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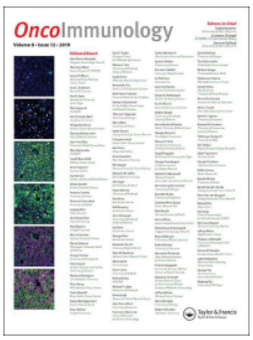

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EDITORIAL

Small cell lung cancer responds to immunogenic chemotherapy followed by PD-1 blockade

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ABSTRACT

Sequential combination of immunogenic cell death (ICD)-induced interventions with subsequent immunotherapy has shown efficacy in preclinical models and clinical evaluation. Recently, a clinical trial enrolling small cell lung cancer patients treated with amrubicin together with PD-1 blockade confirmed the notion that ICD sensitizes tumors to immune checkpoint inhibitors.

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The long-term efficacy of anticancer therapies depends on the reinstatement of immunosurveillance by adaptive immune circuitries and the subsequent generation of immunological memory against tumor-associated antigens (TAAs). Anticancer immunity in cancer patients can be reinstated by chemotherapy- or radiotherapy-elicited immunogenic cell death (ICD). Therapeutic exposure to antineoplastic agents, such as anthracyclines, oxaliplatin, crizotinib, or lubinectidin, all are clinically approved for the treatment of a variety of cancer, can stimulate the tumor to emit danger-associated molecular patterns (DAMPs).[1–3] Via the ligation of pattern recognition receptors (PRR) expressed on antigen presenting cells, DAMPs act as immunological adjuvant signals and ultimately stimulate TAA-specific anticancer immune responses. Thus, the lysosomal secretion of ATP by tumor cells induces the chemotactic attraction of dendritic cells that express purinergic receptor P2X7 (P2RX7). Annexin A1 (ANXA1) released from dying cancer cells can ligate formyl peptide receptor 1 (FPR1) on such DCs, guiding them toward apoptotic malignant cells. Exposure of calreticulin serves as an eat-me signal and stimulates TAA uptake via LDL-receptor-related protein 1 (LRP1, best known as CD91) expressed by DC. Exodus of high mobility group box 1 (HMGB1) stimulates TAA processing via the toll like receptor 4 (TLR4) axis and facilitates MHC class I-restricted cross-presentation of TAA by DC. Together with a type-1 interferon (IFN) response and C-X-C motif chemokine ligand 10 (CXCL10)-mediated stimulation, this ultimately leads to the priming of T cells and the clonal expansion of cancer-specific cytotoxic T lymphocytes.[4,5] Further mechanism that are implicated in the regulation of cancer immunogenicity are complex and include the induction of a DNA damage response, the onset of ER stress and the release of mitochondrial DNA.[6–8]

There is ample preclinical evidence that the induction of ICD can sensitize models of established lung cancer to subsequent immunotherapy with immune check-point blockade in mice. Thus, the tyrosine kinase inhibitor crizotinib, which induces ICD through off-target effects, yields a 90% cure rate in a model of orthotopic non-small cell lung cancers (NSCLC), when combined with standard-of-care chemotherapy and subsequent PD-1-based immune checkpoint blockade.[9] Consistently, in mice bearing genetically induced $KRAS^{+}/TP53^{-}$ NSCLC, the ICD-induced agent oxaliplatin enhances the effect of subsequent CTLA-4 and PD-1-checkpoint inhibition.[10] In both studies, the frequency of tumor-infiltrating immune effectors increased over that of immunosuppressive cells, indicating that the induction of ICD converted 'cold' into 'hot' tumors, rendering them susceptible to subsequent immune checkpoint blockade.

Several clinical reports support the hypothesis that ICD-induced treatments sensitize malignant neoplasms to subsequent immunotherapy with immune checkpoint blockade.[11] NSCLC patients that received a combination of standard of care chemotherapy with immunostimulatory irradiation together with subsequent PD-L1 blockade exhibited a significantly higher overall survival than the placebo group. Thus, the combination of standard-of-care chemotherapy with immunogenic irradiation and immune checkpoint blockade was more efficient than

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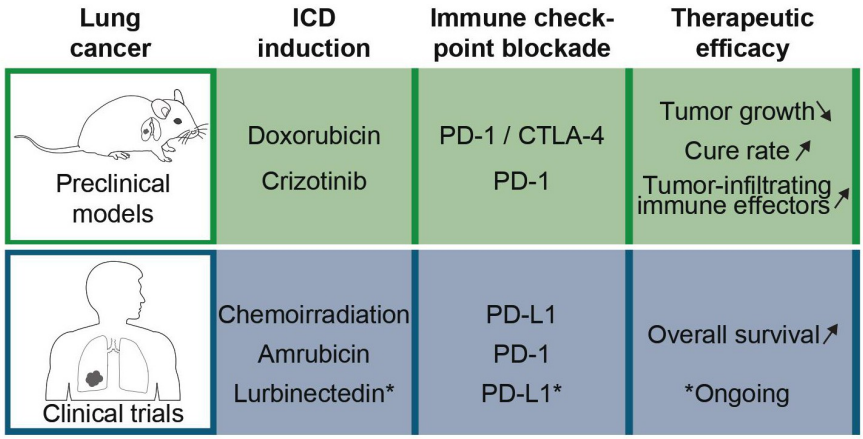

Figure 1. Pre-clinical and clinical evidence for the efficacy of immunogenic chemotherapy plus immune checkpoint blockade in lung cancer. In mouse studies, the induction of immunogenic cell death (ICD) by crizotinib or doxorubicin sensitizes established orthotopic lung cancers to subsequent immunotherapy with immune checkpoint blockade. Consistently, non-small cell lung cancer patients responded to the combination of ICD-inducing chemoradiotherapy or amrubicin with immune checkpoint blockade by an improved overall survival. An ongoing trial evaluates the combination of lurbinectedin with PD-L1 targeting immunotherapy against small cell lung cancers.

chemoradiotherapy alone.[12] Furthermore, induction therapy followed by PD-1 blockade in metastatic triple-negative breast cancer patients yielded the highest objective response rate (35% as compared to 20% in the overall cohort) when the women were initially treated with the ICD-induced anthracycline doxorubicin.[13] Recently, the notion that ICD stimulates tumors to immune checkpoint blockade was corroborated by another study that showed the efficacy of the anthracycline amrubicin (AMR) in combination with anti-PD-1 targeting immunotherapy in patients with relapsed small cell lung cancer (SCLC).[14] Here, the overall response rate (ORR) was 52% with a median progression-free survival (PFS) of 4 months and a PFS rate at 1 year of 14.4%.[14] This warrants further investigation and supports the rationale of other studies that combine immunogenic chemotherapy with immune checkpoint blockade such as the ongoing clinical trial NCT04253145 employing the immunogenic agent lurbinectedin with anti-PD-L1 in SCLC (Figure 1). Similar to chemotherapy, induction of ICD by radiotherapy has been linked to increased sensitivity to immune checkpoint blockade in various preclinical settings[15–17] as well as in some clinical trials targeting lung cancer (notably the PACIFIC study[18] and a recent study by Altorki and colleagues).[19]

A growing literature now points to the critical importance of treatment sequencing for immuno-oncology regimens, especially when it comes to ICD inducers and immune checkpoint inhibitors.[20–24] In sum, ample clinical evidence supports the concept of an ICD-mediated sensitization to immune checkpoint blockade in treatment-resistant diseases such as lung cancer. We anticipate that future clinical trials will establish optimal combination regimens that will further increase efficacy while reducing chemotherapy-associated side effects.

Disclosure statement

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