Supplemental Table 1

Combination in Clinical Trials	Pre-clinical Data	Current Clinical Trials in Children	Current Clinical Trials in Adults
Anti-PD-1 and/or anti-CTLA-4 + anti-VEGF	Anti-VEGF reverses T cell exhaustion and shows synergistic treatment effects when combined with anti-PD-L1 in pre-clinical testing (1)	▪ No trials in children	▪ Glioblastoma (NCT03452579) ▪ HGG (NCT02829931) ▪ NSCLC (NCT02574078) ▪ Brain metastases (NCT02681549) ▪ CRC (NCT03396926) ▪ Ovarian cancer (NCT03596281) ▪ Nasopharyngeal carcinoma (NCT03813394) ▪ RCC (NCT02210117) ▪ Melanoma (NCT01950390, NCT00790010)
Anti-PD-1 and/or anti-CTLA-4 + anti-RANKL	Anti-RANKL disrupts T cell negative selection in the thymus, allowing for the rescue of tumor-specific clones and the enhanced efficacy of anti-PD-1 in pre-clinical testing (2, 3)	▪ No trials in children	▪ Melanoma (NCT03620019, NCT03161756) ▪ NSCLC (NCT03669523, ACTRN12618001121257)
Anti-PD-1 + anti-TGF	Anti-TGF-β promotes T cell penetration into tumors, stimulates anti-tumor immunity and tumor regression when combined with anti-PD-1 in pre-clinical testing (25)	▪ No trials in children	▪ Advanced malignancies (NCT02947165)
Anti-PD-1 and/or anti-CTLA-4 + IDOi	IDOi promotes T cell infiltration and proliferation in tumors and improves tumor control when combined with anti-PD-1 or anti-CTLA-4 in pre-clinical testing (4)	▪ No trials in children	▪ Solid tumors (NCT03491631, NCT02959437, NCT03085914, NCT03459222, NCT03347123) ▪ Gastrointestinal tumors (NCT03291054) ▪ NSCLC (NCT03322540) ▪ Melanoma (NCT04007588, NCT02073123) ▪ Head and neck carcinomas (NCT03358472, NCT03854032) ▪ Pancreatic cancer (NCT03006302) ▪ Glioblastoma (NCT03707457, NCT04047706) ▪ RCC (NCT03260894) ▪ Liver cancer (NCT03695250)

Anti-PD-1 and/or anti-CTLA-4 + HDACi (entinostat)	Entinostat neutralises MDSCs and enhances T cell anti-tumor responses when combined with anti-PD-1 in pre-clinical testing (5, 6)	▪ High-risk cancers (NCT03838042)	▪ Solid tumors (NCT02453620, NCT02909452) ▪ NSCLC (NCT01928576) ▪ Cholangiocarcinoma and pancreatic adenocarcinoma (NCT03250273) ▪ RCC (NCT03552380) ▪ Bladder cancer (NCT03978624) ▪ Melanoma (NCT03765229, NCT02697630) ▪ Breast Cancer (NCT02453620) ▪ NSCLC, CRC, Melanoma (NCT02437136)
Anti-PD-1 and/or anti-CTLA-4 + HDACi (panobinostat)	Panobinostat upregulates PD-L1 expression by tumor cells, and controls tumor progression and improves survival when combined with anti-PD-1 in pre-clinical testing (7)	▪ No trials in children	▪ Melanoma and NSCLC (NCT03982134) ▪ CRC, NSCLC, TBBC, RCC (NCT02890069) ▪ Melanoma (NCT02032810)
Anti-PD-1 and/or anti-CTLA-4 + HDACi (vorinostat)	Vorinostat upregulates PD-L1 and MHC expression by tumor cells, increases T cell infiltration and controls tumor progression and improves survival when combined with anti-PD-1 in pre-clinical testing (8)	▪ No trials in children	▪ RCC and urothelial cell carcinoma (NCT02619253) ▪ Glioblastoma (NCT03426891) ▪ NSCLC (NCT02638090)
Anti-PD-1 and/or anti-CTLA-4 + BRAFi (dabrafenib) + MEKi (trametinib)	BRAFi + MEKi enhances T cell infiltration into tumors, increases tumor antigen expression and is very effective when combined with anti-PD-1 in pre-clinical testing (9)	▪ No trials in children	▪ Melanoma (NCT02130466, NCT01940809, NCT02967692, NCT02858921) ▪ CRC (NCT03668431)
Anti-PD-1 + RTKi (sunitinib)	Sunitinib reduces MDSC, increases CD8+ T cell infiltration, and in combination with anti-PD-1, induces complete tumor regression in pre-clinical testing (10)	▪ No trials in children	▪ Sarcomas (NCT03277924) ▪ RCC (NCT03729245, NCT02960906, NCT03075423) ▪ GIST (NCT03609424)
Anti-PD-1 and/or anti-CTLA-4 + RTKi (cabozantinib)	No preclinical testing of cabozantinib with immune checkpoint inhibitors reported	▪ No trials in children	▪ RCC (NCT03729245, NCT03793166, NCT03937219, NCT03635892, NCT03141177) ▪ TNBC (NCT03316586) ▪ Endometrial Cancer (NCT03367741) ▪ Genitourinary Tumors (NCT03866382, NCT02496208) ▪ Thyroid cancer (NCT03914300) ▪ HCC (NCT01658878, NCT03299946)

Anti-PD-1 and/or anti-CTLA-4 + RTKi (axitinib)	Axitinib reduces MDSCs and significantly improves survival when combined with anti-PD-1 in pre-clinical testing (11)	▪ RCC (NCT03595124), soft tissue sarcomas (NCT02636725)	▪ RCC (NCT03595124, NCT02853331, NCT03172754)
Anti-PD-1 + RTKi (regorafenib)	Regorafenib limits tumor growth, decreases MDSC numbers and increases IFN-γ production when combined with anti-PD-1 in pre-clinical testing (12)	▪ No trials in children	▪ CRC (NCT03657641) ▪ HCC (NCT03347292)
Anti-PD-1 + RTKi (nintedanib)	Nintedanib significantly improves anti-tumor responses when combined with anti-PD-1 in pre-clinical testing (13)	▪ No trials in children	▪ NSCLC (NCT03377023)
Anti-PD-1 and/or anti-CTLA-4 + RTKi (lenvatinib)	Lenvatinib decreases MDSC and increases T cell infiltration in tumors, and significantly improves anti-tumor responses when combined with anti-PD-1 in pre-clinical testing (14, 15)	▪ No trials in children	▪ Solid tumors (NCT03797326) ▪ Gastroesophageal Cancer (NCT03321630) ▪ NSCLC (NCT03976375, NCT03829332, NCT03829319, NCT03516981) ▪ Liver cancers (NCT03895970, NCT03779100, NCT03951597, NCT04042805, NCT03713593) ▪ Endometrial cancers (NCT03517449) ▪ Urothelial cancers (NCT03898180) ▪ Melanoma (NCT03820986)
Anti-PD-1 + RTKi (apatinib)	Apatinib decreases MDSC and increases T cell infiltration in tumors, and significantly improves survival when combined with anti-PD-L1 in pre-clinical testing (16)	▪ Soft tissue sarcoma (NCT03711279), sarcoma (NCT04126993), osteosarcoma (NCT03359018)	▪ Solid tumors (NCT03491631) ▪ Gastric Cancer (NCT03954756, NCT03878472, NCT04006821) ▪ CRC (NCT03912857) ▪ TNBC (NCT03945604, NCT03394287) ▪ SCLC (NCT03417895) ▪ Oesophageal cancer (NCT03736863, NCT03603756) ▪ NSCLC (NCT03777124) ▪ Cervical cancer (NCT03816553) ▪ Liver cancer (NCT03092895) ▪ HCC (NCT03839550, NCT03793725, NCT04014101, NCT03722875) ▪ Ovarian cancer (NCT04068974) ▪ Sarcomas (NCT03711279, NCT03359018) ▪ Melanoma (NCT03955354)
Anti-PD-1 + RTKi (anlotinib)	No preclinical testing of Anlotinib with immune checkpoint inhibitors reported	▪ Soft tissue sarcomas (NCT03946943)	▪ SCLC (NCT04055792) ▪ NSCLC (NCT03765775) ▪ HCC (NCT04052152)

Anti-PD-1 + RTKi (fruquintinib)	Fruquintinib improves anti-tumor response when combined with anti-PD-L1 in pre-clinical testing (17)	▪ No trials in children	▪ Solid tumors (NCT03903705)
Anti-PD-1 + RTKi (imatinib)	Imatinib improves anti-tumor T cell responses when combined with anti-PD-1 in pre-clinical testing (18)	▪ No trials in children	▪ GIST (NCT03609424)

Supplemental Table 1: Immune checkpoint inhibitors in combination with other immunomodulatory drugs in clinical trials for adult and pediatric cancers. BRAFi, BRAF inhibitor; CRC, colorectal cancer; GIST, Gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; HDACi, histone deacetylase inhibitor; HGG, high-grade gliomas; IDO, indoleamine 2, 3 dioxygenase; MDSC, myeloid-derived suppressor cell; MEKi, mitogen-activated protein kinase inhibitor; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand-1; RANKL, receptor activator of nuclear factor kappa-B ligand; RCC, renal cell carcinoma; RTKi, receptor tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor.

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