The most clinically advanced immuno-oncology (IO) therapies are monoclonal antibodies (mAbs), which modulate the activity of T cells by blocking inhibitory pathways that act as immunological checkpoints (for example anti-cytotoxic T–lymphocyte antigen–4 (CTLA–4) mAb, anti-programmed cell death protein 1 (PD–1) mAb)\(^1,2\).

IO therapy has already created a paradigm shift in the treatment of some advanced-stage cancers where it is now the standard of care. However, although these agents can produce long-lasting responses in some cancer patients, the response rate as monotherapies tends to be low. The immunological contexture of a patient’s tumour, the so-called ‘immunoscore’, has been shown to be prognostic for outcome in certain malignancies\(^4,5\). At a basic level, tumours can be broadly described as hot, cold or immunosuppressive, as determined by their profile of immune infiltrates. Tumours defined as hot are those with pre-existing Th1 bias and include tumour-infiltrating CD8+ cytotoxic T cells and natural killer (NK) cells. By contrast, cold tumours are poorly infiltrated by T cells, and immunosuppressive tumours harbour high proportions of suppressive cells such as myeloid-derived suppressor cells (MDSCs). Importantly, hot tumours with a pre-existing T cell infiltrate are most likely to respond to checkpoint therapy\(^6\). Furthermore, MedImmune, the global biologics research and development arm of AstraZeneca, has shown high tumoural IFNγ mRNA and PD–L1 protein expression associates with response to durvalumab (anti-PD–L1 mAb) monotherapy in non-small cell lung cancer (NSCLC) patients\(^7\). Cold tumours, on the other hand, have not yet seen the appropriate danger signals and the adaptive immune system is not primed for an effective anti-tumour immune response. AstraZeneca/MedImmune has started to address this problem by bringing new molecules into the clinic that have the potential to provide the key signals and bridge the innate and adaptive immune response.

Toll-like receptors (TLRs) are promising targets to facilitate T cell priming and stimulate an adaptive immune response. TLRs are expressed on a wide range of myeloid cells and normally function to recognize conserved pathogen-associated molecular patterns. Signalling through TLRs can lead to activation of antigen presenting cells and the production of inflammatory cytokines. Topical administration of synthetic TLR7 or TLR7/8 agonists have demonstrated clinical anti-tumour activity and the TLR7 agonist imiquimod is approved for the treatment of superficial basal cell carcinoma and other indications. Unfortunately, these compounds are not well tolerated when given systemically, limiting their use to cutaneous malignancies.

AstraZeneca/MedImmune is developing a new TLR7/8 agonist, designed for intratumoral injection and with the potential to bring this potent immune-stimulatory mechanism to patients with superficial and deep-seated injectible lesions. MEDI9197 (formerly known as 3M–052) is a potent TLR7 and TLR8 agonist with a long lipid tail to increase retention at the site of administration\(^8\), which induces pro-inflammatory cytokines and chemokines through activation and recruitment of myeloid and lymphoid cells (Figure 1). Preclinical studies indicate that intratumoural injection of MEDI9197 induces upregulation of genes associated with the activation of innate and adaptive immunity in the tumour\(^9\). Importantly, in mouse syngeneic models that respond poorly to mAbs targeting PD–L1...
or CTLA–4, combination with MEDI9197 significantly improved anti-tumour activity when compared to either monotherapy alone. MEDI9197 is currently being evaluated in a Phase 1 study as monotherapy in patients with solid tumours or cutaneous T-cell lymphoma, and in combination with durvalumab in patients with solid tumours (NCT02556463). Preliminary data in patients indicates that MEDI9197 induces pharmacodynamic (PD) effects consistent with its expected mechanism of action. For example, an increase in CD8 (T cells), CD40 (myeloid and B cells), CD56 (NK cells) and PD–L1 (tumour and immune cells) was observed in MEDI9197 injected tumour biopsies based on immunohistochemistry (IHC) analysis. Furthermore, RNAseq analysis of paired tumour biopsies showed an increase in innate and adaptive immune activation signatures consistent with IHC and indicating increased inflammation. These early data highlight the potential for MEDI9197 to stimulate new immune responses in the immunologically cold setting and support the combination with checkpoint therapies, such as durvalumab. AstraZeneca/MedImmune is committed to advancing innovative therapies that have the potential to address unmet clinical need and to bring the promise of immunotherapy to patients that do not respond to checkpoint therapies.

REFERENCES