



The rationale behind targeting the ICOS-ICOS ligand costimulatory pathway in cancer immunotherapy

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ABSTRACT

Inducible T cell costimulator (ICOS, cluster of differentiation (CD278)) is an activating costimulatory immune checkpoint expressed on activated T cells. Its ligand, ICOSL is expressed on antigen-presenting cells and somatic cells, including tumour cells in the tumour microenvironment. ICOS and ICOSL expression is linked to the release of soluble factors (cytokines), induced by activation of the immune response. ICOS and ICOSL binding generates various activities among the diversity of T cell subpopulations, including T cell activation and effector functions and when sustained also suppressive activities mediated by regulatory T cells. This dual role in both antitumour and protumour activities makes targeting the ICOS/ICOSL pathway attractive for enhancement of antitumour immune responses. This review summarises the biological background and rationale for targeting ICOS/ICOSL in cancer together with an overview of the principal ongoing clinical trials that are testing it in combination with anti-cytotoxic T lymphocyte antigen-4 and anti-programmed cell death-1 or anti-programmed cell death ligand-1 based immune checkpoint blockade.

INTRODUCTION

Immune responses are tightly regulated by a variety of coinhibitory and costimulatory pathways that can be targeted in cancer immunotherapy. Using agonistic or antagonistic antibodies (Abs) to manipulate normal immune regulatory pathways, it has been shown that this can reinvigorate or generate de novo memory immune responses to the tumour. This memory then functions to recognise over the long-term circulating, disseminated or residual tumour cells expressing tumour-associated antigens (Ags). Remarkable benefit from immunotherapy has been observed in specific subsets of cancer patients, highlighting the need to optimise patient selection for treatments as well as improve their effectiveness and activity in different settings to broaden the patient population deriving benefit.

Cancer immunotherapy challenges clinicians not only for the differential diagnosis and management of patients^{1–3} but also for the new spectra of emerging and potentially long-lasting toxicities it induces.^{1–3} In

addition, the timing for optimal assessment of responses are variable,⁴ different organ sites may have peculiar patterns⁵ and abscopal effects can occur⁶ with responses obtained in non-irradiated sites after radiotherapy (RT). Another research priority is to overcome resistance to cancer immunotherapy⁷ and further potentiate its activity and effectiveness by using combinational approaches. Currently, a variety of combinations use the established anti-cytotoxic T-lymphocyte Ag-4 (CTLA-4) and anti-programmed cell death-1 (PD-1) and its ligand (PD-L1) Abs with other treatments, including chemotherapy, targeted therapy, RT and other immune checkpoint modulators.

The inducible costimulator (ICOS or cluster of differentiation (CD278)) of T cells and its ligand (ICOSL) play important roles in memory and effector T cell development and specific humoral immune responses. Although their role in cancer is still a subject of investigation, this pathway has been shown to potentiate immunosuppression mediated by some CD4⁺ T cell subsets, such as regulatory T cells (Tregs).⁸ Interactions between ICOS and ICOSL can have antitumour effects as increases in both CD4⁺ICOS⁺ and CD8⁺ICOS⁺ T cell subpopulations, which paralleled an increased ratio of effector T cells (Teff)/Tregs in the tumour microenvironment (TME), were observed in patients treated with anti-CTLA-4 Ab.⁸ Thus, a potential role for this pathway in improving the effectiveness of cancer immunotherapy is being investigated in early phase trials using agonistic or antagonistic Abs administered alone or more often in combination with other immunotherapeutic treatments.

The aim of this review is to summarise the biological background and rationale for targeting the ICOS/ICOSL pathway in tumours, as well as the principal ongoing trials testing it in combination with anti-CTLA-4 and anti-PD-1 or anti-PD-L1 based immune checkpoint blockade (ICB).

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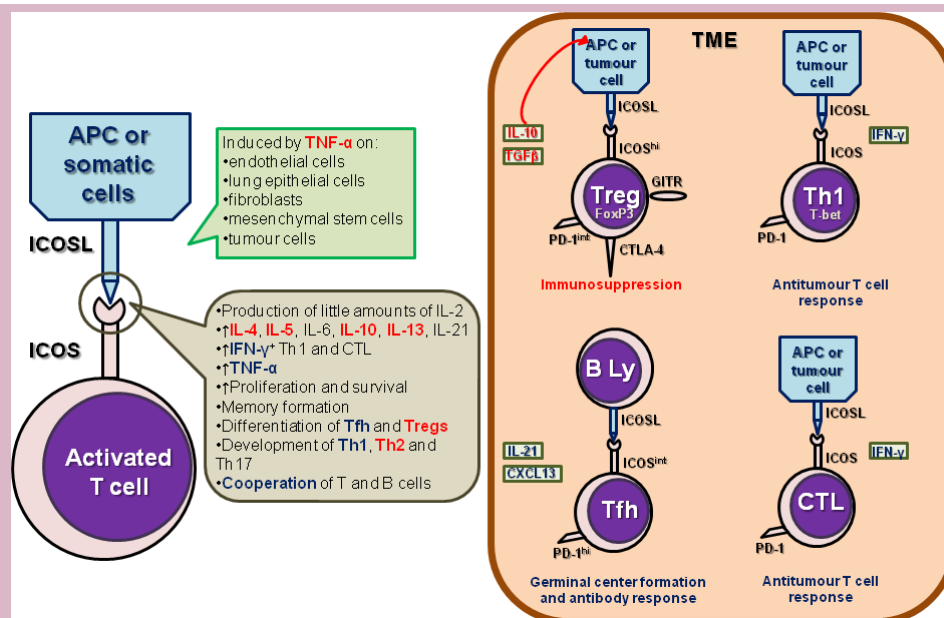


Figure 1 Biology of ICOS in the tumour microenvironment. ICOS is expressed by different T lymphocyte subpopulations, comprising CD8⁺ cytotoxic T lymphocytes (CTL), CD4⁺ helper T cells (Th), including Th1, Th2, Th17 and follicular helper T (Tfh) cells and CD4⁺ FoxP3⁺ regulatory T cells (Tregs). Its main ligand, ICOSL is expressed by antigen-presenting cells (APCs, including B lymphocytes) and by somatic (including tumour) cells. The interaction between ICOS and ICOSL has agonistic/stimulating activities, promoting an antitumour response by Th1, CTL and Tfh and of a protumour response mediated by Tregs and Th2 in the tumour microenvironment. Figure represents the crosstalk between ICOS⁺ T cell subsets and ICOSL-expressing cells and the effects of ICOS/ICOSL interaction. In red: protumour activities or effects; in blue: antitumour activities or effects.

ICOS BIOLOGY

ICOS, first identified in humans 20 years ago, is the third member of the CD28 coreceptor family, which are all involved in regulating T cell activation and adaptive immune responses.⁹ ICOS has significant homology with the other two family members, costimulatory CD28 and coinhibitory receptor CTLA-4. Furthermore, T cells costimulated by ICOS can achieve levels of activation comparable to CD28. ICOS signals induce production of a wide spectra of cytokines by CD4⁺ T helper (Th) cells, CD4⁺ forkhead box P3 (FoxP3⁺) Tregs and CD8⁺ cytotoxic T lymphocytes (CTL) that function to enhance their proliferation and direct memory cell development (figure 1).

Unlike CD28, which is constitutively expressed on both naïve and a majority of memory T cells, ICOS expression is induced after activation with only a small fraction of resting memory T cells expressing it at low levels. ICOSL, the unique ligand of ICOS, is constitutively expressed by professional antigen-presenting cells (APCs), including B cells, macrophages and dendritic cells (DCs).¹⁰ In contrast to the restriction of the CD28 and CTLA-4 ligands (CD80 and CD86) largely to lymphoid tissues, ICOSL is widely expressed on somatic cells (figure 1). It can be induced by tumour necrosis factor- α on many non-lymphoid cells including endothelial cells, lung epithelial cells, fibroblasts, mesenchymal stem cells and tumour cells.^{11–15}

ICOS costimulation, in contrast to the CD28 pathway, results in inefficient IL-2 production by activated T cells; however, other cytokines including IL-4, IL-10 and IL-21

are often more efficiently induced (figure 1).^{9, 16} This confers a specific role for ICOS in regulating Th cell subset differentiation in the early stages of activation. The requirement for ICOS signalling has been most studied in Treg and follicular Th cell (Tfh) differentiation. ICOS is highly expressed on human tonsillar PD-1^{hi} CXCR5^{hi} Tfh, whose function is to promote high-affinity Ag-specific B cell responses (figure 1). In the peripheral blood, CD25^{hi}FoxP3⁺ Tregs express the highest levels of ICOS with ICOS⁺ circulating Tfh a subpopulation shown increased in autoimmune diseases.¹⁷ Furthermore, the differentiation of the Th2 and Th17 subpopulations is also dependent on ICOS and ICOS costimulation can efficiently induce Th1 cytokine expression. In mouse models of infection, ICOS deficiency or ICOS/ICOSL signalling disruption using blocking Abs can either reduce or increase IFN- γ ⁺ Th1 and thereby have an effect on both Th1 and Tregs.¹⁸

In human cancer, ICOS expression on FoxP3⁺ Tregs is well established. In comparison to their counterparts in the periphery, Treg tumour-infiltrating lymphocytes (TIL) express increased levels of FoxP3 and several other markers including CTLA-4, glucocorticoid-induced TNFR family related gene and ICOS in addition to secreting higher levels of IL-10 and TGF β (figure 1). ICOS^{hi} Tregs isolated from melanoma had superior immunosuppressive activities compared with ICOS^{lo} Tregs and were capable of converting CD4⁺CD25⁻ T cells (non-Tregs) into IL-10 expressing suppressive type-1 regulatory T cells (Tr1).¹⁹ Freshly isolated ICOS⁺ Tregs also displayed

high proliferation (Ki67) rates, indicating *in vivo* activation at the tumour site.^{20,21} Plasmacytoid pre-DCs (pDCs) are particularly poised to express ICOSL upon maturation and regulate T cell IL-10 expression.²² Through ICOS/ICOSL interactions, tumour-infiltrating pDCs or tumour cells themselves can support local Treg survival and sustain FoxP3 expression as well as IL-10 production.^{13,20,23} In gastric cancer, despite a decrease in total FoxP3⁺ Tregs in parallel with intensifying tumour stages, the ICOS⁺ subset persisted and ICOS⁺ Treg TIL were associated with shorter survival.²⁴ In primary and secondary liver tumours, a significant Tr1 presence was detected and correlated with intratumoral pDC abundance.²⁵ Similarly, ICOSL signalling from pDCs was shown to be critical for IL-10 induction in lymphocyte-associated gene 3⁺FoxP3⁻CD4⁺ TIL, indicating a functional role of pDCs in generating Tr1 through ICOS activation.

In addition to regulatory TIL populations, a few studies have linked ICOS expression to other Th subsets infiltrating human tumours. Dominant ICOS expression was detected on Th1 TIL expressing the Th1 transcription factor T-bet and producing IFN- γ in colorectal cancer.¹⁴ Further, they found that high levels of ICOS expression were associated with improved clinical outcomes and ICOSL was highly expressed on macrophages. In breast cancer (BC), our studies revealed that activated Treg TIL express high levels of ICOS (ICOS^{hi}) and intermediate levels of PD-1 (PD-1^{int}), while PD-1 high (PD-1^{hi}) effector CD4⁺ TIL (including CXCL13⁺IL21⁺ Tfh) express intermediate levels of ICOS (ICOS^{int}) (figure 1).²¹ Both populations are characterised by prominent proliferation and are positively correlated with one another, except for a few tumours containing unbalanced, high levels of Tregs. ICOS expression on CD8⁺ TIL is less intense than on CD4⁺ TIL, due to the absent versus low expression of FoxP3. Interestingly, we found that PD-1^{hi}ICOS^{int} CD8⁺ BC TIL are similar to their CD4⁺ counterparts and notably express CXCL13 (Gu-Trantien, unpublished observation; Noël *et al*, manuscript in preparation). ICOS ligation is also critical for generating polyfunctional IFN- γ -coexpressing human Th17 that are capable of mediating effective anti-tumour functions.²⁶

ICOS was also shown to be an important element in the persistence of CD4⁺ chimeric Ag receptor (CAR) T cells, a

form of passive immunotherapy which is currently in use in clinical trials, particularly for haematological malignancies.²⁷ A recent study demonstrated that the intracellular signalling domain of ICOS could enhance the *in vivo* persistence of CD4⁺ CAR T cells, which in turn maintain CD8⁺ T cells in mouse tumour models.²⁸ The most effective antitumour activity was reached when ICOS was coupled with the intracellular signalling domain of the costimulatory receptor 4-1BB in CAR T cells.

TARGETED AGENTS UNDER DEVELOPMENT

The ICOS/ICOSL axis has been shown to promote either antitumour T cell responses (when activated in Th1 and other Teff) or protumour responses when triggered in Tregs. Therefore, both agonistic and antagonistic monoclonal Abs (mAbs) targeting this pathway are being investigated for cancer immunotherapy (table 1).²⁹⁻³¹

In preclinical studies, ICOS agonistic mAbs potentiate the effects of anti-CTLA-4. ICOS knockout mice do not respond well to anti-CTLA-4,³² suggesting that ICOS signalling is required for effective antitumour responses, likely mediated by Teff (figure 2). Thus, concomitant CTLA-4 and ICOS stimulation had a superior antitumour effect compared with anti-CTLA-4 alone.³³ Interestingly, mice and patients treated with anti-CTLA-4 or anti-PD-1 expanded the ICOS^{hi} (FoxP3⁻) CD4⁺ and CD8⁺ T cell subpopulations, signalling a treatment benefit³³⁻⁴⁰ with ICOS^{hi} T cells potentially an important biomarker for clinical response.^{39,41} ICOS alone appears to be less potent compared with other pathways targeted by cancer immunotherapies, primarily because of the predominance of CD4⁺ Tregs. Using ICOS agonistic or antagonistic Abs in combination with CTLA-4 or PD-1/PD-L1 has the potential to generate potent synergistic effects (figure 2).^{33,42}

The first-in-human trial, INDUCE-1 (NCT02723955), used an ICOS agonist Ab administered alone (part 1) or in combination with an anti-PD-1 (pembrolizumab; part 2) in patients with advanced solid tumours and had promising results in terms of tolerability, toxicity profile and clinical activity.⁴³ The most frequent treatment-related adverse events (AEs) were: fatigue (15%), fever (8%), elevation of hepatic enzymes (5%, representing also the most frequent grade 3-4 AE) and diarrhoea (3%).

Table 1 Compounds targeting ICOS currently under clinical investigation

Name	Characteristics	Clinical trial phase	Company
Anti-ICOS agonists			
GSK3359609	Anti-ICOS agonist monoclonal antibody (humanised IgG4)	Phase I, II	GlaxoSmithKline
JTX-2011	Anti-ICOS agonist monoclonal antibody (humanised)	Phase I	Jounce Therapeutics
Anti-ICOS antagonists			
MEDI-570	Anti-ICOS monoclonal antibody (Fc-optimised humanised IgG1)	Phase I	National Cancer Institute (NCI)
KY1044	Anti-ICOS monoclonal antibody (fully human) IgG1 κ	Phase I/II	Kymab Limited

Fc, fragment crystallisable; ICOS, inducible T cell costimulator.

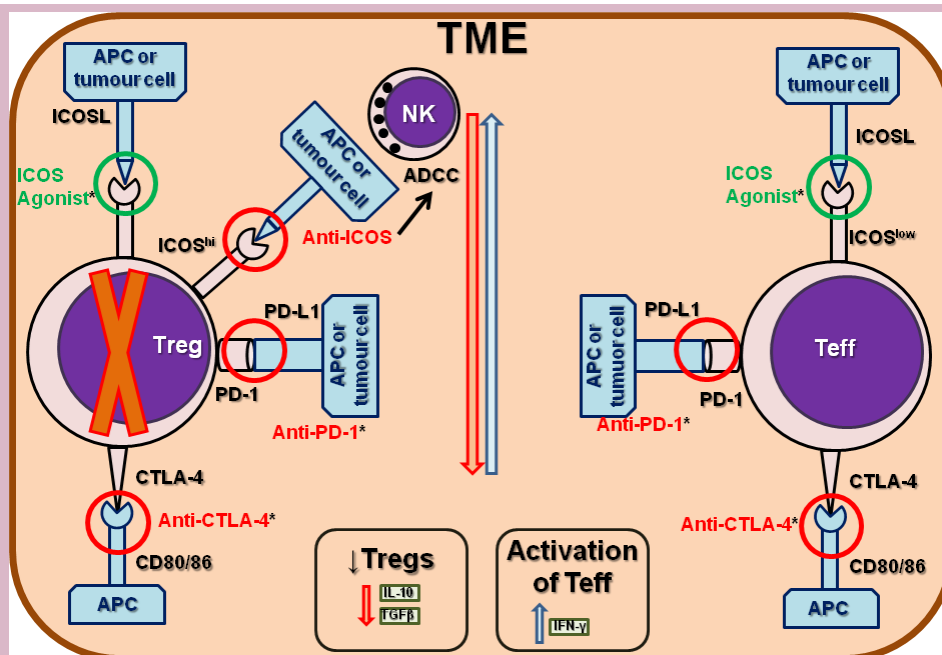


Figure 2 Targeting regulatory and/or effector T cells with ICOS agonistic or antagonistic antibodies. ICOS can be targeted by either agonist (in green) and antagonistic (in red) antibodies (Abs). ICOS agonists are usually administered in concomitance with anti-CTLA-4 or anti-PD-1 Abs, for their ability to synergistically inhibit the suppressive activity of regulatory T cells (Tregs) and to potentiate the antitumour activity of effector T cells (Teff), including CD4⁺ and CD8⁺ subpopulations. One main mechanism of action of ICOS antagonistic Abs is to inhibit Tregs by stimulating the antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by natural killer (NK) cells. CTLA-4, cytotoxic T-lymphocyte Ag-4; PD-1, programmed cell death-1.

One dose limiting grade 3 pneumonitis occurred.⁴⁴ The ICONIC trial (NCT02904226) investigated the role of an ICOS agonist Ab (JTX-2011) given alone (mono arm) or in combination with an anti-PD-1 (nivolumab; combo arm) in patients with relapsed/refractory tumours. Currently, the data show this compound is safe, well tolerated and can generate antitumour responses in heavily pretreated gastric cancer and triple-negative BC patients. The most common dose limiting toxicities were an increase in the hepatic enzymes and pleural effusion in patients from the mono arm. Grade 3–4 drug-related AEs were 8% in the mono, 13% in the combo; immune-related AEs were 4% in the mono, 21% in the combo; infusion-related AEs were 12% in the mono and 19% in the combo. Interestingly, peripheral blood CD4⁺ICOS^{hi} T cell subpopulations appear to be a promising biomarker of response.⁴⁵

ICOS antagonistic Abs have shown limited antitumour activity via their abrogation of Treg-mediated immune suppression and thereby potentially enhancing CTL-mediated immune responses directed to tumour cells. These compounds principally prevent interactions between ICOS⁺ T cells (particularly CD4⁺ Tregs) and ICOSL⁺ pDCs. Their principal activity is to prevent pDC-induced proliferation, the accumulation of ICOS^{hi} Tregs and inhibit IL-10 secretion by CD4⁺ T cells. Noteworthy, fragment crystallisable optimisation has the advantage of inducing antibody-dependent cellular cytotoxicity.⁴⁶

Overall, these data indicate that the ICOS pathway plays a critical role in effective responses to anti-CTLA-4

and perhaps other ICB agents. Similar to T-cell immunoglobulin and mucin-domain containing-3, ICOS mAbs are unlikely to be used as monotherapy because they do not independently induce cytotoxic immune responses.⁴⁷

CURRENT ONGOING CLINICAL TRIALS

Agonistic Abs are currently being administered either alone (NCT03447314, NCT02904226) or in combination with immunotherapy, including ICB as well as with chemotherapy (NCT03693612, NCT03447314, NCT02723955, NCT03739710, NCT02904226). In one trial, the anti-ICOS mAb MEDI-570 is being tested alone (NCT02520791), while in another, the anti-ICOS Ab KY1044 (NCT03829501) is being tested alone (phase I and II arms) or in combination with an PD-L1-based ICB (also phase I and II arms) (table 2). The principal mechanisms of action by either ICOS agonists or antagonists are shown in figure 2. A summary of the early phase ongoing clinical trials is provided in table 2.

CONCLUSIONS

The remarkable benefits observed by targeting the principal inhibitory regulatory pathways of the immune response in a variety of haematological and solid tumours, including CTLA-4 and particularly PD-1 and PD-L1, have stimulated investigation of new targets associated with alternative, non-redundant modulatory immune checkpoints, including ICOS/ICOSL. The emergence

Table 2 Clinical trials testing ICOS targeting antibodies in a variety of tumour types

ClinicalTrial.gov identifier	Tumour type	Setting	Phase	Treatment arms	Target accrual
Anti-ICOS agonists					
NCT03693612 (GSK3359609)	Advanced solid tumours (phase I); RR-HNSCC (phase II)	Advanced (phase I); RR (phase II)	I/II	Part 1: GSK3359609 <i>plus</i> anti-CTLA-4 tremelimumab; Part 2: GSK3359609 <i>plus</i> tremelimumab versus active comparators → single agent standard of care (docetaxel or paclitaxel or cetuximab)	115
NCT03447314 (GSK3359609)	Advanced solid tumours; recurrent, locally advanced or metastatic HNSCC	Advanced; recurrent, locally advanced or metastatic	I	Part 1B: GSK3359609 <i>plus</i> TLR-4 agonist GSK1795091; Part 1: PK/Pharmacodynamic cohort (GSK1795091; GSK3174998; GSK3359609; anti-PD-1 pembrolizumab); Part 2B: GSK1795091 <i>plus</i> GSK3359609	162
NCT02723955 (INDUCE-1) (GSK3359609)	Advanced solid tumours including: bladder/urothelial cancer of the upper and lower urinary tract; cervical; colorectal; esophageal, squamous cell; HNSCC; melanoma; malignant pleural mesothelioma; NSCLC; prostate; Microsatellite Instability-High/deficient mismatch repair tumour (Part 1B and Part 2B) and Human Papilloma Virus-positive or Epstein-Barr-positive tumour (Part 1B and Part 2B)	Locally advanced/metastatic or RR	I	Part 1A (dose escalation): GSK3359609; Part 1B (expansion): GSK3359609; Part 2A (dose escalation/safety run-in GSK3359609): GSK3359609; OX40 agonist GSK3174998; anti-PD-1 pembrolizumab; docetaxel; pemetrexed <i>plus</i> carboplatin; paclitaxel <i>plus</i> carboplatin; gemcitabine <i>plus</i> carboplatin; fluorouracil <i>plus</i> carboplatin or cisplatin; Part 2B (expansion-GSK3359609): GSK3359609 <i>plus</i> fluorouracil (5-FU) <i>plus</i> carboplatin or cisplatin <i>plus</i> pembrolizumab	500
NCT03739710	RR advanced NSCLC	RR advanced (previous first or second line of anti-PD-1/L1 allowed)	II	GSK3359609 <i>plus</i> docetaxel versus docetaxel	105
NCT02904226 (ICONIC) (JTX-2011)	Advanced and/or refractory solid tumours	Advanced and/or refractory	I/II	Part A: JTX-2011; Part B: JTX-2011 <i>plus</i> anti-PD-1 nivolumab; Part C: JTX-2011; Part D: JTX-2011 <i>plus</i> nivolumab; Part E: JTX-2011 <i>plus</i> anti-CTLA-4 ipilimumab; Part F: JTX-2011 <i>plus</i> ipilimumab; Part G: JTX-2011 <i>plus</i> anti-PD-1 pembrolizumab; Part H: JTX-2011 <i>plus</i> pembrolizumab	498
Anti-ICOS antagonists					
NCT02520791 (MEDI-570)	RR peripheral T-cell lymphoma-not otherwise specified; angioimmunoblastic T-cell lymphoma; follicular lymphoma; mycosis fungoides; cutaneous T-cell lymphoma	RR	I	MEDI-570	46
NCT03829501 (KY1044)	Advanced tumours (NSCLC, HNSCC, hepatocellular carcinoma, melanoma, cervical, esophageal, gastric, renal, pancreatic, and triple-negative BC; advanced cancer)	Advanced	I/II	Experimental phase I: KY1044; experimental phase I: KY1044 <i>plus</i> anti-PD-L1 atezolizumab; experimental phase II: KY1044; experimental phase II: KY1044 <i>plus</i> anti-PD-L1 atezolizumab	412

BC, breast cancer;CTLA-4, cytotoxic T-lymphocyte Ag-4; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer;PD-1, programmed cell death-1; PD-L1, programmed cell death – ligand 1; RR, relapsed/refractory; TLR, toll-like receptor.

of resistance to the initial drugs has paved the way for combination strategies using more than one immunomodulatory agent. The most active/successful combination thus far is anti-CTLA-4 *plus* anti-PD-1, despite their association with a significant increase in high grade

toxicities. A multitude of new approaches are being considered and implemented in clinical trials. Targeting the ICOS/ICOSL pathway holds considerable promise primarily because of its role in modulating Treg/Teff functions, including inhibiting Treg interactions with

ICOSL (ICOS antagonists) or potentiating anti-CTLA-4 and anti-PD-1 or anti-PD-L1 mAbs activities (ICOS agonists). The ICOS/ICOSL pathway can also modulate antitumour Teff responses by specifically modulating Th1 and CTL activities. Early phase clinical trials testing ICOS agonist Abs in patients with advanced solid tumours have shown good safety profiles and promising antitumour activities, particularly when the compounds are given as a combination with anti-PD-1 agents (pembrolizumab and nivolumab). Dose-limiting toxicities were not common occurrences, reinforcing these agents as promising new targets for combination cancer immunotherapy.

A variety of questions concerning targeting ICOS/ICOSL pathway in cancer immunotherapy remain unanswered. Studies are needed to understand how, at the fundamental level, targeting ICOS/ICOSL interactions impacts immune responses, including the generation of CD4⁺, CD8⁺ and B cell memory immune responses in tumour-associated tertiary lymphoid structures. In addition, more clinical information is needed on the optimal ICB target (anti-CTLA-4 versus anti-PD-1/PD-L1) for combination with ICOS/ICOSL, the identification of biomarkers for patient selection and the potential for combination with additional targets. More mature preliminary data from the current ongoing clinical trials should help to address some of these issues.

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