Editorial Commentary

Targeting the adenosine 2A receptor in non-small cell lung cancer: shooting with blank bullets?

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Non-small cell lung cancer (NSCLC) represents the 85% of all lung cancer diagnoses in the USA with about 195,000 new cases diagnosed each year (1-3). In the last two decades, we have witnessed a new era in NSCLC with the identification of not only different subtypes of lung cancer according to its molecular alterations (EGFR, ALK, ROS1, MET, BRAF, RET or NTRK) but also with the development of new drugs like immunotherapies [e.g., checkpoint inhibitors targeting programmed death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)], and tyrosine kinase inhibitors (TKIs) targeting these molecular alterations and the immune microenvironment of lung cancer (1-4). Nowadays, NSCLC's treatment includes the use of immunotherapy, targeted agents and classical chemotherapy (2,3). However, despite all the new advances in the treatment of this disease, it is still considered one of the leading causes of cancer death worldwide with an only 19% of patients are alive 5 years after the diagnosis (1-4). Because of the high incidence and poor prognosis of NSCLC, research for the discovery of new therapeutic approaches continues and it is currently an area of major interest in oncology (5).

Checkpoint inhibitors such as anti-CTLA-4, anti-PD(L)-1 have shown to stop cancer-generated immunotolerance and improve survival of patients with different cancers over the last twenty years (6). However, due to the large number of immunosuppressive mechanisms used by tumors, it is becoming increasingly clear that targeting multiple immunosuppressive pathways may increase therapeutic efficacy (7,8). Indeed, much of the research effort is focused on better understanding the tumor microenvironment and turning it into an additional therapeutic weapon against cancer in the era of immunotherapy (7,9). One of these immunosuppressive pathways is the adenosine-CD39-CD73 axis.

Adenosine has been shown to limit inflammatory responses by binding to the adenosine 2A receptor (A2AR), reducing collateral damage performed by inflammatory cells and cytokines in normal tissue (9-11). Adenosine is overexpressed in the tumor microenvironment as a consequence of the Warburg effect (anaerobic metabolism in hypoxic regions and a preference for aerobic metabolism in non-hypoxic areas), resulting from rapid cell growth, death and stress, leading to up-regulation of CD39, CD73 and A2AR expression and, ultimately, secretion of anti-inflammatory cytokines, promoting up-regulation of PD-1 and CTLA-4, generation of LAG-3 and Foxp3+ regulatory T cells (9-12). Ultimately, promoting T-cell anergy (12).

Considering that A2AR activation inhibits immune response, it has been tested if A2AR antagonists alone or in combination with anti-PD-1 have any effect in cancer cells (11). Beavis *et al.* discovered that the administration of an antagonist of A2AR in monotherapy in mice with

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Table 1 Clinical trials targeting ADOA2AR in oncology

NCT code	Status	Study title	Condition	Phase
NCT05501054	Not yet recruiting	Phase 1b/2 Trial of Ipilimumab, Nivolumab, and Ciforadenant (Adenosine A2a Receptor Antagonist) in First-line Advanced Renal Cell Carcinoma	Renal cell carcinoma	Phase I/II
NCT03207867	Active, not recruiting	A Phase 2 Study of NIR178 in Combination With PDR001 in Patients With Solid Tumors and Non-Hodgkin Lymphoma	Non-small cell lung cancer, renal cell cancer, pancreatic cancer, urothelial cancer, head and neck cancer, diffused large b cell lymphoma, microsatellite stable colon cancer, triple negative, breast cancer, melanoma, metastatic castration resistant prostate cancer	Phase II
NCT02403193	Completed	Trial of PBF-509 and PDR001 in Patients With Advanced Non-small Cell Lung Cancer (NSCLC) (AdenONCO)	Non-small cell lung cancer	Phase I
NCT03549000	Terminated	A Phase I/Ib Study of NZV930 Alone and in Combination With PDR001 and /or NIR178 in Patients With Advanced Malignancies	Non-small cell lung cancer, triple negative breast cancer, pancreatic ductal adenocarcinoma, colorectal cancer microsatellite stable, ovarian cancer, renal cell carcinoma, metastatic castration resistant prostate cancer	Phase 1
NCT04969315	Not yet recruiting	TT-10 as a Single Agent in Subjects With Advanced Selected Solid Tumors	Renal cell cancer, castrate resistant prostate cancer, non-small cell lung cancer	Phase 1/2
NCT03381274	Active, not recruiting	Oleclumab (MEDI9447) Epidermal Growth Factor Receptor Mutant (EGFRm) Non-small Cell Lung Cancer (NSCLC) Novel Combination Study	Non-small cell lung carcinoma	Phase 1/2
NCT04089553	Active, not recruiting	An Open-label, Phase II Study of AZD4635 in Patients With Prostate Cancer	Prostate cancer, metastatic castration-resistant prostate cancer	Phase 2
NCT02655822	Completed	Phase 1/1b Study to Evaluate the Safety and Tolerability of Ciforadenant Alone and in Combination With Atezolizumab in Advanced Cancers	Renal cell cancer, metastatic castration resistant prostate cancer	Phase 1
NCT03454451	Active, not recruiting	CPI-006 Alone and in Combination With Ciforadenant and With Pembrolizumab for Patients With Advanced Cancers	Non-small cell lung cancer, renal cell cancer, colorectal cancer, triple negative breast cancer, cervical cancer, ovarian cancer, pancreatic cancer, endometrial cancer, sarcoma, squamous cell carcinoma of the head and neck, bladder cancer, metastatic castration resistant prostate cancer, non-Hodgkin lymphoma	Phase 1

NCT, National Clinical Trial.

breast cancer or melanoma enhanced natural killer (NK) maturation and cytotoxic function, reduced metastasis and boosted NK cell expression of granzyme B (13). In a more recent paper, Mittal *et al.* tested the combination of an A2AR antagonist with an anti-PD-1 monoclonal antibody in experimental and spontaneous mouse models of melanoma and breast cancer (8). They showed that the combination was superior to the monotherapy in terms of reducing metastatic burden and prolonging survival (8). This efficacy was dependent on NK cells and interferon gamma (IFNg), and to a lesser extent, $CD8^+$ T cells and its effector molecule, perforin (8).

Due to these good results in mouse models, A2AR antagonists have been tested in patients with cancer and other non-oncological diseases like neurodegenerative diseases or coronary syndromes (*Table 1*).

Chiappori *et al.* have recently published the results of a phase 1 clinical trial with the administration of an oral A2AR antagonist, taminadenant (PBF509/NIR178) alone or in combination with intravenous anti-PD-1, spartalizumab, in patients with NSCLC who had previously progressed to, at least, one previous line of therapy (5). The drug was well tolerated and the recommended phase 2 dose as single agent was 480 mg twice daily (BID) and 240 mg BID in combination with 400 mg spartalizumab Q4W. The efficacy results are, however, disappointing: an objective response rate of 9.5% and 8.3% for single agent and combination respectively. The authors, in fact note that

Table 2 Clinical trials targeting ADOA2AR and CD73

NCT code	Status	Study Title	Condition	Phase
NCT03381274	Active, not recruiting	Oleclumab (MEDI9447) Epidermal Growth Factor Receptor Mutant (EGFRm) Non-small Cell Lung Cancer (NSCLC) Novel Combination Study	Non-small cell lung cancer	Phase 1/2
NCT03549000	Terminated	A Phase I/Ib Study of NZV930 Alone and in Combination With PDR001 and /or NIR178 in Patients With Advanced Malignancies.	Non-small cell lung cancer, triple negative breast cancer, pancreatic ductal adenocarcinoma, colorectal cancer microsatellite stable, ovarian cancer, renal cell carcinoma, metastatic castration resistant prostate cancer	Phase 1
NCT04660812	Active, not recruiting	An Open Label Study Evaluating the Efficacy and Safety of Etrumadenant (AB928) Based Treatment Combinations in Participants With Metastatic Colorectal Cancer. (ARC-9)	Metastatic colorectal cancer	Phase 1/2

the follow up phase 2 study (NCT03207867) confirmed that the combination of taminadenant plus spartalizumab did not show sufficient activity in patients with NSCLC and therefore, it will not be further developed for this indication. Similar results in terms of safety and efficacy were found with a different A2AR antagonist, ciforadenant, alone or in combination with atezolizumab in patients with refractory renal cell cancer (9).

With these disappointing results, other potential targets in the adenosine-CD39-CD73 axis are getting tested. CD73 and CD39 are ecto-nucleotidases responsible for converting adenosine triphosphate (ATP) into adenosine monophosphate (AMP) and finally into adenosine, which eventually binds to A2AR (14,15). In fact, several preclinical models have demonstrated that CD73 is upregulated in different solid tumors, including NSCLC, making its overexpression a poor prognostic factor (5,14,15).

Several clinical trials are currently active, testing the potential effect of an anti-CD73 antibody, alone and in combination with an A2AR inhibitor and an anti-PD-(L)1 in patients with advanced solid tumors (14). Preclinical studies showed that co-targeting A2AR and CD73 together increases the therapeutic efficacy of clinically approved immunotherapies in terms of tumor initiation, growth and metastasis (14). Clinical trials are ongoing testing the combination of A2AR inhibitors and anti-CD73 antibodies in patients with advanced malignancies, with no published results yet (*Table 2*).

A deeper understanding of the mechanisms of cancer immune evasion beyond CTLA-4, PD1 and PDL1 blockade may increase survival in cancer patients as shown with the results of anti-LAG3 therapy for metastatic melanoma (NCT03470922) (16). Of these, the adenosine-CD39-CD73 pathway is a promising one, with solid preclinical background. In this regard, the observation reported by Chiappori *et al.* shows how blockage of the adenosine-CD39-CD73 axis using an A2AR antagonist (taminadenant) alone or in combination with anti-PD-1 is clinically feasible, but not sufficient to achieve a meaningful effect in patients with NSCLC. Further studies with additional combinations will be required to place this axis in the treatment algorithms for this disease (5).

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Adaptimmune, ADC Therapeutics, Aduro, Agenus, Amcure, Amgen, Astellas, AstraZeneca Bayer Beigene BioInvent International AB, BMS, Boehringer, Boheringer, Boston, Celgene, Daichii Sankyo, DEBIOPHARM ,Eisai, e-Terapeutics, Exelisis, Forma Therapeutics, Genmab, GSK, Harpoon, Hutchison, Immutep, Incyte, Inovio, Iovance, Janssen, Kyowa Kirin, Lilly, Loxo, MedSir, Menarini, Merck, Merus, Millennium, MSD, Nanobiotix, Nektar, Novartis, Odonate Therapeutics, Pfizer, Pharma Mar, PharmaMar, Principia, PsiOxus, Puma, Regeneron, Rigontec, Roche, Sanofi, Sierra Oncology, Synthon, Taiho, Takeda, Tesaro, Transgene, Turning Point Therapeutics and Upshersmith. The other author has no conflicts of interest to declare.

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