Editorial Commentary

Durvalumab plus novel agents in non-small cell lung cancer—a new COAST on the horizon?

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Non-small cell lung cancer (NSCLC) (80–85% of all lung cancers) continues to be one of the major causes of cancer related deaths around the world (1). Immunotherapy with monoclonal antibodies targeting programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) has become a standard of care treatment for patients with advanced or metastatic (NSCLC) in first and later treatment lines, however, prolonged and durable responses are only seen in approximately 10–20% of patients treated (2), and novel immune therapy strategies are urgently needed to improve patients' outcome.

Amongst these inhibitors durvalumab (Imfinzi®, AstraZencea, London, UK) is a highly specific human monoclonal antibody (IgG1-kappa) which inhibits the interaction of PD-L1 with PD-1 and CD80, but not PD-L2 (3). Treatment with durvalumab, either alone or in combination with chemotherapy, has demonstrated a significantly improved median overall survival (mOS) in NSCLC (PACIFIC Trial, NCT02125461; POSEIDON Trial, NCT03164616) (*Table 1*).

NKG2 (CD159) is belongs to a family of natural killer (NK) cell receptors (types A-F and H) [expressed on CD56-positive NK cells and cytotoxic T cells (CTLs)]. Receptor binding of NKG2A on NK cells and on CTLs leads to dimerisation with NKG2D (CD94) and results in NK cell or CTL inhibition (7). Tumour cells can bind NKG2A via HLA-E [human leukocyte antigen, belongs to the MHC-I (Major Histocompatibility class) family] and thereby inactivating NK cells and CTLs (8). Monalizumab is a first-in-class humanised IgG_4 antibody which blocks NKG2A-CD94 dimerisation, thereby preventing its interaction with HLA-E on tumour cells (9) (*Figure 1A*). NKG2A blockade has also been shown to be synergistic with PD-1 axis inhibition (10). CD56-positive NK cells express high levels of NKG2A, but low levels of killer cell immunoglobulin-like receptors (KIRs) suggesting that the selective inhibition might have greater activation potential (11).

Adenosine within the tumour microenvironment (TME) down-regulates the immune system ("adenosine cloud") by inhibiting the development and proliferation of T effector cells (12). In a first step ATP is cleaved into adenosine monophosphate (AMP) by CD39. CD39 is an ectonucleotidase expressed by B cells, innate cells, regulatory T cells as well as activated CD4 and CD8 T cells, which, in coordination with CD73 (a 5'-nucleotidase) can result in local production of adenosine leading to an immunosuppressive environment (12) (*Figure 1B*). To date, four different adenosine receptors have been identified: A1, A2A, A2B, A3, however, only types A2A and A2B are immune checkpoints and can be used as targets for cancer therapies (13).

Several adenosine A2A/B receptor antagonists have been evaluated in phase I/II trials [reviewed by Guerrero (14)]. Amongst them, oleclumab is monoclonal antibody targeting CD73 (15). In an early phase I/II study (N=21, NCT03381274) oleclumab plus osimertinib were studied in second-line NSCLC (epidermal growth factor receptor mutation, T790M negative, one prior line with

Table 1 Overall survival benefit following treatment with durvalumab alone or in combination with chemotherapy

Trial	NCT	N	Design	mOS	Reference
PACIFIC	NCT02125461	713	Durvalumab *vs.* Placebo after radio-chemotherapy (stage III, 1st line)	47 *vs.* 29.1 months	Antonia *et al.* 2018 (4)
POSEIDON	NCT03164616	1,013	Durvalumab plus Chemotherapy *vs.* Durvalumab + Tremelimumab + Chemotherapy *vs.* Chemotherapy (stage IIIB/IV, 1st line)	13.3 *vs.* 14.0 *vs.* 11.7 months (significant only for durvalumab plus tremelimumab and chemotherapy)	Johnson *et al.* 2021 (5), Doyle 2021 (6)

mOS, median overall survival; N, number of patients.

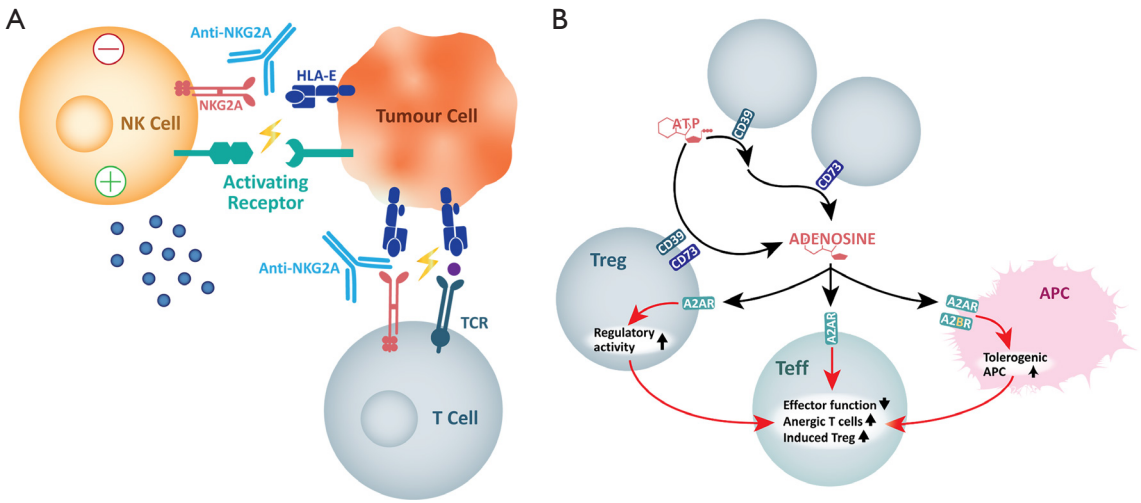

Figure 1 Molecular pathways involved in the inhibition of NK and T cells. (A) Binding of the NKG2A receptor on NK cells by HLA-E on tumour cells results in a depletion of NK cell activity and increased tumour cell survival. The monoclonal antibody monalizumab can restore the NK and T cell activity. (B) The cell surface markers CD39 and CD73 are expressed on various cells in the TME. Both molecules can convert AMP to adenosine ("adenosine cloud") which is a strong inhibitor of the T cell activity. Inhibitors of the adenosine receptors have been shown to overcome adenosine-induced T cell depletion. NKG2A, natural killer cell receptor G2A; HLA, human leukocyte antigen; AMP, adenosine monophosphate; TME, tumour microenvironment.

a TKI). The overall response rate (ORR) was found to be 19%, treatment-related AEs (all grade) were 81%.

In an attempt to further evaluate synergistic effects of PD-L1 blockade and inhibition of NKG2A or A-A2A receptors in NSCLC patients the COAST trial has been conducted. COAST (NCT03822351) is a global phase II study of durvalumab alone or combined with oleclumab or monalizumab as consolidation therapy (16). NSCLC patients with unresectable stage III disease and no progression after radio-chemotherapy were randomised to receive durvalumab alone or in combination combined with oleclumab (q2w first 2 cycles, then q4w) or monalizumab (q2w) for up to 12 months. The primary endpoint was ORR, secondary endpoints included progression-free survival (PFS) and safety.

A total of 186 patients received durvalumab (N=66), durvalumab plus oleclumab (N=59), or durvalumab plus monalizumab (N=61). Both combination treatments increased ORRs (38.1% *vs.* 37.1% *vs.* 25.4%, respectively), and significantly improved median progression-free survival (mPFS) versus durvalumab alone (not reached *vs.* 15.1 *vs.* 6.3 months, respectively). Overall, the most common grade 3/4 adverse events (AEs) were pneumonia (5.9%) and decreased lymphocyte count (3.2%); both were more common with durvalumab and durvalumab plus oleclumab than with durvalumab plus monalizumab. Combined rates

of pneumonitis and radiation pneumonitis of any grade were reported to be 21.2% with durvalumab, 28.8% with durvalumab plus oleclumab, and 21.3% with durvalumab plus monalizumab, with grade ≥3 events in 3.0%, 3.4% and 1.6%, respectively (16).

Collectively, the NKG2 inhibitor monalizumab is the first-in-class molecule with significant activity in NSCLC. The combination with immunotherapy in NSCLCs appeared to be feasible and is well tolerated. As a result, a phase III trial with a registrational intent is being planned. The vast majority of trials targeting the adenosine pathway (anti-CD73, A-A2A-R) are phase I/II trials (ciforadenant, CPI-006, oleclumab, BMS-986179, etc.). The results reported for the COAST trial now provide further evidence that complete and prolonged A-A2A-R inhibition is active and well tolerated in combination with an anti-PD-L1 monoclonal antibody. Predictive biomarkers, however, are needed to identify patients most likely to benefit from adenosine pathway blockade. The potential biomarker signature might extend from single analyte to multiplex analysis (multiple analytes) evaluated within the framework of biomarker development programmes contributing to patient stratification, pharmacokinetic/pharmacodynamic insights, target confirmation, and eventual efficacy assessments within controlled investigations. In addition, dual blockade of the adenosine pathway (either A-A2A/A2B-Rs or A-A2A-R plus CD73) might be the treatment of choice. This novel concept is currently evaluated in the ongoing ARC-7 trial (ARC-7, NCT04262856, N=150, first-line NSCLC): zimberelimab (anti-PD-1) versus zimberelimab plus domvanalimab (anti-TIGIT) versus zimberelimab plus domvanalimab + etrumadenant (dual adenosine receptor antagonist, A2a/A2B). The first interim analysis demonstrated no significant safety issues and promising efficacy (17).

Interestingly, despite the fact that the target population of the PACIFC and the COAST trials were identical, a huge difference in the reported mPFS values for durvalumab mono-therapy was observed (COAST *vs.* PACIFIC: 6.3 *vs.* 16.8 months) which clearly raises the question how reproducible trials with anti-PD-L1 monoclonal antibodies can be acknowledging that between trial heterogeneity in study characteristics and unexplored patient covariates may be as influential as the pharmacological properties of the test agent.

PD-L1 is constitutively expressed on different types of tumour cells including NSCLC, and PD-L1 expression has been reported to be upregulated by two general mechanisms: (I) innate immune response (resistance), and (II) and adaptive immune response (resistance) (18). PD-L1 expression is upregulated in some tumour cells by constitutive oncogenic signaling through aberrant activation of the PI3K-AKT pathway or chromosomal alterations and amplifications which is found in some cancers, independent of inflammatory signals in the TME (innate immune response) (18). In contrast, PD-L1 is not constitutively expressed in some tumour cells, but rather is inducibly expressed (i.e., adaptive immune resistance) in response to inflammatory signals elaborated by active antitumour immune responses, and many cytokines can induce or maintain PD-L1 expression (e.g., interferon-γ) (19).

These molecular mechanisms may add weight to the speculation that PD-L1 is a biological continuum and, therefore, is not just "present" (positive) or "absent" (negative)—a proposal which might explain, at least in part, the huge discrepancy of mPFS values seen for durvalumab in the PACIFC and the COAST studies.

Different immunologic approaches targeting immune checkpoint pathways have showing promise in development, and preclinical and clinical evidence provides the rationale for investigating the combination of co-stimulatory and inhibitory monoclonal antibodies to establish a novel or re-instating a pre-existing anti-tumour immune response. To improve response rates following immune therapy and to overcome resistance, studies with novel second- and third generation immuno-oncology drugs (e.g., NKG2, CD73) are clearly needed to significantly increase the current curative immune response rates in a diverse population of different cancers patients which will almost certainly require multiple complementary therapeutic modalities to overcome the immunesuppressive TME of established cancers exploiting some of the more innovative trial designs evaluating complementary pharmacotherapy and patient subgroups encountered in an era of precision oncology (20). In this regard, confirmatory trials are planned or ongoing, and results are eagerly awaited.

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Footnote

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