Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
Witte 1998 **Topotecan**	N=44, confirmed incurable advanced urothelial carcinoma, ECOG PS <2, measurable lesion, one prior cytotoxic therapy and up to one biological response modifier regime, adequate organ function,	Median age 62 (36-83) 89% M/11% F	77% previous platinum-based chemo, 9% RT 5% local only disease, 14% local and systemic, 82% systemic only 36% soft tissue, 52% lymph node, 11% osseous, 36% lung, 32% liver 93% TCC, 5% adenocarcinoma	Topotecan 1.5mg/m^2 i.v. 30mins daily for 5 consecutive days, every 3 weeks for 6 cycles. If responding by end of 6 cycles, treatment could continue for 12 cycles. Doses modified for leukopenic fever, thrombocytopenic bleeding, and grade3-4 toxicity. Median 2 cycles (1-12). 7 dose reductions, 15 delays	Tumour response (ECOG criteria) Toxicity – NCI-CTC PFS Overall survival	
Beer (2008) Phase II **Iritonecan**	N=40, confirmed, measurable TCC of the urothelial tract stage T2-4, N0-3, M1 or unresectable stage T2-4, N+, and M0. Zubrod PS 0-2. Evidence of disease progression following one prior chemo regimen inc. Cisplatin or carboplatin	Median age 64.4 (46.4-81.5) 75% M / 25% F	25% PS 0, 60% PS 1, 10% PS2 73% visceral mets, 27% other (lymph, abodominal/pelvic wall, penis) 73% primary bladder 30% previous radiation	Iritonecan 350mg/m^2 (300mg in patients with previous RT to the pelvis) i.v. over 90mins, every 21 days. Starting dose of 50mg/m^2 allowed for patients over 65 years, PS 2, or increased bilirubin levels at discretion of physician. Standard antiemetics – dexamethasone 10mg i.v. and a 5-HT3 blocker were recommended. Median duration =2 months. 21 patients required at least 1 dose reduction.	Tumour response (RECIST) Overall survival PFS Toxicity	Treatment discontinued due to progression in 23 patients and toxicity in 6.
Wulfing 2009 **Lapatanib**	N=59, aged≥18 years, confirmed measurable locally advanced or metastatic TCC with progression after 1st-line platinum-based chemo. Karnofsky PS ≥70%, LVEF in normal limits, adequate organ function. Neo-/adjuvant prior therapy permitted.	Median age 64 (41-78) 71% M/ 29% F	22% PS 100, 27% PS 90, 36% PS 80, 15% PS 70 63% prior GC chemo, 10% prior MVAC chemo. 34% progressed within 3 months from prior therapy	Oral lapatinib 1250mg once daily. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Dosage reduced to 1000mg/day when ≥grade 3 toxicity. All patients had a least 1 dose of lapatinib, median 8.14 weeks, range 0.40-55.10 weeks	Tumour response (RECIST) Toxicity – NCI-CTC PFS Overall survival	42% were non-assessable for response. 22 withdrew for progression, 13 SAEs, 1 withdrawal of consent
Gomez-Aubin 2007 **Bortezomib**	N=21, (17 with prior chemo for metastatic cancer) confirmed TCC with measurable metastatic disease, no more than 2 lines of chemo for metastatic disease (adjuvant and neoadjuvant allowed if >12mo before study), ECOG PS ≤1, adequate organ function.	Median age 70 (49-81) 70% M/ 30% F	50% PS 0, 50% PS 1 95% primary bladder 75% liver mets, 75% lung, 50% pelvis, 25% abdomen 40% prior adjuvant chemo, 55% systemic chemo	Bortezomib 1.3mg/m^2/day bolus i.v. on dyas 1,4,8,11, repeated every 21 days. Antiemetics not required. Median 3 cycles (1-3)	Tumour response (RECIST) PFS Overall survival Toxicity	Trial stopped early due to lack of treatment activity. 6-month survival = 34%
Rosenberg 2008 **Bortezomib**	N=24, confirmed urothelial TCC, one prior chemo for advanced or	Median age 64 (IQR, 57-72)	67% primary bladder, 38% renal pelvis, 29% ureter	Bortezomib at 1.3mg/m^2 i.v. days 1,4,8and 11 of a 21 day cycle. Given as	Tumour response (RECIST)	Study closed after interim analysis for

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
	metastatic disease, with progression during or after treatment. CTC PS 0-2 and ≤grade 1 neuropathy, RT or chemo completed >4 wks before trial. Adequate renal, liver function.	75% M/25% F	71% visceral metastases, 29% nodal mets only 54% prior Gem/Cis chemo, 25% prior Gem/Carbo	rapid bolus over 3-5s. Antiemtic premedications given at discretion of physician. Treatment continued if no disease progression and ≤grade 3 toxicity attributed to therapy lasting for 3 weeks. Up to two dose reductions were allowed. Median 2 cycles (1-12)	Toxicity (NCI-CTCAE) PFS Overall survival	lack of activity of therapy. One patient alive after 20 month f/up
Dreicer (2009) Phase II **Sorafenib**	N=22, confirmed TCC (pure or mixed) of the urothelium with progressive, regional or metastatic disease. ECOG PS 0-1. Progression after 1 chemo (metastatic setting). Adequate renal and hepatic function and marrow reserve.	Median age 66 (37-81) 64% M /36% F	36% ECOG PS 0, 64% PS1 68% primary bladder cancer 36% distant node mets, 46% liver mets, 41% bone mets, 64% lung mets Bajorin prognostic factors, 14% none, 86% 1 factor 77% prior surgery, 27% prior RT	Sorafenib: orally 400mg (2 tablets) twice daily for a total daily dose of 800mg. One cycle=56 days of therapy. No dose escalation was permitted. Modifications were allowed: dose level 2, 400mg/day; dose level 3, 400mg every other day. Modifications specified for myelosupression, and any grade 3-4 toxicity. Median cycles = 1 (1-4)	Tumour response (RECIST) Toxicity (NCI-CTC) 4-month PFS rate Overall survival	68% went off treatment due to progression, 18% due to toxicity. 4-months PFS =11%
Gomez-Aubin 2007 **Bortezomib**	N=21, (17 with prior chemo for metastatic cancer) confirmed TCC with measurable metastatic disease, no more than 2 lines of chemo for metastatic disease (adjuvant and neoadjuvant allowed if >12mo before study), ECOG PS ≤1, adequate organ function.	Median age 70 (49-81) 70% M/ 30% F	50% PS 0, 50% PS 1 95% primary bladder 75% liver mets, 75% lung, 50% pelvis, 25% abdomen 40% prior adjuvant chemo, 55% systemic chemo	Bortezomib 1.3mg/m^2/day bolus i.v. on dyas 1,4,8,11, repeated every 21 days. Antiemetics not required. Median 3 cycles (1-3)	Tumour response (RECIST) PFS Overall survival Toxicity	Trial stopped early due to lack of treatment activity. 6-month survival = 34%
Winquist 2005 **Oxaliplatin**	N=20, confirmed, measurable TCC, no more than 1 prior chemo regimen for metastatic disease. Patients may have additionally received adjuvant chemotherapy provided inthe interval between this and the first therapy for metastatic cancer was ≥6 months. ECOG PS 2 or less,	Median age 64 (45-81) 95% M/5% F	25% ECOG PS 0, 55% PS 1, 20% PS2, 45% prior chemo for metastatic disease, 35% prior adjuvant chemo 35% lung, 35% lymph node, 20% bladder/pelvis 55% platinum sensitive, 45% platinum resistant	Oxaliplatin 130mg/m^2 2-hour i.v. every 3 weeks. Antiemetic therapy with corticosteroids and a serotonin-receptor antagonist was required. Avoid cold drinks, water and air during treatment period. Discontinued if progression, illness or intolerable toxicity. Median 2 cycles (1-6).	Tumour response (WHO criteria) Toxicity	Trial stopped early due to lack of treatment activity. 2 patients discontinued due to pulmonary thromboembolism and 18 because of progression.
Galsky (2007) Phase II **Pemetrexed**	N=13, confirmed TCC of urothelial tract, One prior chemo regimen which included Cis, Carbo, Pac, Doc, or Gem. Neodjuvant or adjuvant or metastatic. Age>18years, PS >60%, adequate hematologic, hepatic, and renal function.	Median age 65 (57-82) Gender not reported	All patients received platinum-based therapy, 9/13 received carboplatin. Median PS 80 (70-90) 77% primary bladder, 77% prior chemo for metastatic disease. 100% had metastatic disease	Pemetrexed 500mg/m^2 i.v. over 10mins, every 21days. Dexamethasone 4mg orally twice daily on the day before, the day of, and the day after Pemetrexed. Folic acid 350-1000mg daily and vitamin B12 1000mcg every 9 weeks. Up to 9 cycles provided no evidence of progression or intolerable	Toxicity (NCI-CTC) Tumour response (RECIST)	8/13 stopped due to progression 3/13 due to toxicity. Study closed due to low response rates

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
				toxicity. Median 3 cycles (1-10)		
Sweeny 2006 **Pemetrexed**	N=47, confirmed stage IV urothelial TCC (pure/mixed) 1 prior chemo regime with progression any time after therapy for metastatic disease, or within 12 months of neo/ adjuvant setting. PS 0-1, adequate marrow, hepatic function & creatine clearance	Median age 64 (26-83) 81% M/ 19% F	98% TCC 60% PS 0, 34% PS 1, 4% PS2 16/39 platinum refractory 18 neo/adjuvant chemo, 29 metastatic chemo	Pemetrexed 500mg/m^2 as 10 min i.v. on day 1 of each 21 day cycle. Cycles repeated until progression or intolerable toxicity. 2 dose reductions allowed. GCSF only for grade 4 neutropenia, more than 3 days, neutropenic fever or infections in neutropenic patients.	Tumour response (SWOG criteria) Toxicity – NCI-CTC Overall survival PFS	Median f/up 9.2 months. 29 patients with prior metastatic therapy - 28% response rate, median survival 9.2 months.
McCaffrey (1997) **Docetaxel**	N=31 (30 assessable), confirmed advanced or metastatic TCC of the urothelial tract, relapsing or refractory to no more than 1 prior cisplatin-containing chemo. 4 weeks since prior chemo. Over 18yrs, PS ≥60%, adequate renal, and marrow function	Median age 61 (27-72) 83% M /17% F	Median PS 80 (70-90) 83% primary bladder, 17% renal pelvis. Median no. Of MVAC cycles 4 (2-8). Interval median 8 (1-64) months. 57% MVAC for metastatic disease, 43% adjuvant or neoadjuvant.	Docetaxcel: 100mg/m^2 over 1 hour i.v. every 21 days. Dexamethasone 20mg orally 12 and 6 hrs before therapy, followed by i.v. dexamethasone 20mg and diphenhydramine 50mg, 30mins before docetaxel. Median cycles 3 (1-11)	Toxicity (NCI-CTC) Tumour response	1 patient removed for recurrent mylosurpression, 2 patients deteriorated before 2nd cycle and failed to receive further therapy.
Choueiri 2012 **Docetaxel**	N=72 docetaxel+placebo, confirmed locally advanced or metastatic UC, progression of disease after platinum-containing chemotherapy. Age ≥18years, ECOG PS 0-1, No prior docetxel. Up to 3 prior therapies allowed (metastatic and/or within 2yrs of adjuvant or neoadjuvant). Adequate hematologic, renal and hepatic function.	46% aged ≥65 years 68% M/ 32% F	53% ECOG PS 1 64% visceral metastases, 38% liver metastases 39% >1 prior systemic therapy, 14% >2 prior systemic therapy 50% prior cystectomy, 21% prior RT, 11% prior paclitaxel, 69% bellmunt risk score >0	Docetaxel 75mg/m^2 1-hr infusion, day 1 and dexamethasone 8mg at 12, 3 and 1 hr before docetxel. Placebo for Vandetanib (1 tablet orally once daily). 21 day cycle. versus Docetaxel plus 100mg Vandetanib. Median f/up 7.1 months	Tumour response (RECIST) Toxicity – NCI-CTC PFS Overall survival	Double blind RCT of Docetaxel +Vandetanib vs. Docetaxel +placebo
Pronzato 1997 **Ifosfamide**	N=20, Metastatic or surgically unresectable TCC of the bladder, one line of prior systemic chemo, ≤75 years old, normal plasma bilirubin and creatinine, no cardiac disease,	Median age 68 (52-75) 80% M/ 20% F	Median PS 2 (1-2) Dominant tumour site: 15% lung, 25% lymph nodes, 30% bladder, 15% bone, 15% liver 50% prior MVAC, 15% CISCA, 30% Carbo/M/V	Ifosfamide 1000mg/m^2 2-hr infusion, 5 consecutive days, day 1-5. Mesna i.v. at 20% of ifosfamide dose, before treatment and orally at 40% after 4 &8 hrs from ifosfamide infusion. Treatment every 3 weeks provided bone marrow recovery occurred for 6 cycles.	Tumour response (WHO criteria) Toxicity	All patients died due to neoplastic disease progression.
Witte (1997) **Ifosfamide**	N=56, confirmed advanced TCC beyond surgical cure, PS <3, no more than one prior cytoxic therapy, no prior malignancies, adequate renal function.	Median age 67 (49-83) 77% M/23% F	71% PS 0-1, 29% PS2, 62% previous MVAC, 21% CMV, 11% other cisplatin combination, 6% other 32% soft tissue, 52% lymph node, 30% lung, 27% liver, 2% bone marrow	Ifosfamide i.v. over 4 hours at 3750mg/m^2 for 2 consecutive days every 3 weeks with mesna 2250mg/m^2 i.v. in three divided doses (every 4 hrs for 3 doses) starting just before ifosfamide daily for 2 days. Excessive renal and CNS toxicity was observed by	Tumour response (ECOG criteria) Toxicity (NCI-CTC) PFS Overall survival	No differences in PFS or OS between the 2 treatment schedules.

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
			84% primary bladder tumour, 14% renal pelvis 95% TCC, 3% adenocarcinoma, 2% squamous	the first 26 patients on this schedule. The remaining 30 patients recieved Ifosfamide i.v. 1500mg/m^2 daily for 5 days with mesna 750mg/m^2 i.v. in three divided doses (every 4 hrs for 3 doses) starting just before ifosfamide, for 5 days. All patients received the same total dose of ifosfamide (7.5g/m^2) during each course of therapy		
Gallagher 2010 **Sunitinib**	N=77, previously treated progressive metastatic urothelial carcinoma, one to four prior cytotoxic treatments in perioperative or metastatic setting. 4 weeks since end of prior treatment. PS ≥60, aged over 18 years, adequate organ function	Median age 64 (39-82) cohort A, 68 (45-84) cohort B 69% M/ 31% F	15% PS 60-70, 43% PS 80, 48% PS 90 64% primary bladder, 21% renal pelvis 82% visceral metastases, 18% lymph node only 61% metastatic setting, 39% perioperative	Sunitinib orally 50mg/day for 4 consecutive weeks, followed by 2 week rest – cohort A, or 37.5 mg continuously – cohort B Cohort B added as amendment after some recurrence of disease-related symptoms during 2-week break. Therapy continued until disease progression or unacceptable toxicity	PFS Overall survival Tumour response (RECIST) Toxicity – NCI-CTC	
Joly (2009) Phase II **Paclitaxel**	N=45, TCC of bladder or urothelial tract, progressive measurable disease after previous 1st line chemo for advanced disease (neoadjuvant, adjuvant or metastatic), life expectancy ≥3months, PS 0-2, normal hematology and serum bilirubin.	Mean age 64 (47-79) 80% M/20% F	82% PS 0-1, 18% PS2, 84% bladder primary, 96% TCC 7% locoregional relapse, 93% distant metastases 55% nodal mets, 52% pulmonary mets, 38% liver, 33% bone, 5% soft tissue, 87% previous surgery, 36% irradiation, 71% adjuvant chemo, 29% palliative chemo, 89% Gem/platinum regime	Paclitaxcel 80mg/m^2 i.v. over 1 hour days 1,8,&15 of a 28 day course, for a maximum of 6 cycles. Premedication with dexamethasone, dexchlopheniramine and ranitidine given i.v. before paclitaxel. Treatment stopped if persistent grade ¾ nonhematologic toxicity. Median 2 cycles (1-6)	Toxicity (NCI-CTC) Tumour response (RECIST) Quality of life (FACT-G, FACT bl, FACT-Taxane)	1-yr OS rate =22%. 62% stopped for progression, 13% for toxicity, 11% death. No decrease in QoL scores during chemo.17% improved QoL in at least 1 domain.
Papamichael (1997) **Paclitaxel**	N=14, advanced bladder or ureteric TCC. All patients received one treatment regimen before paclitaxel	Median age 68 (40-73) 64% M/36% F	21% ECOG PS 0, 50% PS1, 29% PS2 29% locally advanced, 79% metastatic disease	Paclitaxel 200mg/m^2 i.v. over 3 hours. Dexamethasone 20mg p.o. 12 and 6 hours before Pac, chlorpheniramine 10mg i.v. and cimetidine 300mg i.v. 30 min before treatment. Every 3 weeks.	Tumour response Toxicity	Short communication paper. Median f/up 54 days (1-240)
Vaughn 2002 **Paclitaxel**	N=31, 18 years or older, confirmed urothelial cancer, with progression regional or metastatic disease and one prior regimen of chemo. ECOG PS 0-2, adequate hematologic, renal and hepatic function. Life expectancy 3 months or longer,	Median age 66 (48-83) 84% M /16% F	87% ECOG PS 0-1, 13% PS2 87% TCC. 94% primary bladder cancer, 77% visceral (bone, liver or lung) metastases. 16% prior adjuvant chemotherapy, 39% MVAC for advanced disease, 13%	Paclitaxel 80mg/m^2 i.v. 1-hour, 4 weekly treatments. 20mg dexamethasone , 50mg diphenhydramine, cimetidine 300mg 30-60 mins before paclitaxel. Treatment until progression or intolerable toxicity. Median 3 cycles (1-8)	Toxicity – NCI-CTC Tumour response Overall survival	

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
			Pac/carbo, 42% RT			
Albers (2002) **Gemcitabine**	N=30, proven, measurable recurrent or progressing TCC, prior cisplatin-based chemo. No prior gemcitabine, chemo or RT within 4 weeks prior to study, no karnofsky PS <40, adequate liver and renal function.	Not reported	86% prior radical surgery with adjuvant MVAC/MVEC or CM, 7% cystectomy with neoadjuvant MEC, 7% primary MVEC/MVAC without radical surgery 43% regional lymph node and distant metastases	Gemcitabine 1250mg/m^2 on day 1 & 8 of a 21-day course i.v. 30 mins. Maximum 6 courses (18 weeks) 9/28 completed 6 courses of treatment, 15 did not receive maximum number due to progression, 4 dropped out due to toxicity or personal reasons	Tumour response (WHO criteria) Toxicity (WHO criteria) Quality of life (questionnaire from Spitzer et al) PFS Overall survival	
Lorusso (1998) **Gemcitabine**	N=35, inoperable or metastatic TCC of urinary tract who had previously received one platinum-containing chemo regimen	Median age 64 (38-74) 83% M/ 17% F	40% PS 0-1, 57% PS 2, 3% PS 3 83% previous radical cystectomy, 29% previous radiotherapy 83% received at least one previous cisplatin-based chemo for advanced disease (usually MVAC), 17% for adjuvant treatment, after removal of primary cancer, in absence of distant mets	Gemcitabine 1200mg/m^2 i.v. over 30 mins, days 1, 8 &15 of a 28 day cycle. 8mg odansetron 8mg i.v. prior to Gemcitabine. Maximum 8 cycles in responding patients or stable disease, discontinued if disease progression or severe toxicity. Mean 2.7 cycles	Tumour response (WHO criteria) Toxicity Overall survival PFS	
Akaza (2007) Phase II **Gemcitabine**	N=44, confirmed advanced or metastatic TCC of urothelium, with evidence of recurrence or progression following 1st line platinum chemo. ECOG PS 0-2, life expectancy of at least 3 months, age 20-74 years. No previously irradiated lesions	Median age 65 (35-74) 73% M / 27% F	68% PS 0, 27% PS 1, 5%, PS 2 2% Stage III, 21% Stage IV, 77% relapse after surgery 39% lung mets, 36% lymph node mets, 21% bone mets 46% primary bladder, 54% renal pelvis 80% previous MVAC, 9% MEC, 9% MVAC +other medication	Gemcitabine (monotherapy) 1000mg/m^2 i.v. 30mins, over 28 days (1 cycle), 3 consecutive weeks treatment (days 1, 8 and 15) followed by week of rest. Cycle repeated at least 3 times, or until disease progression or an intolerable adverse event. Dose reduction allowed (not lower than 800mg/m^2) if neutropenia, leucopoenia or thrombocytopenia. Median 3 cycles (1-21). 3 discontinued for safety reasons	Toxicity (WHO criteria) Tumour response Progression-free survival Overall survival	Open label study
Gebbia (1999) **Gemcitabine**	N=24, measurable urothelial carcinoma previously treated with chemotherapy and not more amenable with surgery, age ≤75 years, Karnofsky PS ≥60, life expectancy ≥3 months, adequate bone marrow function, at least 4 weeks since last treatment, no severe chemo-	Median age 61 (40-75) 79% M / 21% F	83% TCC, 62% previous surgery, 17% previous RT. 54% adjuvant chemo, 28% advanced disease chemo, 42% prior MVAC Sire of disease: 37% bone, 42% node, 37% liver, 33% lung, 33% pelvis 29% single site, 71% multiple	Gemcitabine (monotherapy) 1000mg/m^2/week i.v. diluted in 250cc of normal saline, 30mins once a week for 3 weeks followed by 1 week rest. Repeated every 28 days. Metoclopramide was employed as antiemetic therapy 15 mins before chemo, and as needed. If partial response or stable disease achieved,	Tumour response (WHO criteria) Overall survival Toxicity (WHO criteria)	

Study	No. of patients	Patient age / Gender	Patient characteristics	Chemotherapy regimen	Outcomes	Additional comments
	related toxicities,		sites	chemotherapy was continued until progression or unacceptable toxicity. Chemo stopped at 6 months when complete regression. In cases of progressive disease, 3rd line chemo or best supportive care were given		
Halim 2013 Phase II **Methotrexate, Paclitaxel, epirubicin, carboplatin**	N=38, proven TCC treated with 1st line GC, PS 0-2, adequate bone marrow, platelet count, liver and renal function.	Median age 62 (range 46-69). 80% male, 20% female.	Metastatic sites: lymph nodes 40%, lung 35%. 75% ECOG PS 1, 25% PS2. Median time since prior chemo was 8 months (range 6-11)	Carboplatin (dose according to Calvert formula AUC 5) followed by i.v. Paclitaxel 175mg/m^2 for 1h on day 1. 30min before Paclitaxel, 20mg of dexamethasone with 4mg chlorpheniramine and 50mg ranitidine. Methotrexate 40mg/m^2 and epirubicin 40mg/m^2 both given as slow bolus on day 15. Repeated every 4 weeks. Continued until progression, severe toxicity, or up to 6 cycles.	Toxicity NCI-CTC Tumour response (WHO criteria) QoL assessed according to influence of therapy on PS, urological complaints, and pain.	2 patients with liver mets refused further treatment after 1st cycle.