First trial of its kind opens in Ireland to examine the next step in the multimodal treatment of head and neck cancer - combining immunotherapy with chemoradiotherapy (CRT).

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The JAVELIN Head and Neck 100 trial is a Phase III double-blind randomised controlled trial (RCT) studying the effect of avelumab, versus placebo, in combination with standard of care CRT in the frontline treatment of patients with high risk locally advanced squamous cell carcinoma of the head and neck (SCCHN).

The trial has opened in St Luke's Radiation Oncology Network in Rathgar and St James's Hospital, Dublin. It is funded by Pfizer and with the support of St Luke's Institute of Cancer Research and Cancer Trials Ireland.

The trial strengthens Cancer Trials Ireland's collaborative international links and increases opportunities for Irish patients with head and neck cancer to avail of the most up to date treatment approaches. It increases future opportunities for further collaboration and the ongoing recruitment of Irish patients to high quality international studies.

In 2012, there were almost 140,000 new cases of head and neck cancer diagnosed in Europe, the majority of which are squamous cell carcinoma. In Ireland, almost 500 people are diagnosed with cancer of the mouth or pharynx annually. Risk factors include smoking, alcohol, and infection with Human Papilloma Virus (HPV). Of newly diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease, for whom standard of care is combination CRT with cisplatin. In this group, locoregional failure rates can range between 35-65% (depending on tumour site, stage, and HPV status), with 10-30% of patients developing distant metastases. A 3-year progression free survival (PFS) rate of approximately 61.2% is reported. Outcomes for both locoregional and distant recurrences are poor, with limited effective treatment options, and high morbidity and mortality. Thus, there is a push to explore avenues to optimise multimodal treatment and improve PFS in the upfront treatment setting.

Ionising radiation causes cell death through the generation of free oxygen radicals and double strand DNA breaks, resulting in mitotic catastrophe. The tumour is targeted with normal tissue relatively spared with the use of modern techniques including intensity modulated radiotherapy (IMRT). Cisplatin added to radiation therapy in the treatment of SCCHN has been shown to improve overall survival by 6.5% at 5 years.

A key step in the development and progression of cancer is the ability to evade and inhibit the body's normal immune response to tumour cells. Avelumab is a fully human IgG1 monoclonal antibody (mAb) which selectively binds to PD-L1 (present on some cancer cells) and competitively blocks its interaction with PD-1 (on cytotoxic T cells), thereby reactivating the immune system's response to cancer. Radiation increases PD-L1 expression, and so adding avelumab results in a synergistic therapeutic effect (see Figure). There is also emerging clinical data suggesting the development of an immune anti-tumour memory after such combination therapy.

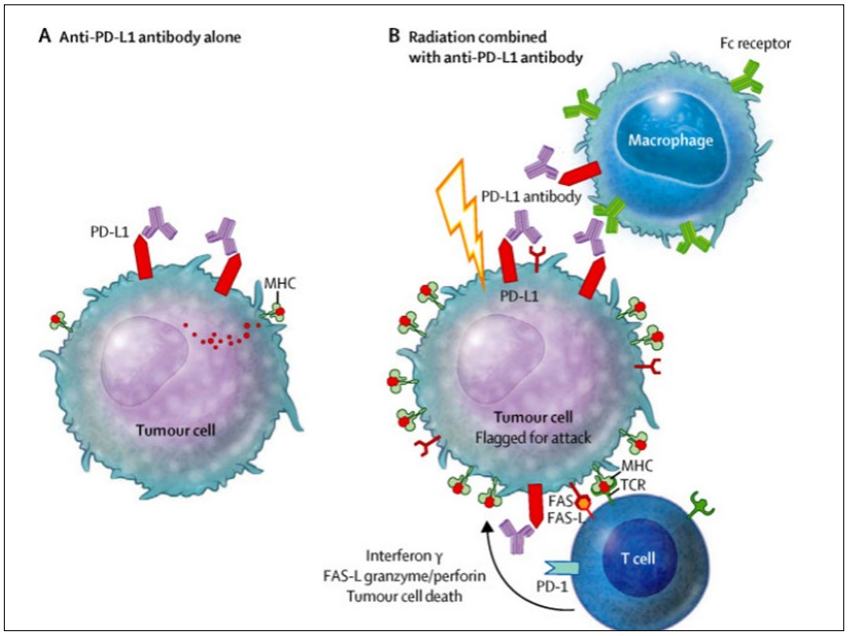

Figure: Synergistic therapeutic effect of Anti-PD-L1 antibody and radiotherapy

The primary hypothesis of this trial is that the addition of avelumab to standard of care cisplatin-based CRT will improve PFS in the upfront treatment of locally advanced SCCHN. Secondary endpoints include overall survival, and evaluation of safety and tolerability of the combined treatment. Both patients and physicians are blinded to the treatment allocation.

Participation in this trial follows the successful enrolment of patients within the St Luke's Radiation Oncology Network to earlier head and neck studies. The Cancer Research UK DARS trial is a phase III, multicentre randomised radiotherapy trial examining whether dysphagia (swallowing difficulties) optimised intensity modulated radiotherapy (Do-IMRT) compared to standard IMRT (S-IMRT) improves post radiotherapy dysphagia in patients with head and neck cancer. A second trial, De-ESCALaTE HPV, is a phase III randomised trial in patients with HPV positive oropharyngeal carcinoma to compare the acute and late effects using cetuximab with radiotherapy versus cisplatin with radiotherapy. These trials were sponsored (DARS) or coordinated (De-ESCALaTE HPV) in Ireland by Cancer Trials Ireland, and are now closed to accrual with follow up ongoing and early results awaited.