

SUPPLEMENTARY MATERIAL

Different Chemotherapy Regimens in the Management of Advanced or Metastatic Urothelial Cancer: a Bayesian Network Meta-Analysis of Randomized Controlled Trials

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Fig. S1. The efficacy and tolerability of different chemotherapy regimens using HRs, ORs and corresponding 95% CrIs. (A) Overall response rate (ORR); (B) Overall survival (OS); (C) Progression-free survival (PFS)/Time to progression (TTP); (D) Thrombocytopenia; (E) Neutropenia; (F) Anemia; (G) Leukopenia; (H) Diarrhea.

PCG	A									
1.4 (0.63, 2.7)	GC									
1.6 (0.49, 5.0)	1.2 (0.47, 3.0)	GC+Monoclonal								
2.4 (0.60, 8.1)	1.7 (0.58, 4.8)	1.4 (0.35, 5.8)	LC							
1.7 (0.60, 4.2)	1.2 (0.64, 2.3)	1.0 (0.34, 3.2)	0.71 (0.21, 2.5)	MVAC						
3.4 (0.75, 14.0)	2.4 (0.69, 8.5)	2.1 (0.44, 9.7)	1.4 (0.29, 7.4)	2.0 (0.69, 5.8)	DC					
2.2 (0.41, 10.0)	1.5 (0.36, 6.5)	1.3 (0.24, 7.1)	0.92 (0.16, 5.5)	1.3 (0.35, 4.6)	0.64 (0.12, 3.4)	CP				
2.1 (0.48, 8.8)	1.5 (0.44, 5.4)	1.3 (0.27, 6.2)	0.90 (0.18, 4.7)	1.3 (0.31, 5.2)	0.62 (0.11, 3.7)	0.99 (0.15, 6.6)	G+Carboplatin			
1.1 (0.26, 4.4)	0.80 (0.24, 2.7)	0.69 (0.15, 3.1)	0.47 (0.096, 2.4)	0.66 (0.17, 2.6)	0.33 (0.057, 1.9)	0.52 (0.079, 3.5)	0.53 (0.092, 3.1)	GC+Sorafenib		
5.2 (1.5, 17.0)	3.7 (1.5, 10.0)	3.2 (0.85, 12.0)	2.2 (0.56, 9.7)	3.1 (1.5, 6.7)	1.5 (0.43, 5.9)	2.4 (0.56, 11.0)	2.4 (0.51, 12.0)	4.6 (1.0, 23.0)	Cisplatin	

PCG	C									
0.87 (0.58, 1.3)	GC									
0.83 (0.46, 1.5)	0.95 (0.62, 1.5)	GC+Monoclonal								
0.52 (0.28, 0.98)	0.60 (0.37, 0.96)	0.63 (0.33, 1.2)	LC							
0.86 (0.54, 1.4)	0.99 (0.78, 1.3)	1.0 (0.64, 1.7)	1.7 (0.98, 2.8)	MVAC						
0.54 (0.27, 1.1)	0.61 (0.35, 1.1)	0.65 (0.32, 1.3)	1.0 (0.50, 2.1)	0.62 (0.38, 1.0)	DC					
0.61 (0.28, 1.3)	0.70 (0.36, 1.4)	0.74 (0.34, 1.6)	1.2 (0.52, 2.6)	0.71 (0.38, 1.3)	1.1 (0.52, 2.5)	CP				
0.85 (0.43, 1.7)	0.97 (0.55, 1.7)	1.0 (0.51, 2.1)	1.6 (0.78, 3.3)	0.98 (0.53, 1.8)	1.6 (0.72, 3.5)	1.4 (0.59, 3.3)	G+Carboplatin			
0.92 (0.46, 1.9)	1.1 (0.60, 1.9)	1.1 (0.54, 2.3)	1.8 (0.85, 3.7)	1.1 (0.58, 2.0)	1.7 (0.77, 3.8)	1.5 (0.64, 3.7)	1.1 (0.49, 2.4)	GC+Sorafenib		
0.45 (0.23, 0.87)	0.52 (0.32, 0.85)	0.55 (0.29, 1.1)	0.87 (0.43, 1.7)	0.52 (0.34, 0.81)	0.84 (0.44, 1.6)	0.74 (0.35, 1.6)	0.53 (0.25, 1.1)	0.49 (0.23, 1.0)	Cisplatin	

PCG	E									
1.8 (0.49, 6.3)	GC									
2.1 (0.39, 14.0)	1.2 (0.36, 4.7)	GC+Monoclonal								
6.7 (1.1, 43.0)	3.8 (1.0, 15.0)	3.1 (0.46, 18.0)	LC							
1.1 (0.24, 5.0)	0.60 (0.27, 1.4)	0.50 (0.10, 2.2)	0.16 (0.034, 0.78)	MVAC						
2.5 (0.35, 20.0)	1.4 (0.30, 7.5)	1.2 (0.15, 8.8)	0.37 (0.049, 3.1)	2.4 (0.62, 9.3)	DC					
5.5 (0.68, 49.0)	3.1 (0.57, 18.0)	2.6 (0.29, 21.0)	0.81 (0.095, 7.5)	5.2 (1.1, 23.0)	2.1 (0.29, 17.0)	CP				
1.1 (0.17, 7.3)	0.63 (0.15, 2.6)	0.52 (0.072, 3.2)	0.16 (0.023, 1.1)	1.0 (0.19, 5.2)	0.43 (0.050, 3.5)	0.20 (0.021, 1.8)	G+Carboplatin			

PCG	G									
1.9 (0.030, 110)	GC									
1.1 (0.0032, 380)	0.60 (0.0093, 39.0)	GC+Monoclonal								
10.0 (0.031, 3400)	5.5 (0.095, 340)	9.2 (0.026, 3300)	LC							
2.3 (0.0064, 780)	1.2 (0.019, 78.0)	2.0 (0.0056, 740)	0.22 (0.0006, 73.0)	MVAC						
0.87 (0.0025, 280)	0.46 (0.0075, 28.0)	0.76 (0.0022, 260)	0.083 (0.0002, 29.0)	0.38 (0.001, 130)	G+Carboplatin					
4.6 (0.012, 1600)	2.4 (0.036, 160)	4.1 (0.01, 1500)	0.44 (0.0012, 150)	2.0 (0.0054, 730)	5.4 (0.015, 1900)	GC+Sorafenib				
130 (0.088, 280000)	71. (0.17, 46000)	120 (0.080, 260000)	13.0 (0.0086, 26000)	57.0 (0.71, 8200)	160 (0.10, 340000)	29.0 (0.019, 64000)	Cisplatin			

PCG	B									
0.86 (0.62, 1.2)	GC									
0.92 (0.49, 1.7)	1.1 (0.62, 1.8)	GC+Monoclonal								
0.71 (0.41, 1.2)	0.83 (0.52, 1.3)	0.78 (0.38, 1.6)	LC							
0.89 (0.63, 1.3)	1.0 (0.87, 1.3)	0.98 (0.56, 1.7)	1.3 (0.77, 2.1)	MVAC						
0.69 (0.40, 1.2)	0.80 (0.51, 1.3)	0.75 (0.37, 1.5)	0.96 (0.51, 1.9)	0.77 (0.50, 1.2)	DC					
0.72 (0.37, 1.4)	0.84 (0.46, 1.6)	0.78 (0.35, 1.8)	1.0 (0.48, 2.2)	0.80 (0.44, 1.4)	1.0 (0.51, 2.1)	CP				
0.44 (0.21, 0.94)	0.51 (0.26, 1.0)	0.48 (0.20, 1.1)	0.62 (0.27, 1.4)	0.49 (0.24, 0.99)	0.64 (0.28, 1.5)	0.61 (0.24, 1.5)	G+Carboplatin			
0.86 (0.43, 1.7)	1.0 (0.55, 1.8)	0.94 (0.42, 2.1)	1.2 (0.57, 2.6)	0.96 (0.50, 1.8)	1.2 (0.58, 2.7)	1.2 (0.50, 2.8)	2.0 (0.78, 4.9)	GC+Sorafenib		
0.55 (0.36, 0.89)	0.64 (0.47, 0.91)	0.60 (0.32, 1.1)	0.78 (0.44, 1.4)	0.62 (0.48, 0.80)	0.80 (0.49, 1.3)	0.77 (0.41, 1.5)	1.3 (0.59, 2.7)	0.64 (0.33, 1.3)	Cisplatin	

PCG	D									
0.86 (0.17, 5.9)	GC									
1.6 (0.13, 24.0)	1.8 (0.27, 13.0)	GC+Monoclonal								
14.0 (0.75, 370)	17.0 (1.3, 210)	9.1 (0.39, 220)	LC							
3.2 (0.32, 34.0)	3.7 (0.75, 15.0)	2.0 (0.16, 22.0)	0.22 (0.011, 3.8)	MVAC						
30.0 (0.63, 3200)	34.0 (0.99, 2400)	19.0 (0.33, 2000)	2.1 (0.026, 280)	9.2 (0.42, 540)	DC					
8.4 (0.25, 320)	9.6 (0.41, 210)	5.3 (0.13, 200)	0.59 (0.010, 29.0)	2.6 (0.17, 42.0)	0.28 (0.002, 19.0)	CP				
0.61 (0.031, 15.0)	0.71 (0.056, 8.9)	0.39 (0.016, 9.5)	0.043 (0.0012, 1.5)	0.19 (0.011, 4.0)	0.021 (0.0002, 1.6)	0.073 (0.0014, 4.4)	G+Carboplatin			
1.3 (0.062, 36.0)	1.5 (0.11, 21.0)	0.83 (0.032, 23.0)	0.091 (0.0024, 3.5)	0.41 (0.021, 9.2)	0.043 (0.0003, 3.7)	0.16 (0.0028, 9.8)	2.1 (0.053, 84.0)	GC+Sorafenib		
15.0 (0.40, 710)	17.0 (0.65, 480)	9.6 (0.20, 430)	1.0 (0.016, 65.0)	4.7 (0.28, 100)	0.49 (0.004, 40.0)	1.8 (0.035, 100)	24.0 (0.38, 1500)	12.0 (0.16, 770)	Cisplatin	

PCG	F									
0.76 (0.083, 7.2)	GC									
0.89 (0.042, 17.0)	1.1 (0.14, 8.4)	GC+Monoclonal								
0.96 (0.039, 24.0)	1.2 (0.13, 13.0)	1.1 (0.052, 25.0)	LC							
1.4 (0.11, 19.0)	1.9 (0.53, 6.8)	1.6 (0.16, 19.0)	1.5 (0.11, 21.0)	MVAC						
2.0 (0.066, 61.0)	2.6 (0.20, 34.0)	2.3 (0.087, 63.0)	2.1 (0.064, 66.0)	1.4 (0.14, 13.0)	DC					
20.0 (0.59, 880)	26.0 (1.7, 550)	23.0 (0.79, 940)	14.0 (0.59, 950)	14.0 (1.2, 220)	10.0 (0.37, 350)	CP				
0.56 (0.025, 12.0)	0.73 (0.082, 6.5)	0.64 (0.034, 13.0)	0.59 (0.024, 14.0)	0.39 (0.030, 4.7)	0.28 (0.0094, 8.3)	0.028 (0.0007, 0.92)	G+Carboplatin			
0.84 (0.036, 20.0)	1.1 (0.12, 10.0)	0.95 (0.050, 20.0)	0.89 (0.034, 21.0)	0.59 (0.044, 7.6)	0.43 (0.014, 13.0)	0.042 (0.00096, 1.4)	1.5 (0.066, 34.0)	GC+Sorafenib		
1.5 (0.013, 170)	2.0 (0.030, 130)	1.7 (0.018, 190)	1.6 (0.013, 190)	1.1 (0.019, 60.0)	0.78 (0.008, 74.0)	0.073 (0.00064, 8.2)	2.7 (0.025, 320)	1.8 (0.016, 210)	Cisplatin	

PCG	H									
1.3 (0.17, 10.0)	GC									
0.58 (0.030, 11.0)	0.44 (0.050, 3.8)	GC+Monoclonal								
0.31 (0.018, 5.5)	0.24 (0.032, 1.8)	0.54 (0.029, 11.0)	LC							
0.43 (0.029, 6.5)	0.33 (0.056, 1.9)	0.73 (0.045, 12.0)	1.4 (0.095, 19.)	MVAC						
0.77 (0.021, 31.0)	0.59 (0.031, 12.0)	1.3 (0.036, 57.0)	2.5 (0.072, 94.0)	1.8 (0.17, 22.0)	DC					
0.89 (0.045, 17.0)	0.68 (0.080, 5.7)	1.5 (0.072, 32.0)	2.8 (0.15, 51.0)	2.1 (0.13, 33.0)	1.1 (0.028, 43.0)	G+Carboplatin				
0.20 (0.0094, 4.1)	0.16 (0.015, 1.4)	0.35 (0.015, 7.8)	0.65 (0.031, 12.0)	0.47 (0.026, 8.0)	0.26 (0.0058, 10.0)	0.23 (0.0099, 4.8)	GC+Sorafenib			

Table S1. Treatment groups and response and survival rates for studies included in this network meta-analysis.

Study	Year	Treatment	Time period	Therapy setting	Age (years)	ECOG-PS (a range)	Overall response rate		OS			PFS/TTP				
							Responders	SampleSize	HR	95%CI	SampleSize	HR	95%CI	SampleSize		
Hsieh [25]	2016	MVAC	2000-2014	1st line	NA	NA	NA	NA	0.76	0.5	1.17	50	NA	NA	NA	NA
		GC			NA	NA	NA	Ref.			80	NA	NA	NA	NA	
Oudard [26]	2015	GC	2004-2009	1st line	45-80	0-2	19	29	0.95	0.46	1.99	29	0.95	0.55	1.65	29
		GC+Monoclonal			0-2	17	32	Ref.			31	Ref.			31	
Hussain [27]	2014	GC	2008-2011	1st/2nd line	32.8-79.9	0-2	16	28	1.17	0.6	2.3	28	0.94	0.61	1.46	28
		GC+Monoclonal			0-2	35	57	Ref.			57	Ref.			57	
Kerge [28]	2014	GC+sorafenib	2006-2010	1st line	64.4 mean	NA	21	40	1	0.58	1.72	40	0.95	0.61	1.48	40
		GC			NA	23	49	Ref.			49	Ref.			47	
Sternberg [29]	2013	LC	2008-2010	1st line	35-85	0-2	28	90	1.21	0.83	1.76	56	1.67	1.24	2.25	101
		GC			0-2	44	103	Ref.			51	Ref.			83	
Bellmunt [30]	2012	PCG	2001-2004	1st line	27-80	NA	173	312	0.85	0.72	1.02	312	0.87	0.74	1.03	312
		GC			NA	137	314	Ref.			314	Ref.			314	
Bamias [31]	2012	GC	2003-2008	1st line	34-80	0-1	32	49	1.15	0.64	2.05	63	0.79	0.51	1.22	63
		MVAC			0-1	27	45	Ref.			63	Ref.			63	
Dogliotti [32]	2007	GC	2000-2002	1st line	32-80	0-2	27	41	0.52	0.27	0.98	55	0.97	0.63	1.51	55
		G+Carboplatin			0-2	22	39	Ref.			55	Ref.			55	
Roberts [33]	2006	GC	1996-1998	1st line	63 mean	NA	NA	NA	0.99	0.79	1.23	203	1.01	0.81	1.25	203

MVAC					NA	NA	NA	R				202	R				202
Bamias [34]	2004	DC	1997-2002	1st line	32-75	0-2	34	91	1.31	0.94	1.81	111	1.61	1.15	2.26	111	
MVAC					0-2	45	83	R				109	R				109
Dreicer [35]	2004	MVAC	1998-2001	1st line	64 mean	0-2	14	39	0.8	0.48	1.34	41	0.71	0.43	1.17	34	
CP					0-2	12	39	R				39	R				37
Lorusso [36]	2004	PCG	N A	1st line	NA	NA	18	42	N A	N A	N A	NA	N A	N A	N A	NA	
GC					NA	19	43	N A	N A	N A	NA	N A	N A	N A	NA		
Lehman n [37]	2003	GC	1997-1998	1st line	38-78	NA	19	35	1.19	0.71	1.99	35	1.25	0.74	2.12	35	
MVAC					NA	16	34	R				34	R				34
Maase [38]	2000	GC	1996-1998	1st line	63 mean	NA	99	182	0.95	0.74	1.22	203	0.99	0.79	1.24	203	
MVAC					NA	93	181	R				202	R				202
Saxman [39]	1997	Cisplatin	1985-1995	1st line	NA	NA	56	122	1.62	1.26	2.07	122	N A	N A	N A	NA	
MVAC					NA	86	133	R				133	N A	N A	N A	NA	
Loehrer [40]	1992	Cisplatin	1984-1989	1st line	30-82	NA	14	120	1.63	1.27	2.09	120	1.9	1.51	2.4	120	
MVAC					NA	49	126	R				126	R				126

PCG=paclitaxel/cisplatin/gemcitabine; GC=gemcitabine/cisplatin; monoclonal=trastuzum/cetuximab; MVAC=methotrexate/vinblastine/doxorubicin/cisplatin; LC=larotaxel/cisplatin; DC=docetaxel/cisplatin; CP=carboplatin/paclitaxel; GC+sorafenib=gemcitabine/cisplatin/sorafenib; G+Carboplatin=gemcitabine/carboplatin; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; OS: Overall survival; PFS/TTP: Progression-free survival/Time to progression; Ref: reference; NA: not available;

Table S2. Treatment groups and response rates of different adverse events in individual studies included in this network meta-analysis.

Study	Year	Treatment	Sample Size	Thrombocytopenia		Neutropenia		Anemia		Leukopenia		Diarrhea	
				Grade 1-2 (n/%)	Grade 3-5 (n/%)	Grade 1-2 (n/%)	Grade 3-5 (n/%)	Grade 1-2 (n/%)	Grade 3-5 (n/%)	Grade 1-2 (n/%)	Grade 3-5 (n/%)	Grade 1-2 (n/%)	Grade 3-5 (n/%)
Oudard [26]	2015	GC	29	12(41.4%)	14(48.3%)	6(20.7%)	22(75.9%)	16(55.2%)	12(41.4%)	NA	NA	8(27.6%)	1(3.4%)
		GC+Monoclonal	32	15(46.9%)	12(37.5%)	8(25%)	22(68.8%)	19(59.4%)	12(37.5%)	NA	NA	15(46.9%)	1(3.1%)
Hussain [27]	2014	GC	28	NA	11(39.2%)	NA	12(42.9%)	NA	3(10.7%)	NA	6(21.4%)	NA	NA
		GC+Monoclonal	59	NA	15(25.4%)	NA	24(40.7%)	NA	5(8.5%)	NA	18(30.5%)	NA	NA
Kerge [28]	2014	GC+sorafenib	40	1(2.5%)	5(12.5%)	NA	NA	6(15.0%)	4(10.0%)	0(0.0%)	5(12.5%)	11(27.5%)	3(7.5%)
		GC	49	4(8.2%)	6(12.2%)	NA	NA	6(12.2%)	7(14.3%)	6(12.2%)	6(12.2%)	4(8.2%)	0(0.0%)
Sternberg [29]	2013	LC	162	66(40.7%)	3(1.9%)	46(28.4%)	55(34.0%)	144(88.9%)	12(7.4%)	91(56.2%)	26(16.0%)	54(33.3%)	20(12.3%)
		GC	166	78(47.0%)	75(45.2%)	43(25.9%)	100(60.2%)	125(75.3%)	36(21.7%)	85(51.2%)	70(42.2%)	26(15.7%)	2(1.2%)
Bellmunt [30]	2012	PCG	302	NA	104(34.4%)	NA	194(64.2%)	NA	NA	NA	NA	NA	14(4.6%)
		GC	305	NA	159(52.1%)	NA	154(50.5%)	NA	NA	NA	NA	NA	11(3%)
Bamias [31]	2012	GC	59	NA	5(8.5%)	NA	8(13.6%)	NA	6(10.2%)	NA	NA	NA	NA
		MVAC	61	NA	5(8.2%)	NA	12(19.7%)	NA	7(11.5%)	NA	NA	NA	NA
Dogliotti [32]	2007	GC	55	NA	17(30.9%)	NA	19(34.5%)	NA	11(20.0%)	NA	9(16.4%)	NA	8(14.5%)
		G+Carboplatin	55	NA	21(38.2%)	NA	25(45.5%)	NA	14(25.5%)	NA	16(29.1%)	NA	11(20.0%)
Bamias [34]	2004	MVAC	103	NA	6(5.8%)	NA	37(35.9%)	NA	8(7.8%)	NA	NA	NA	5(4.9%)
		DC	104	NA	1(1.0%)	NA	20(19.2%)	NA	6(5.8%)	NA	NA	NA	3(2.9%)
Dreicer [35]	2004	MVAC	43	NA	9(20.9%)	NA	29(67.4%)	NA	16(37.2%)	NA	NA	NA	NA
		CP	41	NA	4(9.8%)	NA	12(29.3%)	NA	2(4.9%)	NA	NA	NA	NA
Lorusso [36]	2004	PCG	42	NA	15(35.7%)	NA	NA	NA	8(19.0%)	NA	21(50.0%)	NA	NA
		GC	43	NA	9(20.9%)	NA	NA	NA	10(23.3%)	NA	15(34.9%)	NA	NA
Lehmann [37]	2003	GC	35	NA	19(54.3%)	NA	17/30(56.7%)	NA	18(51.4%)	NA	18(51.4%)	NA	1(2.9%)
		MVAC	30	NA	5(16.7%)	NA	14/23(60.9%)	NA	6(20%)	NA	14(46.7%)	NA	2(6.7%)
Maase [38]	2000	GC	203	NA	116(57.1%)	NA	144(70.9%)	NA	55(27.1%)	NA	NA	NA	6(3.0%)
		MVAC	202	NA	42(20.8%)	NA	166(82.2%)	NA	36(17.8%)	NA	NA	NA	17(8.4%)
Loehrer [40]	1992	Cisplatin	120	NA	2(1.7%)	NA	NA	NA	1(0.8%)	NA	1(0.8%)	NA	NA
		MVAC	126	NA	8(6.3%)	NA	NA	NA	1(0.8%)	NA	30(23.8%)	NA	NA

PCG=paclitaxel/cisplatin/gemcitabine; GC=gemcitabine/cisplatin; monoclonal=trastuzumab/cetuximab; MVAC=methotrexate/vinblastine/doxorubicin/cisplatin; LC=larotaxel/cisplatin; DC=docetaxel/cisplatin; CP=carboplatin/paclitaxel; GC+sorafenib=gemcitabine/cisplatin/sorafenib; G+Carboplatin=gemcitabine/carboplatin; NA=not available;