

# The emerging role of epigenetic therapeutics in immuno-oncology

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Supplementary Table S1 | Ongoing clinical trials of combined epigenetic therapy and immune-checkpoint inhibition

ClinicalTrials.gov identifier (study name)	Cancer type	Epigenetic agent	Immune-checkpoint inhibitor	Study Phase
<b>Combinations with DNMTi</b>				
NCT03264404	Advanced-stage PDAC	Azacitidine	Pembrolizumab (anti-PD-1 antibody)	Phase II
NCT02260440	Refractory metastatic CRC	Azacitidine	Pembrolizumab	Phase II
NCT03769532 (PEMAZA)	<i>NPM1</i> -mutated AML	Azacitidine	Pembrolizumab	Phase II
NCT02845297	R/R AML or newly diagnosed AML (in patients aged $\geq 65$ years)	Azacitadine	Pembrolizumab	Phase II
NCT03094637	MDS	Azacitidine	Pembrolizumab	Phase II
NCT02397720	AML	Azacitidine	Nivolumab (anti-PD-1 antibody) $\pm$ ipilimumab (anti-CTLA-4 antibody)	Phase II
NCT02530463	MDS	Azacitidine	Nivolumab and/or ipilimumab	Phase II
NCT02775903	Newly diagnosed high-Risk MDS or AML (in patients aged $\geq 65$ years)	Azacitidine	Durvalumab (anti-PD-L1 antibody)	Phase II
NCT02951156 (Javelin DLBCL)	R/R DLBCL	Azacitidine	Avelumab (anti-PD-L1 antibody) + utomilumab (anti-4-1BB agonistic antibody) $\pm$ rituximab and bendamustine	Phase I/III
NCT02959437 (ECHO-206)	Advanced-stage solid tumours, including previously treated stage IIIB or stage IV NSCLC or stage IV MSS CRC	Azacitidine	Pembrolizumab + epacadostat (IDO1 inhibitor)	Phase I/II
NCT03628209	Resectable recurrent osteosarcoma	Azacitidine	Nivolumab	Phase I/II
NCT03825367	Paediatric R/R AML	Azacitidine	Nivolumab	Phase I/II
NCT03161223	R/R PTCL	Azacitidine	Durvalumab ( $\pm$ romidepsin)	Phase I/II
NCT03019003	Recurrent and/or metastatic HNSCC previously treated with immune-checkpoint inhibition	Azacitidine	Durvalumab + tremelimumab (anti-CTLA-4 antibody)	Phase I/II
NCT03699384	AML with minimal residual disease (detectable at any level by multiparameter flow cytometry of a bone marrow aspirate)	Azacitidine	Avelumab	Phase I/II
NCT02953561	R/R AML, including AML arising from previous MDS, CMML or myeloproliferative neoplasm	Azacitidine	Avelumab	Phase I/II
NCT03390296	AML	Azacitadine	Avelumab (+ gemtuzumab ozogamicin or venetoclax), or avelumab + PF-04518600 (anti-OX40 agonistic monoclonal antibody)	Phase I/II
NCT02117219	MDS	Azacitidine	Durvalumab $\pm$ tremelimumab	Phase I
NCT02546986	Advanced-stage NSCLC (previously treated)	CC-486 (oral azacitidine)	Pembrolizumab	Phase II
NCT02816021	Advanced-stage melanoma with or without prior PD-1 treatment	CC-486	Pembrolizumab	Phase II
NCT02900560	Platinum-resistant and/or platinum refractory epithelial ovarian, fallopian tube or primary peritoneal cancer	CC-486	Pembrolizumab	Phase II
NCT02811497 (METADUR)	Advanced-stage solid tumours, including MSS CRC, platinum-resistant epithelial ovarian cancer type II or oestrogen receptor-positive and HER2-negative breast cancer	CC-486	Durvalumab	Phase II
NCT02512172	Advanced-stage MSS CRC	CC-486	Pembrolizumab	Phase I
NCT02957968	HER2-negative, hormone receptor-positive or triple-negative locally advanced breast cancer	Decitabine	Pembrolizumab (prior to standard neoadjuvant therapy)	Phase II
NCT03250962	R/R Hodgkin lymphoma	Decitabine	Camrelizumab (SHR-1210;	Phase II

			anti-PD-1 antibody)	
NCT02996474	R/R AML	Decitabine	Pembrolizumab	Phase I/II
NCT03346642	PMBCL	Decitabine	Camrelizumab (+ gemcitabine, vinorelbine and doxorubicin chemotherapy)	
NCT03969446	MDS or AML	Decitabine	Pembrolizumab	Phase I
NCT03240211	PTCL or CTCL	Decitabine	Pembrolizumab (± pralatrexate)	Phase I
NCT03445858	R/R non-primary CNS solid tumours or lymphomas (in paediatric or young adult patients)	Decitabine	Pembrolizumab + hypofractionated index site radiation	Early phase I (pilot)
NCT02890329	R/R MDS or AML	Decitabine	Ipilimumab	Phase I
NCT03395873	AML (in patients who are unfit for first-line intensive chemotherapy)	Decitabine	Avelumab	Phase I
NCT03358719	MDS or AML	Decitabine	Nivolumab, poly ICLC and CDX-1401 (anti-DEC-205 antibody–NY-ESO-1 fusion protein, which is a DC-targeted cancer vaccine)	Phase I
NCT03066648	High-risk MDS or AML	Decitabine	Spartalizumab (anti-PD-1 antibody) and/or MBG453 (anti-TIM3 antibody)	Phase I
NCT02664181 (PRECISE)	Advanced-stage NSCLC (second line)	Tetrahydrouridine (cytidine deaminase inhibitor) + oral decitabine (THU-DAC)	Nivolumab	Phase II
NCT03233724	Advanced-stage NSCLC (first line)	THU-DAC	Pembrolizumab	Phase I/II
NCT02901899	Recurrent, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer	Guadecitabine	Pembrolizumab	Phase II
NCT03179943	Recurrent and/or metastatic urothelial carcinoma that is R/R to PD-1 or PD-L1 immune-checkpoint inhibition	Guadecitabine	Atezolizumab (anti-PD-L1 antibody)	Phase II
NCT03576963	Refractory metastatic CRC	Guadecitabine	Nivolumab	Phase I/II
NCT03308396	Advanced-stage clear cell RCC	Guadecitabine	Durvalumab	phase I/II
NCT02935361	Advanced-stage MDS or R/R CMML	Guadecitabine	Atezolizumab	Phase I/II
NCT02998567 (HyPeR)	Advanced-stage CRPC, NSCLC or other solid tumours	Guadecitabine	Pembrolizumab	Phase I
NCT03257761	Advanced-stage hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer or PDAC	Guadecitabine	Durvalumab	Phase I
<b>Combinations with HDACi</b>				
NCT03765229	Non-inflamed stage III–IV melanoma	Entinostat	Pembrolizumab	Phase II
NCT02697630 (PEMDAC)	Metastatic uveal melanoma	Entinostat	Pembrolizumab	Phase II
NCT03978624	Muscle-invasive bladder cancer	Entinostat	Pembrolizumab	Phase II
NCT03179930	R/R lymphomas	Entinostat	Pembrolizumab	Phase II
NCT03250273	Previously treated advanced-stage cholangiocarcinoma or PDAC	Entinostat	Nivolumab	Phase II
NCT03552380	RCC previously treated with nivolumab + ipilimumab	Entinostat	Nivolumab + ipilimumab	Phase II
NCT02437136	Advanced-stage NSCLC, melanoma or mismatch repair-proficient CRC	Entinostat	Pembrolizumab	Phase Ib/II
NCT02708680	Triple-negative breast cancer	Entinostat	Atezolizumab	Phase Ib/II
NCT02915523	Advanced-stage epithelial ovarian, peritoneal or fallopian tube cancer	Entinostat	Avelumab	
NCT03838042 (INFORM2 NivEnt)	Children and adolescents with high-risk refractory malignancies	Entinostat	Nivolumab	Phase I/II
NCT03024437	Advanced-stage RCC	Entinostat	Atezolizumab (+ bevacizumab)	Phase I/II
NCT03280563	Advanced-stage hormone receptor-positive,	Entinostat	Atezolizumab (± fulvestrant	Phase I/II

(MORPHEUS)	HER2-negative breast cancer (after progression on CDK4/6 inhibitor)		and ipatasertib)	
NCT02909452	Advanced-stage solid tumours	Entinostat	Pembrolizumab	Phase I
NCT02936752	MDS after failure of DNMTi therapy	Entinostat	Pembrolizumab	Phase I
NCT02453620	Advanced-stage solid tumours, including HER2-negative breast cancer	Entinostat	Nivolumab + ipilimumab	Phase I
NCT02395627	Metastatic oestrogen receptor-positive, hormone therapy-resistant breast cancer	Vorinostat	Pembrolizumab (± tamoxifen)	Phase II
NCT02638090	Metastatic NSCLC	Vorinostat	Pembrolizumab	Phase I/II
NCT02538510	Advanced-stage, recurrent HNSCC or salivary gland cancer	Vorinostat	Pembrolizumab	Phase I/II
NCT02619253	Advanced prostate or urothelial carcinoma, or RCC	Vorinostat	Pembrolizumab	Phase I/Ib
NCT03426891	Newly diagnosed glioblastoma	Vorinostat	Pembrolizumab (+ temozolomide and radiotherapy)	Phase I
NCT03150329	R/R DLBCL, follicular lymphoma or Hodgkin lymphoma	Vorinostat	Pembrolizumab	Phase I
NCT02954991	NSCLC	Mocetinostat	Nivolumab	Phase II
NCT02805660	Advanced-stage NSCLC or other solid tumours	Mocetinostat	Durvalumab	Phase I/II
NCT03565406	Advanced-stage melanoma	Mocetinostat	Nivolumab + ipilimumab	Phase Ib
NCT03278782	R/R PTCL	Romidepsin	Pembrolizumab	Phase I/II
NCT02393794	Triple-negative breast cancer	Romidepsin	Nivolumab (+ cisplatin)	Phase I/II
NCT03161223	R/R PTCL	Romidepsin	Durvalumab (± azacitidine or pralatrexate)	Phase I/II
NCT03357757 (LATENT)	Virus-associated cancers	Valproic Acid	Avelumab	Phase II
NCT02032810	Advanced-stage melanoma	Panobinostat	Ipilimumab	Phase I
<b>Combinations with EZH2i</b>				
NCT03525795 (ORION-E)	Various advanced-stage solid tumours previously treated with a PD-1 or PD-L1 inhibitor	CPI-1205	Ipilimumab	Phase I/II
NCT03854474	Advanced-stage urothelial carcinoma	Tazemetostat	Pembrolizumab	Phase I/II
NCT02220842	R/R follicular lymphoma or DLBCL	Tazemetostat	Atezolizumab	Phase I
<b>Combinations with LSD1i</b>				
NCT02712905	Advanced-stage SCLC that has previously progressed on platinum-based treatment	INCB059872	Pembrolizumab	Phase I/II
NCT02959437 (ECHO-206)	Advanced-stage solid tumours, including previously treated stage IIIB or stage IV NSCLC or stage IV MSS CRC	INCB059872 (LSD1i)	Pembrolizumab + epacadostat (IDO1 inhibitor)	Phase I/II
NCT02712905	Advanced-stage solid tumours or haematological malignancies	INCB059872 (plus azacitidine in those with treatment-naïve AML)	Nivolumab (in those with advanced-stage SCLC)	Phase I/II
<b>Combinations with BETi</b>				
NCT02959437 (ECHO-206)	Advanced-stage solid tumours, including previously treated stage IIIB or stage IV NSCLC or stage IV MSS CRC	INCB057643 (BETi)	Pembrolizumab + epacadostat (IDO1 inhibitor)	Phase I/II
NCT02419417 (BET)	Selected advanced-stage solid tumours or haematological malignancies	BMS-986158 (BETi)	Nivolumab	Phase I/IIa
<b>Combinations with multiple epigenetic agents</b>				
NCT01928576	Recurrent and/or metastatic NSCLC	Azacitidine + entinostat	Nivolumab	Phase II
NCT03161223	R/R PTCL	Azacitidine + romidepsin	Durvalumab	Phase I/II
NCT03220477	Advanced-stage NSCLC (that has progressed on treatment involving an anti-PD-1 or anti-PD-L1 antibody)	Guadecitabine + mocetinostat	Pembrolizumab	Phase I

AML, acute myeloid leukaemia; BETi, bromodomain and extra-terminal motif protein inhibitor; CMML, chronic myelomonocytic leukaemia; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTCL, cutaneous T cell lymphoma; CTLA-4, cytotoxic T lymphocyte protein 4; DLBCL, diffuse large B cell lymphoma; DNMTi, DNA methyltransferase inhibitor; EZH2, enhancer of Zeste homologue 2; HDACi, histone deacetylase inhibitor; HNSCC,

head and neck squamous cell carcinoma; IDO1, indoleamine 2,3-dioxygenase 1; LSD1i, lysine-specific histone demethylase 1A (also known as KDM1A) inhibitor; MDS, myelodysplastic syndrome; MSS, microsatellite stable; NSCLC, non-small-cell lung cancer; NY-ESO-1, New York esophageal squamous cell carcinoma 1; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; PDAC, pancreatic ductal adenocarcinoma; PMBCL, primary mediastinal large B cell lymphoma; PTCL, peripheral T cell lymphoma; RCC, renal cell carcinoma; R/R, relapsed and/or refractory; SCLC, small-cell lung cancer; TIM3, T cell immunoglobulin and mucin-domain containing 3 (also known as HAVCR2).