

Merkel Cell Carcinoma—Update on Diagnosis, Management and Future Perspectives

Table S1. Available active and/or recruiting and/or not yet recruiting, interventional clinical trials and expanded access programs (EAP) for combination therapies with checkpoint inhibitors for advanced unresectable or metastatic MCC available at <https://clinicaltrials.gov/> as of April 2022. N: Number of patients for original estimated enrollment, RP2D: Recommended phase 2 dose, TLR: Toll like receptor, BORR: Best overall response rate, MTD: Maximum tolerated dose.

Available Clinical trials with Checkpoint Inhibitors in Combination Therapies for Advanced Unresectable or Metastatic MCC					
NCT number	Phase	N	Drugs	Mode of action	Primary objective
04393753	2	40	- Domatinostat - Avelumab in patients progressing under anti-PD1/PD-L1	- Histone deacetylase inhibitor - Anti-PD-L1	ORR
03787602	1b/2	27	- KRT-232 +/- - Avelumab in p53 Wild-Type MCC	- Oral inhibitor of MDM2, an E3 ubiquitin ligase - Anti-PD-L1	RP2D of KRT-232 ORR
04261855	1b/2	65	- Avelumab + Lutetium-177-Dotatate - Avelumab + External Beam Radiation	- Anti-PD-L1 - Peptide receptor radionuclide therapy	PFS at 12 months
04590781	1b/2	142	- XmAb18087 +/- - Pembrolizumab	- Monoclonal antibody targeting somatostatin receptor 2 and CD3 - Anti-PD-1	Treatment-emergent adverse events ORR, CR, PR rate
03901573	1b/2a	64	- Atezolizumab - NT-17	- Anti-PD-L1 - Efineptakin Alfa, a fusion protein of recombinant IL-7 and a hybrid Fc region	MTD, RP2D of NT-17
02978625	2	68	- Intralesional TVEC followed by TVEC and Nivolumab	- Oncolytic herpes virus immunotherapy - Anti-PD-1	Response rate to TVEC alone BORR to combination
04916002	2	268	- Intralesional CMP-001 - Cemiplimab-rwlc	- TLR9 agonist - Anti-PD-1	ORR
04116320	1	32	- Focused US Ablation +/- - Standard-of-care anti-PD1 +/- - Imiquimod	- Continuous high-intensity focused US to ablate tissue - Anti-PD-1 - TLR7/8 agonist	Safety of FUSA Proportion of patients with increased CD8+ T cell tissue infiltration
03747484	1/2	16	- FH-MCVA2TCR - Avelumab or Pembrolizumab,	- Autologous MCPyV-specific HLA-A02-restricted TCR-	Toxicity BORR

			- Radiation therapy	transduced CD4+ and CD8+ T-cells - Anti-PD-1	
03435640	1/2	393	- Intralesional NKTR-262 - Bempegaldesleukin - +/-Nivolumab	- TLR7/8 agonist - CD122 agonist - Anti-PD-1	Safety and tolerability ORR
03000257	1	118	- Venetoclax - Rovzalpituzumab Tesirine - ABBV-181	- BCL-2 inhibitor - Antibody-drug conjugate directed against delta-like protein 3 - Anti-PD-1	Safety Pharmacokinetics of venetoclax and ABBV-181
02635672	1	50	- VIP152 with dose-escalation - Pembrolizumab	- CDK9 inhibitor - Anti-PD-1	Safety Pharmacokinetics MTD, RP2D
04458259	1	37	- PF-07265807 +/- - Sasanlimab	- Axl/mertk tumor-associated macrophage kinase inhibitor - Anti-PD-1	Safety ORR and CR rate
04551885	1	27	- FT516 - Avelumab	- CD16 Fc receptor - Anti-PD-1	Dose-limiting toxicities
05069935	1	189	- FT538 - Avelumab	- Allogeneic NK-cell immunotherapy - Anti-PD-L1	Safety RP2D
03841110	1	64	- FT500 +/- - ICI (nivolumab, pembrolizumab, atezolizumab) +/- - IL-2	- Allogeneic, iPSC-derived NK cell immunotherapy - ICI	Dose-limiting toxicity
03228667	2	105	- N803 - PD-1/PD-L1 inhibitors +/- - PD-L1 t-haNK	- IL15 superagonist complex combined with BCG - NK-92 expressing IL-2, CD16 and a CAR recognizing PD-L1	ORR
04234113	1/1b	96	- SO-C101 +/- - Pembrolizumab	- IL15 superagonist - Anti-PD-1	Safety Dose-limiting toxicities
03074513	2	160	- Atezolizumab - Bevacizumab	- Anti-PD-L1 - Anti-VEGF	ORR
04902040	1b/2	12	- Radiation therapy - PD-1/PD-L1 inhibitors +/- - Plinabulin after progression on anti-PD-(L)1	- Radiation therapy - PD-1/PD-L1 inhibitors +/- - Polymerization of tubulin blockade	Safety ORR
05269381	1	36	-Cyclophosphamide - Neoantigen peptide vaccine - Sargramostim - Pembrolizumab	- Chemotherapy - Vaccine - GM-CSF - Anti-PD-1	Safety
03236935	1b	12	- L-NMMA - Pembrolizumab	- NG-monomethyl-L-arginine, a pan-nitric oxide synthase inhibitor - Anti-PD-1	MTD
04725331	1/2a	48	- Intralesional BT-001 - Pembrolizumab	- Oncolytic Vaccinia virus encoding for human CTLA4-specific antibody 4-E03 and human GM-CSF - Anti-PD-1	Safety RP2D ORR Disease control rate

05086692	1/2	80	- MDNA11 +/- - Anti-PD1 or Anti-PD-L1	- Long-acting "beta-only" recombinant interleukin-2 (rIL- 2) albumin fusion - Anti-PD1 or Anti-PD-L1	Safety RP2D
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Table S2. Available active and/or recruiting and/or not yet recruiting, interventional clinical trials and expanded access programs (EAP) for checkpoint inhibitors in advanced unresectable or metastatic MCC available at <https://clinicaltrials.gov/> as of April 2022. N: Number of patients for original estimated enrollment, RP2D: Recommended phase 2 dose, EAP: expanded access program, TLR: Toll like receptor, MTD: Maximum tolerated dose.

Available Clinical Trials with Checkpoint Inhibitors in Advanced Unresectable or Metastatic MCC

NCT number	Phase	N	Drugs	Mode of action	Primary objective
03783078	3	50	- Pembrolizumab as first-line agent	- Anti-PD-1	ORR
04792073	2	36	- Avelumab - Comprehensive Ablative Radiotherapy	- Anti-PD-L1	PFS
03599713	2	90	- Retifanlimab	- Anti-PD-1	ORR
03089658	EAP		- Avelumab	- Anti-PD-L1	Available results [15]
03071406	2	50	- Nivolumab - Ipilimumab - +/- Stereotactic body radiation	- Anti-PD-1 - Anti-CTLA4	ORR Preliminary results available [102]
02155647 JAVELIN Merkel 200	2	84	- Avelumab Part A: after chemotherapy failure Part B: first-line	- Anti-PD-L1	Part A: BORR Part B: Durable response rate Available results [7, 9, 11]
03304639	2	96	- Pembrolizumab +/- - Stereotactic body radiation	- Anti-PD-1	PFS
03071757	1	180	- ABBV-368 +/- ABBV-181	- Anti-OX40 agonist - Anti-PD-1	Safety Pharmacokinetics of ABBV-368
03212404	1	80	- Cosibelimab	- Anti-PD-1	Dose-limiting toxicity Safety ORR
04187872	1	15	- Laser Interstitial Thermal Therapy - Pembrolizumab in patients with brain metastasis after failure of stereotactic therapy	- Minimally invasive neurosurgical technique - Anti-PD-1	Immune effect of combination therapy
04260802	1b/2a	80	- OC-001 +/- - Anti-PD1 or Anti-PD-L1	- Targets tumor necrosis factor receptor - Anti-PD1 or Anti-PD-L1	Dose-limiting toxicity Safety
04157985	3	578	Treatment duration of PD-1/PD-L1 inhibitors among responders	- Anti-PD-1/PD-L1	PFS
04140526	1a/2b	91	- ONC-392 +/- - Pembrolizumab	- Humanized anti-CTLA4 - Anti-PD-1	MTD, RP2D Dose-limiting toxicity Safety
05078047	3	646	Evaluation of a reduced dose intensity among responders to ICI	- ICI	PFS

Table S3. Available active and/or recruiting and/or not yet recruiting, interventional clinical trials and expanded access programs (EAP) for targeted therapies and immune based strategies in advanced unresectable or metastatic MCC available at <https://clinicaltrials.gov/> as of April 2022. N: Number of patients for original estimated enrollment, RP2D: Recommended phase 2 dose, EAP: expanded access program, TLR: Toll like receptor, MTD: Maximum tolerated dose, TIL: Tumor infiltrating lymphocytes.

Available Clinical Trials with Targeted Therapies and Immune-based Strategies in Advanced Unresectable or Metastatic MCC					
NCT number	Phase	N	Drugs	Mode of action	Primary objective
02465957	2	24	- aNK - ALT-803	- Activated NK-92 (allogenic Natural Killer cell line) - IL-15 superagonist complex	PFS
02036476	2	12	- Cabozantinib after platinum-based therapy progression	- Multi-target tyrosine kinase inhibitors	Disease Control Rate, Available results [97]
02819843	2	34	- T-VEC +/- - Hypofractionated radiotherapy for skin metastasis	- Oncolytic herpes virus immunotherapy	CR and PR rate
04160065	1	20	- Intralesional IFx-Hu2.0 for skin, LN metastasis	- Plasmid DNA vaccine encoding for a streptococcal membrane protein, Emm55	Treatment-emergent adverse events
04349436	1b/2	30	- Intralesional RP1 in organ transplant recipients for skin, LN metastasis	- Oncolytic herpes virus 1	Adverse events ORR
05120271	1/2	98	- BOXR1030 - Lymphodepleting chemotherapy for GPC3+ MCC	- GPC3-targeted CAR T Cell therapy	Treatment-emergent adverse events, MTD, Dose-limiting toxicity
04853602	EAP		- Intralesional IFx-Hu2.0 for skin, LN metastasis	- Plasmid DNA vaccine encoding for Emm55	
04047251	2	96	- FF-10850 Topotecan Liposome Injection	- A novel liposomal form of Topotecan	Dose-limiting toxicity, Adverse events, MTD, RP2D
05267626	1/2	126	- AU-007	- Anti-IL-2 antibody inhibiting IL-2Ra binding	Dose-limiting toxicity, Adverse events, MTD, RP2D
03544723	2	40	- Intralesional Adp53 - ICI	Adenoviral p53 gene therapy	ORR Safety
04276597	2	50	- 177Lu-DOTATOC	- 177Lu labeled somatostatin receptors targeting ligand	ORR

02479698	2	30	- BK-CTLs	- Allogeneic, HLA-matched BK-specific cytotoxic T-lymphocytes	Safety Incidence of GVHD Response rate
04246671	1	45	- TAEK-VAC-HerBy vaccine	- Therapeutic vaccine	Dose-limiting toxicity
04242199	1	140	- INCB099280	- Targets microsatellite instability-high/mismatch repair deficient tumors	Treatment-emergent adverse events
04272034	1	140	- INCB099318	- Targets microsatellite instability-high/mismatch repair deficient tumors	Treatment-emergent adverse events
04596033	1	24	- GEN-011 - IL-2 +/- - Lymphodepletion (fludarabine, cyclophosphamide)	- Adoptive T cell therapy with identified immunogenic neoantigens from each tumor	Safety
03935893	2	240	- Lymphodepletion - Autologous TIL - IL-2	- Adoptive transfer of autologous TIL	ORR
05076760	1	18	- Intralesional MEM-282 with expected abscopal effect	- Oncolytic adenovirus encoding for IFN β and CD40-ligand	MTD Safety