

# Supplementary Materials: Precision Medicine to Treat Urothelial Carcinoma – The Way Forward

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**Table S1.** Clinical Trials with Results for Targeted Therapies for Urothelial Carcinoma (Monotherapy and Combination Therapies). [1–25]

Name	Target/ MOA	Trials	Phase, progress	n	Study arms	Primary endpoint(s)	Results
Pembrolizumab	PD-1	NCT02335424 (KEYNOTE-052)	II, completed	370	pembrolizumab as first-line therapy for locally advanced or metastatic cisplatin-ineligible UC	ORR	ORR: 28.6%, 95% CI 24.1–33.5
							PFS: 2.1 months (95% CI 2.0–2.2) vs 3.3 months (95% CI 2.4–3.6) (HR 0.96; 95% CI 0.79–1.16; $P=0.31295$ )
		NCT02256436 (KEYNOTE-045)	III, completed	542	pembrolizumab vs chemotherapy (investigator's choice of paclitaxel, docetaxel or vinflunine)	PFS and OS	OS: 10.1 months (95% CI 8.0–12.3) vs 7.3 months (95% CI 6.1–8.1) (HR: 0.70; 95% CI 0.57–0.85; $P<0.001$ )
							> 2 years follow up OS: 26.9% vs 14.3% > 2 years follow up PFS: 12.4% vs 3.0%
		NCT01848834 (KEYNOTE-012)	Ib, completed	33	pembrolizumab (MK-3475) for advanced UC (Cohort C)	AEs, ORR	ORR: 26%, 95% CI 11–46
		NCT02500121	II, completed	108	pembrolizumab vs placebo	PFS	PFS: 5.4 months (95% CI, 3.1 to 7.3) vs 3.0 months (95% CI; 2.7 to 5.5) (HR 0.65, $p = 0.04$ )
Pembrolizumab + Chemotherapy		NCT02853305 (KEYNOTE-361)	III, completed	1010	pembrolizumab with gemcitabine + cisplatin or carboplatin vs pembrolizumab or chemotherapy	PFS and OS	PFS: 8.3 months (95% CI 7.5–8.5) in P + chemotherapy vs 7.1 months (CI 6.4–7.9) in chemotherapy (HR: 0.78, 95% CI 0.65–0.93; $p=0.0033$ ) OS: 17.0 vs 14.3 months (HR 0.86, 95% CI 0.72–1.02; $p=0.0407$ )
Atezolizumab	PD-L1	NCT02108652 (IMvigor210 cohort B)	II, completed	119	atezolizumab in cisplatin-ineligible mUC	ORR	ORR: 23% (95% CI 16 to 31)

		NCT02302807 (IMvigor211)	III, completed	931	atezolizumab vs chemotherapy (investigator's choice of vinflunine, paclitaxel, or docetaxel)	OS	OS: 11.1 months (95% CI 8.6-15.5) vs 10.6 months (95% CI 8.4-12.2) (HR 0.87, 95% CI 0.63-1.21; p=0.41)
		NCT02807636 (IMvigor130)	III, active, not recruiting	1213	Group A: atezolizumab + platinum-based chemotherapy (gemcitabine plus either carboplatin or cisplatin) Group B: atezolizumab monotherapy Group C: placebo + platinum-based chemotherapy	OS, PFS, and AEs	OS: Group A 16.0 months (95% CI 13.9-18.9) vs Group B 15.7 months (95% CI 13.1-17.8) vs Group C 13.4 months (95% CI 12-15.2)  PFS: Group A 8.2 months (95% CI 6.5-8.3) vs Group C 6.3 months (95% CI 6.2-7.0) (HR 0.82, 95% CI 0.70-0.96, p=0.007)
Atezolizumab + Rogaratinib	PD-L1 and FGFR	NCT03473756 (FORT-2)	Ib/II, active, not recruiting	26	Rogaratinib + atezolizumab in cisplatin-ineligible advanced/ mUC	DLTs, TEAEs	TEAEs: diarrhea, hyperphosphatemia, nausea. Favorable safety profile.
		NCT02387996 (CheckMate275)	II, completed	265	Nivolumab as a second-line for mUC	ORR	ORR: 19.6% (95% CI 15.0- 24.9)
Nivolumab	PD-1	NCT02632409 (CheckMate274)	III, active, not recruiting	709	nivolumab vs placebo in muscle- invasive urothelial carcinoma after radical cystectomy	DFS	DFS: 20.8 months (95% CI 15.6-27.6) vs 10.8 months (95% CI 8.3-13.9)
Nivolumab + Ipilimumab		NCT01928394 (CheckMate032)	I/II, active, not recruiting	274	Nivolumab monotherapy every 2 weeks (NIVO3) vs nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks (NIVO3+IPI1 )vs nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks (NIVO1+IPI3)	ORR	ORR: NIVO3 arm: 25.6% (95% CI, 16.4-36.8) NIVO3+IPI1 arm: 26.9% (95% CI, 18.7-36.5%) NIVO1+IPI3 arm: 38% (95% CI, 28.1-48.8)
Nivolumab + NKTR-214 (bempegaldesle ukin)	PD-1 and interleukin-2 cytokine prodrug	NCT02983045 (PIVOT-02)	I/II, completed	34	NKTR-214 + nivolumab in advanced/ mUC	ORR	ORR: 48% (95% CI 27-69)

		NCT01772004 (JAVELIN Solid Tumor)	I, completed	249	Avelumab after first-line platinum-based chemotherapy	Best overall response	Best overall response (complete or partial response): 17% (95% CI 11–24)
Avelumab	PD-L1	NCT02603432 (JAVELIN Bladder 100)	III, active, not recruiting	700	maintenance avelumab vs best supportive care (gemcitabine + cisplatin or carboplatin)	OS	OS: 23.8 months vs 15 months (HR 0.76, 95% CI 0.631-0.915, p=0.0036) PFS: 5.5 months vs 2.1 months (HR 0.54, 95% CI 0.457-0.645, p<0.0001)
Durvalumab	PD-L1	NCT01693562	I/II, completed	191	durvalumab in advanced/mUC with progression of disease or treatment-naive mUC	DLTs AEs, ORR	ORR: 17.8% (95% CI 12.7-24.0)
Durvalumab + Tremelimumab	PD-L1 and CTLA-4	NCT02516241 (DANUBE)	III, active, not recruiting	1032	durvalumab with or without tremelimumab (a CTLA-4 inhibitor) as first-line treatment for mUC vs chemotherapy	OS	OS: 14.4 months (95% CI 10.4–17.3) in the durvalumab monotherapy group, 15.1 months (13.1–18.0) in the durvalumab plus tremelimumab group, and 12.1 months (10.9–14.0) in the chemotherapy group (HR 0.85, 95% CI 0.72–1.02; p=0.075)
Cetrelimab + Erdafitinib	PD-1 and FGFR	NCT03473743 (NORSE)	Ib/II, active, not recruiting	125	Erdafitinib with or without cetrelimab	DLTs, ORR, AEs	Ib ORR: 52% II ORR: 68% in combination vs 33% in erdafitinib alone
Rogaratinib	FGFR	NCT03410693 (FORT-1)	II, III, completed	175	Rogaratinib vs chemotherapy in FGFR positive UC with disease progression during or after treatment with at least one platinum-containing regimen	ORR	ORR 20.7% (95% CI 12.7-30.7) vs 19.3% (95% CI 11.7-29.1)
Erdafitinib	FGFR	NCT02365597	II, active, not recruiting	99	Metastatic or surgically unresectable UC with disease progression despite chemotherapy	ORR	ORR: 40%
Enfortumab vedotin	Nectin-4 and MMAE	NCT03474107 (EV-301)	III, active, not recruiting	608	Enfortumab vedotin vs investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine)	OS	OS: 12.88 months vs 8.97 months (HR 0.70, 95% CI 0.56-0.89, p=0.001) PFS: 5.55 months vs 3.71 months (HR 0.62, 95% CI 0.51-0.75, p<0.001)

		NCT03219333 (Cohort 2 of EV-201)	II, active, not recruiting	89	Enfortumab vedotin for platinum-naive and cisplatin-ineligible advanced/mUC	ORR	ORR: 52% (95% CI 41-62)
		NCT02091999 (EV-101)	I, active, not recruiting	112	Enfortumab vedotin as monotherapy for mUC	AEs, ORR	ORR: 42% (95% CI 31.2-52.5)
Enfortumab vedotin + pembrolizumab		NCT03288545 (EV-103)	III, active, recruiting	45	Previously untreated locally advanced/mUC	Safety	Manageable safety profile. ORR: 73.3% (95% CI, 58.1 to 85.4) OS: 26.1 months
Feladilimab (GSK3359609) + pembrolizumab + chemotherapy	Humanized IgG4 antibody with activity against T cell co-stimulator	NCT02723955 (INDUCE-1)	I, active, not recruiting	45	Feladilimab monotherapy vs fedladilimab + pembrolizumab	AEs, DLTs	ORR: 8% 95% CI: 0.2-36.0) in monotherapy vs 22% (95% CI 9.3-40) in combination therapy OS: 14.5 months (95% CI 2.8, NR) in monotherapy vs 10.7 months (95% CI: 5.2-18.1) in combination therapy
Autologous genetically modified MAGE-A4c1032 T cells	Adoptive T cell therapy	NCT03132922	I, active, not recruiting	60	HLA-A2+ patients with MAGE-A4 Positive Tumors	AE, DLT	ORR: 24% (95% confidence interval (CI): 11.4-40.2)
Infilgratinib	FGFR	NCT04197986 (PROOF-302)	III, terminated	218	UC post resection	DFS	<b>Terminated</b>
Pemigatinib	FGFR	NCT04294277 (PEGASUS)	Terminated	2	Pemigatinib for UC who have received radical surgery	Relapse-free survival rate	<b>Terminated</b>

MOA: mechanism of action; UC: urothelial carcinoma; ORR: Objective Response Rate; CI: confidence interval; P: pembrolizumab; PFS: Progression Free Survival; OS: Overall Survival; HR: hazard ratio; PD-1: programmed cell death protein 1; AE: adverse event; PD-L1: programmed death ligand-1; mUC: metastatic urothelial carcinoma; FGFR: fibroblast growth factor receptor; DLT: dose-limiting toxicity; TEAE: treatment-emergent adverse events; DFS: Disease Free Survival; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; MMAE: monomethyl auristatin E; NR: not reached

**Table S2.** Currently Ongoing Clinical Trials Pending Results for Targeted Therapies for Urothelial Carcinoma (Monotherapy).

Name	Target/ MOA	Trials	Phase	n	Study arms	Primary Endpoint(s)
Sacituzumab Govitecan	Anti-Trop-2 humanized monoclonal antibody + SN-38	NCT03547973 (TROPHY-U-01)	II, active, recruiting	643	Sacituzumab govitecan (6 cohorts)	ORR, PFS
Disitamab Vedotin	HER2 (hertuzumab and MMAE)	NCT04879329	II, active	270	Disitamab Vedotin monotherapy (only cohorts A and B) for HER2+ locally	Confirmed ORR

					advanced unresectable or mUC	
Pemigatinib	FGFR	NCT03914794	II, active, recruiting	43	high-risk UC post radical surgery	CR
4SCAR-PSMA 4SCAR-FRa	Adoptive T cell therapy	NCT03185468	I/II, active, recruiting	20	locally advanced or mUC with no further treatment available	OS, AEs
CCT301-59 CAR T	Adoptive T cell therapy	NCT03960060	I, active, not recruiting	18	recurrent or refractory solid tumors including bladder cancer	Safety, efficacy
TBI-1301 (NY-ESO-1 Specific TCR Gene Transduced Autologous T Lymphocytes)	Adoptive T cell therapy	NCT02869217	Ib, active, not recruiting	22	NY-ESO-1 expressing solid tumors in HLA-A2 positive patients (including BC)	Safety profile
HER2 specific CAR T cells + intra-tumor injection of CAdVEC	Adoptive T cell therapy	NCT03740256	I, active, recruiting	45	Advanced HER2 positive solid tumors including BC	DLTs

MOA: mechanism of action; ORR: Objective Response Rate; PFS: Progression Free Survival; HER2: human epidermal growth factor receptor 2; MMAE: monomethyl auristatin E; FGFR: fibroblast growth factor receptor; CR: Confirmed Response; OS: Overall Survival; AE: adverse event; mUC: metastatic urothelial carcinoma; UC: urothelial carcinoma; BC: bladder cancer; CAR: chimeric anti-gen receptor; DLT: dose-limiting toxicity

**Table S3.** Currently Ongoing Clinical Trials Pending Results for Targeted Therapies for Urothelial Carcinoma (Combination Therapy).

Name(s)	Target/ MOA	Trials	Phase	n	Study arms	Primary Endpoint(s)
Atezolizumab + CRT	PD-L1 + CRT	NCT03775265	III, active, recruiting	475	RT + chemotherapy vs CRT + atezolizumab in localized MIBC	Bladder intact event-free survival
Pembrolizumab + CRT	PD-1 + CRT	NCT04241185 (KEYNOTE-992)	III, active, recruiting	636	Pembrolizumab + CRT vs placebo + CRT in MIBC	Bladder intact event-free survival
Enfortumab vedotin + pembrolizumab + platinum-based chemotherapy	Nectin-4 and MMAE + PD-1	NCT03288545 (EV-103)	I/II, active, not recruiting	457	UC	ORR, pCR, AEs
Sacizumab-govitecan + pembrolizumab	Anti-Trop-2 humanized monoclonal antibody + PD-1/PD-L1	NCT05535218 (SURE-02)	II, active, recruiting	48	MIBC	pCR
Sacituzumab-govitecan + Atezolizumab		NCT03869190 (MORPHEUS-UC)	Ib/II, active, recruiting	645	MIBC or locally advanced or mUC who progressed with platinum therapy	ORR, pCR
Sacituzumab-govitecan + Avelumab		NCT05327530 (JAVELIN Bladder Medley)	II, active, recruiting	252	MIBC or locally advanced or mUC who progressed with platinum therapy	PFS, AEs

Disitamab Vedotin + Pembrolizumab		NCT04879329	II, active	270	Disitamab Vedotin monotherapy (only cohort C) for HER2+ locally advanced unresectable or mUC	Confirmed ORR
Disitamab Vedotin + Toripalimab	HER2 (hertuzumab and MMAE) + PD-1/PD-L1	NCT05302284	III, active, recruiting	456	untreated unresectable locally advanced or metastatic HER2 positive UC	PFS, OS
RC48-ADC (Disitamab Vedotin) + Toripalimab		NCT04264936	Ib/II, active, unknown recruitment status	36	RC48-ADC and JS001 for locally advanced/mUC	AEs and maximal tolerated dose
EphB4-human serum albumin + pembrolizumab	EphB4-human serum albumin + PD-1	NCT02717156	II, active, recruiting	170	EphB4-HAS + pembrolizumab in solid tumors	Toxicities and AEs
Cabozantinib + avelumab (VEGF TKI + PD-L1 inhibitor)	VEGF TKI + PD-L1 inhibitor	NCT05092958 (MAIN-CAV)	III, active, recruiting	654	Avelumab vs avelumab + cabozantinib in mUC	OS

MOA: mechanism of action; CRT: chemoradiotherapy; PD-L1: programmed cell death ligand-1; RT: radiotherapy; PD-1: programmed cell death protein 1; MIBC: muscle invasive bladder cancer; MMAE: monomethyl auristatin E; UC: urothelial carcinoma; ORR: Objective Response Rate; pCR: pathological complete response; AE: adverse event; PFS: Progression Free Survival; mUC: metastatic urothelial carcinoma; OS: Overall Survival; HER2: human epidermal growth factor receptor 2; MMAE; ADC: antibody-drug conjugate; VEGF: vascular endothelial growth factor; TKI: tyrosine kinase inhibitor

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