. However, serious life-threatening toxicities do occur. Early identification of irAEs is critical in minimising further complications; specific management algorithms exist to guide severity assessment and appropriate treatment. In general, irAEs will respond to corticosteroids, however, for more severe toxicity escalating levels of immunosuppression are required.

Targeted therapy has been the other major breakthrough for eligible patients with a targetable mutation (Grob et al, 2015). It remains unclear how best to sequence all these new treatments, and studies are being designed to address this. Many other new strategies are also showing real promise, including new checkpoint inhibitors, oncolytic virus, vaccines and cytokines.

Immunotherapy has been a major advance in the management of melanoma and other cancers (including lung cancer and renal). The recent approval by NICE of nivolumab is very important, with many patients now set to benefit for this huge advance. Many challenges remain, including appropriate patient selection; identifying tumour biomarkers to predict outcomes; overcoming an inactive immune

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system; and managing adverse events.

On a more practical level, a major concern is the exceptionally high cost of nivolumab and pembrolizumab and the uncertainty about the optimal duration of treatment. The current recommendation is to continue treatment until disease progression or severe toxicity. However continuing systemic therapy indefinitely every 2 weeks (nivolumab) or 3 weeks (pembrolizumab) has major implications in terms of costs, resource use, capacity and impact on the patient’s quality of life. Extrapolating this to lung cancer—the most common cause of cancer death—highlights the magnitude of the potential benefits and challenges we can expect. [BJHCM](#)

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