

Supplementary Table S1: Patient Demographics

Variable	N = 514 ¹
Age (median (range))	61 (24, 93)
Sex	
Female	310 (60%)
Male	204 (40%)
PD-L1 immunohistochemistry >=1	156 (30%)
(Missing)	1
Microsatellite instability high	15 (3.4%)
(Missing)	74
Tumor mutational burden ≥10 mutations/mb	33 (7.3%)
(Missing)	64
High ADORA2A expression	
High (≥75 th percentile rank)	107 (20.8%)
Low	407 (79.2%)
Cancer Types	
Adrenal Gland Cancer	3 (0.6%)

Variable	N = 514 [†]
Basal Cell Carcinoma of the Skin	1 (0.2%)
Bladder Cancer	4 (0.8%)
Brain and Nervous System Cancer	3 (0.6%)
Breast Cancer	49 (9.5%)
Cervical Cancer	5 (1.0%)
Colorectal Cancer	140 (27%)
Esophageal Cancer	17 (3.3%)
Gallbladder/Extrahepatic Bile Duct Cancers	4 (0.8%)
Head and Neck Cancer	12 (2.3%)
Kidney and Renal Pelvis Cancer	3 (0.6%)
Lipomatous Neoplasms	2 (0.4%)
Liver and Bile Duct Cancer	19 (3.7%)
Lung Cancer	20 (3.9%)
Melanoma	6 (1.2%)
Mesothelioma	2 (0.4%)
Neuroendocrine Tumors	15 (2.9%)

Variable	N = 514 [†]
Ocular melanoma	1 (0.2%)
Ovarian Cancer	43 (8.4%)
Pancreatic Cancer	55 (11%)
Primary peritoneal carcinoma	1 (0.2%)
Prostate Cancer	4 (0.8%)
Sarcoma	24 (4.7%)
Small Intestine Cancer	12 (2.3%)
Squamous Cell Carcinoma of the Skin	3 (0.6%)
Stomach Cancer	25 (4.9%)
Thymic Cancer	1 (0.2%)
Thyroid Cancer	3 (0.6%)
Carcinoma of unknown primary (CUP)	13 (2.5%)
Uterine Cancer	24 (4.7%)

Supplementary Table S2. Examples of completed or ongoing trials of adenosine receptor antagonists in oncology

Drug	Target	Diseases	Company	Number of clinical trials registered in NCT (clinicaltrials.gov)	Comment/Results
NIR178 in combination with PDR001 Phase II Active but not recruiting.	NIR178 is an A2A adenosine receptor antagonist. PDR001 is an anti PD1	NSCLC RCC Pancreatic Cancer Urothelial Cancer HNSCC Diffused Large B Cell Lymphoma Microsatellite Stable Colon Cancer TNBC Melanoma Metastatic CRPC	Novartis	NCT03207867	
Etrumadenant (AB928) in combination with mFOLFOX Phase I/Ib completed.	Etrumadenant is an A2A and A2B adenosine receptor antagonist.	Advanced stage Gastroesophageal cancer Colorectal cancer.	Arcus Biosciences, Inc.	NCT03720678	None yet
PBF-509 +PDR001 Phase I completed.	PBF-509 (A2A adenosine receptor antagonist)	NSCLC	Novartis	NCT02403193	
Drug: Ciforadenant (arm 1) Ciforadenant +Atezolizumab (arm 2)	Ciforadenant, an oral small molecule targeting the-A2A adenosine receptor.	RCC CRPC	Genentech	NCT02655822	For cifrodenant monotherapy arm high-grade arthralgia, peripheral edema and anemia were

Phase I completed					<p>observed in 3% cases. For combination arm grade $\frac{3}{4}$ abdominal, pain, high AST, hypophosphatemia and arthralgia was observed in 2.9% cases.</p> <p>Ciforadenant plus atezolizumab showed a partial response of 11%</p>
SRF617 in combination with etrumadenant and zimberelimab Phase II Recruiting	<p>Etrumadenant is an A2aR and A2bR antagonist. SRF 617 is CD39 inhibitor.</p> <p>Zimberelimab is a fully human anti-PD-1 monoclonal antibody.</p>	Metastatic CRPC	Arcus Biosciences, Inc.	NCT05177770	
Zimberelimab + Domvanalimab + Etrumadenant Phase 2 Recruiting	<p>Etrumadenant is an A2A and A2B adenosine receptor antagonist. Zimberelimab is an anti PD1 antibody, Domvanalimab is anti TIGIT antibody.</p>	NSCLC	Arcus Biosciences	NCT04262856	
DFF332 + +PDR001 (Spartalizumab) +NIR178 (Taminadenant)	DFF332(Hif2alpha inhibitor) + PDR001 is anti PD1 inhibitor + NIR178 which is an adenosine A2A adenosine receptor antagonist.	RCC	Novartis	NCT04895748	
Etrumedanant + Zimberelimab	Etrumedanant is an A2A adenosine receptor antagonist.	NSCLC, HNSCC, CRC, Melanoma, Bladder Cancer,	Arcus Bio	NCT03629756	

Phase I completed	Zimberelimab is an anti PD1 antibody	Ovarian Cancer, Endometrial Cancer, RCC, CRPC			
Etrumadenant IPI- 549 Pegylated Liposomal Doxorubicin (PLD) Nanoparticle albumin-bound paclitaxel	Etrumedenant is an A2A adenosine receptor antagonist. IPI-549 is PI3kinase gamma inihibitor	TNBC Ovarian Cancer	Arcus Bio	NCT03719326	
Preladenant, pembrolizumab Phase I	Preladenant is A2A adenosine receptor antagonist.	Solid tumors	Merck Sharp & Dohme Corp.	NCT03099161	
AZD4635	A2A adenosine receptor antagonist.	Solid tumors	Astrazeneca	NCT03980821	
Regorafenib, atezolizumab, imprime PGG, bevacizumab, isatuximab, selicrelumab, idasanutlin, AB928	AB928 is a small-molecule A2A/A2B adenosine receptor antagonist	CRC	Hoffmann–La Roche	NCT03555149	
PBF1129. Nivolumab	A2B Receptor Inhibitor	NSCLC	Palobiofarma	NCT05234307	
Inupadenant	A2A Receptor Inhibitor	Solid tumors	iTeos Therapeutics	NCT05060432	

Foot note: Data search as of June17th, 2023 (Pubmed and Clinicaltrials.gov).

Abbreviations: Castrate-resistant prostate cancer (CRPC); Colorectal cancer (CRC); Head and neck squamous cell carcinoma (HNSCC); Non-small cell lung cancer (NSCLC); Renal cell carcinoma (RCC); Triple-negative breast cancer (TNBC).