Supplementary Materials - ten Hoorn S., de Back T.R., Sommeijer D.W., Vermeulen L.

Supplementary Table 1. Study characteristics of included articles (N = 23)

Study	Design	N	Stages	Taxonomy	CMS classifier	CMS classes					Survival outcomes	Treatment regimens
						CMS1	CMS2	CMS3	CMS4	Unknown		
Allen et al. 2018 (1)	Retrospective	820	II-III	CMS	CMS R package	143 (17.4)	281 (34.3)	115 (14.0)	144 (17.6)	137 (16.7)[a]	OS	5-FU-based adjuvant chemotherapy
Budinska et al. 2013 (2)	Retrospective	1110	II-III	Budinska	NA	C (CMS1)	B (CMS2)	A (CMS3)	D/E (CMS4)	Unknown	OS, RFS, SAR	Surgery alone
						129 (18.8)	236 (34.3)	66 (9.6)	178 (25.9)	79 (11.5)		NA
Dienstmann et al. 2019 (3)	Retrospective	2636	II-III	CMS	CMS R package	507 (19.2)	1062 (40.3)	337 (12.8)	551 (20.9)	179 (6.8)	RFS	NA
Dunne et al. 2016 (4)	Retrospective	460	II-III	CMS	CMS R package	80 (17.4)	193 (42.0)	50 (10.9)	99 (21.5)	38 (8.3)	RFS	FULV
Haasnoot et al. 2020 (5)	Retrospective	223	I, III	CMS	IHC	CMS1	CMS2/3		CMS4	Unknown	LNM, recurrence	NA
						16 (7.2)	203 (91.0)[a]		4 (1.8)	0 (0.0)		
Jary et al. 2020 (6)	Retrospective	1443	I-III	CMS	CMS R package	258 (17.8)	456 (31.6)	182 (12.6)	393 (27.2)	154 (10.7)	OS	NA
Kwon et al. 2017 (7)	Retrospective	101	III	CMS	CMS R package	10 (9.9)	38 (37.6)	13 (12.9)	19 (18.8)	21 (20.8)	OS, RFS	NA
Li et al. 2020 (8)	Retrospective	165	II	CMS	IHC	CMS1	CMS2/3		CMS4	Unknown	OS, RFS	Adjuvant chemotherapy
						30 (18.2)	119 (72.1)		16 (9.7)	0 (0.0)		
Piskol et al. 2019 (9) AVANT Cohort	Retrospective	1062	III	CMS	NanoString	209 (19.7)	509 (47.9)	60 (5.6)	215 (20.2)	69 (6.5)	OS, PFS, RFS, SAR	NA
Roepman et al. 2014 (10)	Retrospective	731	II-III	Roepman	NA	A-type (CMS1)	B-type (CMS2)		C-type (CMS4)	Unknown	OS, DMFS	5-FU
						182 (24.9)	434 (59.4)[a]		115 (15.7)	0 (0.0)		Surgery alone
Shinto et al. 2020 (11)	Retrospective	232	II	CMS	CMS R package	18 (7.8)	87 (37.5)	13 (5.6)	114 (49.1)	0 (0.0)	RFS	NA
Song et al. 2016 (12)	Retrospective	1729	II-III	Sadanandam	NA	IF (CMS1)	EC/TA (CMS2)	GL (CMS3)	SL (CMS4)	Unknown	RFS	FOLFOX
						405 (23.4)	578 (33.4)	142 (8.2)	478 (27.6)	126 (7.3)		FULV
Williams et al. 2018 (13)	Prospective	142	II-III	CMS	CMS R package	20 (14.1)	52 (36.6)	33 (23.2)	7 (4.9)	30 (21.1)	RFS	NA
De Sousa e Melo et al. 2013 (14)	Retrospective	90	I-IV	De Sousa e Melo	NA	CMS1	CMS2/3		CMS4	Unknown	RFS, RR	Cetuximab monotherapy
						22 (24.4)	44 (48.9)		24 (26.7)	0 (0.0)		
Guinney et al. 2015 (15)	Retrospective	3962	I-IV	CMS	CMS R package	555 (14.0)	1466 (37.0)	515 (13.0)	911 (23.0)	515 (13.0)	OS, RFS, SAR	NA
Trinh et al. 2017 (25) LUMC Cohort	Retrospective	240	I-IV	CMS	IHC	CMS1	CMS2/3		CMS4	Unknown	RFS	NA
						35 (14.6)	102 (42.5)		103 (42.9)	0 (0.0)		NA

(continued)

Supplementary Table 1 (continued)

Study	Design	N	Stages	Taxonomy	CMS classifier	CMS classes					Survival outcomes	Treatment regimens
						CMS1	CMS2	CMS3	CMS4	Unknown		
						n (%)	n (%)	n (%)	n (%)	n (%)		
Cremolini et al. 2019 (16)	Retrospective	9	IV	CMS	NanoString	1 (11.1)	3 (33.3)	0 (0.0)	4 (44.4)	1 (11.1)	RR	Irinotecan +/- anti-EGFR
				Sadanandam								
Del Rio et al. 2017 (17)	Retrospective	143	IV	CMS	CMS R package	15 (10.5)	29 (20.3)	24 (16.8)	36 (25.2)	39 (27.3)[a]	OS, PFS, RR	FOLFOX
				De Sousa e Melo								FOLFIRI-based
				Sadanandam								FOLFIRI + bevacizumab
Kawazoe et al. 2020 (18)	Prospective	23	IV	CMS	CMS R package	5 (21.7)	6 (26.1)	3 (13.0)	6 (26.1)	3 (13.0)	irORR	Napabucasin + pembrolizumab
Lenz et al. 2019 (19)	Retrospective	663	IV	CMS	NanoString	104 (15.7)	242 (36.5)	68 (10.3)	167 (25.2)	82 (12.4)	OS, PFS	FOLFOX/FOLFIRI + cetuximab
												FOLFOX/FOLFIRI + bevacizumab
Lenz et al. 2020 (20)	Retrospective	231	IV	CMS	CMS R package	4 (1.7)	64 (27.7)	2 (0.9)	119 (51.5)	42 (18.2)	OS, PFS	Nintedanib
												Placebo
Mooi et al. 2018 (21)	Retrospective	237	IV	CMS	CMS R package	42 (17.7)	113 (47.7)	28 (11.8)	54 (22.8)	0 (0.0)	OS, PFS	Capecitabin
												Capecitabin, mitomycin C and bevacizumab
Morris et al. 2020 (22)	Retrospective	331	IV	CMS	NanoString	17 (5.1)	111 (33.5)	25 (7.6)	178 (53.8)	0 (0.0)	OS	NA
Okita et al. 2018 (23)	Retrospective	193	IV	CMS	CMS R package	21 (10.9)	53 (27.5)	69 (35.8)[a]	50 (25.9)	0 (0.0)	OS, PFS, RR, DCR	Oxaliplatin-based chemotherapy
												Irinotecan-based chemotherapy
Piskol et al. 2019 (9) Procured and Dareck Cohort	Retrospective	234	IV	CMS	NanoString	37 (15.8)	115 (49.1)	4 (1.7)	64 (27.4)	14 (6.0)	OS, PFS, RFS, SAR	NA
Schlicker et al. 2020 (24)	Retrospective	51	IV	CMS	CMS R package	1 (2.0)	16 (31.4)	2 (3.9)	32 (62.7)	0 (0.0)	OS	NA
Stintzing et al. 2019 (25)	Retrospective	514	IV	CMS	CMS R package	61 (11.9)	162 (31.5)	66 (12.8)	149 (29.0)	76 (14.8)	OS, PFS, RR	FOLFIRI + cetuximab
												FOLFIRI + bevacizumab
Trinh et al. 2017 (26) CAIRO2 Cohort	Retrospective	339	IV	CMS	IHC	CMS1	CMS2/3		CMS4	Unknown	OS, RR	CAPOX + bevacicumab
						8 (2.3)	161 (47.5)		170 (50.1)	0 (0.0)		CAPOX + bevacicumab + cetuximab
Woolston et al. 2019 (27)	Prospective	25	IV	CMS	CMS caller	4 (16.0)	13 (52.0)	3 (12.0)	5 (20.0)	0 (0.0)	OS, PFS, RR	Cetuximab monotherapy
				Sadanandam								

[a] Aberrant number of labels based on high pearson residuals (>8, data not shown)

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CMS, consensus molecular subtypes; DCR, disease control rate; DMFS, distant metastasis–free survival; EC/TA, enterocyte / transit-amplifying; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FULV, fluorouracil and leucovorin; GL, goblet-like; IF, inflammatory; IHC, immunohistochemistry; LNM, lymph node metastasis; NA, not applicable; OS, overall survival; PFS, progression-free survival; RR, response rate; RFS, relapse-free survival; SAR, survival after relapse; SL, stem-like.

Supplementary Table 2. Study characteristics of included abstracts (N = 8)

Study	Conference	Design	N	Stage	Taxonomy	CMS classifier	CMS classes					Survival outcomes	Treatment regimens
							CMS1	CMS2	CMS3	CMS4	Unknown		
							n (%)	n (%)	n (%)	n (%)	n (%)		
Marisa et al. 2017 (28)	ASCO	Retrospective	1781	III	CMS	NanoString	297 (16.7)	585 (32.8)	68 (3.8)	770 (43.2)[a]	61 (3.4)	OS	FOLFOX + cetuximab
Pogue-Geile et al. 2019 (29)	ASCO	Retrospective	590	III	Sadanandam	NA	NR	NR	NR	NR	NR	OS	5-FU +/- FOLFOX
Borelli et al. 2020 (30)	ASCO	Retrospective	426	IV	CMS	NanoString	4 (0.9)[a]	142 (33.3)	58 (13.6)	222 (52.1)[a]	0 (0.0)	OS, PFS	FOLFOX + bevacizumab
Gomez et al. 2020 (31)	EMSO	Retrospective	195	IV	CMS	IHC	CMS1	CMS2/3		CMS4	Unknown	OS, TTP	FOLFOXIRI + bevacizumab Oxaliplatin-based +/- anti-EGFR Irinotecan-based +/- anti-EGFR
							8 (3.7)	109 (49.8)		78 (35.6)	0 (0.0)		
Lam et al. 2020 (32)	ASCO	Retrospective	117	IV	CMS	NanoString	7 (6.0)	43 (36.8)	8 (6.8)	55 (47.0)	4 (3.4)	OS	NA
Lee et al. 2019 (33)	ASCO	Retrospective	68	IV	CMS	Multinomial elastic net CMS classifier	8 (11.8)	43 (63.2)	3 (4.4)	14 (20.6)	0 (0.0)	OS, PFS, TTP	NA
Sarshekeh et al. 2020 (34)	ASCO	Prospective	53	IV	CMS	NanoString	0 (0.0)	0 (0.0)	0 (0.0)	53 (100.0)	NR	OS, PFS, RR	Bintrafusp alfa (M7824) + RT
Yuki et al. 2020 (35)	ASCO	Retrospective	308	IV	CMS	CMS R package	47 (15.3)	72 (23.4)	99 (32.1)[a]	90 (29.0)	0 (0.0)	OS, PFS	mFOLFOX/CAPOX + bevacizumab S-1 + Irinotecan + bevacizumab

[a] Aberrant number of labels based on high pearson residuals (>8), data not shown)

Abbreviations: AJCC-TRG, American Joint Committee on Cancer - tumor regression grading; ASCO, American Society of Clinical Oncology; CAPOX, capecitabine and oxaliplatin; CMS, consensus molecular subtypes; DCR, disease control rate; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin and irinotecan; IHC, immunohistochemistry; JCO, Journal of Clinical Oncology; mFOLFOX modified FOLFOX; NR, not reported; NA, not available; OS, overall survival; PFS, progression free survival; RR, response rate; TTP, time to progression

Supplementary Table 3. Prediction model Risk of Bias Assessment Tool (PROBAST)

Study	ROB				Applicability			Overall		Analysis	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability	Prognostic	Predictive
Allen et al. 2018 (1)	+	+	+	+	+	+	?	+	?	no	yes
Budinska et al. 2013 (2)	+	+	+	+	+	-	?	+	-	yes	no
Cremolini et al. 2019 (16)	+	+	+	-	-	-	-	-	-	no	yes
De Sousa e Melo et al. 2013 (14)	+	+	+	+	+	-	?	+	-	no	yes
Del Rio et al. 2017 (17)	+	+	+	+	+	+	+	+	+	yes	yes
Dienstmann et al. 2019 (3)	+	+	+	+	+	-	+	+	-	yes	no
Dunne et al. 2016 (4)	+	+	+	+	+	?	+	+	?	no	yes
Guinney et al. 2015 (15)	+	+	+	+	+	+	+	+	+	yes	no
Haasnoot et al. 2020 (5)	+	+	+	+	+	-	+	+	-	yes	no
Jary et al. 2020 (6)	+	+	+	+	+	+	+	+	+	yes	no
Kawazoe et al. 2020 (18)	+	+	+	-	+	+	+	-	+	no	yes
Kwon et al. 2017 (7)	+	+	+	-	+	+	?	-	?	yes	no
Lenz et al. 2019 (19)	+	+	+	+	+	-	+	+	-	yes	yes
Lenz et al. 2020 (20)	+	+	+	+	+	+	+	+	+	yes	yes
Li et al. 2020 (8)	+	+	+	+	+	-	+	+	-	yes	yes
Mooi et al. 2018 (21)	+	+	+	+	+	+	+	+	+	yes	yes
Morris et al. 2020 (22)	+	+	+	+	+	-	+	+	-	yes	no
Okita et al. 2018 (23)	+	+	+	+	-	+	+	+	-	yes	yes
Piskol et al. 2019 (9)	+	+	+	+	+	-	+	+	-	yes	no
Roepman et al. 2014 (10)	+	+	+	+	+	-	?	+	-	yes	yes
Schlicker et al. 2020 (24)	+	+	+	-	+	+	+	-	+	yes	no
Shinto et al. 2020 (11)	+	+	+	+	+	+	+	+	+	yes	no
Song et al. 2016 (12)	+	+	+	+	+	-	+	+	-	yes	yes
Stintzing et al. 2019 (25)	+	+	+	+	+	+	+	+	+	yes	yes
Trihn et al. 2017 (26)	+	+	+	+	+	-	+	+	-	no	yes
Williams et al. 2018 (13)	+	+	+	+	+	+	+	+	+	yes	no
Woolston et al. 2019 (27)	+	+	+	-	-	-	+	-	-	no	yes

Abbreviations: PROBAST, Prediction model Risk of Bias Assessment Tool; ROB, risk of bias.

+ indicates low ROB/low applicability concern; - indicates high ROB/high applicability concern; ? Indicates unclear ROB/unclear applicability concern

Supplementary Table 4. Distribution of CMS labels in the local versus metastatic setting.

		CMS1		CMS2		CMS3		CMS4		Unknown	
	N	n	%	n	%	n	%	n	%	n	%
Local	16	2334	18.7	4986	39.9	1079	8.6	3205	25.6	894	7.2
Metastatic	17	386	9.9	1388	35.5	462	11.8	1415	36.1	261	6.7

Pearson's Chi-squared test: X-squared = 304.65, df = 4, P value < 0.001

Abbreviations: CMS, consensus molecular subtypes; N, Number of studies; n, number of patients

Supplementary Table 5. Sensitivity analyses to explore heterogeneity in the pairwise prognostic CMS comparisons per survival outcome in local and metastatic disease.

	Original values		Adjusted values sensitivity analyses		Excluded studies
Meta-analyses	HR (95% CI)	Heterogeneity	HR (95% CI)	Heterogeneity	Reference
CMS4 versus CMS1					
OS local	3.28 (1.27 to 8.47), P = 0.01	I^2 = 83.0%, P < 0.001	4.54 (2.68 to 7.70), P < 0.001	I^2 = 0.0%, P = 0.65	Jary et al. 2020 (6)
PFS metastatic	0.52 (0.38 to 0.75), P < 0.001	I^2 = 57.1%, P = 0.03	0.46 (0.35 to 0.61), P < 0.001	I^2 = 0.0%, P = 0.71	Lenz et al. 2019 (19)
RFS local	1.84 (1.35 to 2.51), P < 0.001	I^2 = 58.6%, P = 0.047	2.18 (1.69 to 2.81), P < 0.001	I^2 = 0.0%, P = 0.46	Dienstmann et al. 2019 (3)
CMS2 versus CMS1					
OS metas	0.33 (0.23 to 0.48), P < 0.001	I^2 = 62.8%, P = 0.009	0.30 (0.22 to 0.41), P < 0.001	I^2 = 31.8%, P = 0.19	Lenz et al. 2019 (19)
PFS metas	0.53 (0.35 to 0.81), P = 0.003	I^2 = 74.7%, P < 0.001	0.72 (0.54 to 0.96), P = 0.03	I^2 = 38.4%, P = 0.17	Piskol et al. 2019 (9)
CMS3 versus CMS1					
OS metastatic	0.55 (0.32 to 0.93), P = 0.03	I^2 = 74.1%, P = 0.004	0.45 (0.32 to 0.62), P < 0.001	I^2 = 0.0%, P = 0.72	Lenz et al. 2019 (19)
PFS metastatic	0.89 (0.60 to 1.34), P = 0.59	I^2 = 55.2%, P = 0.06	1.02 (0.71 to 1.48), P = 0.91	I^2 = 39.8%, P = 0.17	Okita et al. 2018 (23)
CMS4 versus CMS3					
RFS local	1.23 (0.82 to 1.84), P = 0.32	I^2 = 50.3%, P = 0.09	1.30 (0.94 to 1.79), P = 0.12	I^2 = 35.6%, P = 0.20	Williams et al. 2019 (13)

Abbreviations: 95% CI, 95% confidence interval; CMS, consensus molecular subtypes; HR, Hazard ratio; RFS, relapse-free survival; PFS, progression- free survival; OS, overall survival

Supplementary Table 6. Data and weight information for the meta-analyses into median overall survival of stage IV colorectal cancer per CMS

CMS	Study	N	Classification method	Median OS in months (95% CI)	Weight (%)	Pooled median OS in months (95% CI)
1	Okita et al, 2018 (anti-EGFR cohort) (23)	14	CMS R package	5.70 (1.10 to ND)	14.3	11.20 (7.69 to 14.71)
	Piskol et al, 2018 (DARECK cohort) (9)	14	NanoString	5.80 (3.70 to ND)	17.7	
	Mooi et al, 2018 (21)	42	CMS R package	8.80 (6.50 to 16.00)	13.1	
	Piskol et al, 2018 (PROCURED cohort) (9)	9	NanoString	10.00 (3.00 to ND)	10.8	
	Guinney et al, 2015 (15)	7	CMS R package	13.00 (5.10 to ND)	9.7	
	Lenz et al, 2019 (19)	104	NanoString	15.00 (11.70 to 22.40)	12.6	
	Stintzing et al, 2019 (25)	61	CMS R package	15.90 (11.00 to 20.80)	13.8	
	Okita et al, 2018 (chemotherapy cohort) (23)	21	CMS R package	21.40 (13.30 to 35.50)	6.2	
	Morris et al, 2020 (22)	17	NanoString	24.80 (19.90 to 59.20)	1.8	
2	Mooi et al, 2018 (21)	113	CMS R package	24.20 (19.10 to 27.40)	14.2	36.39 (30.44 to 42.33)
	Okita et al, 2018 (anti-EGFR cohort) (23)	39	CMS R package	26.60 (13.70 to 34.80)	10.1	
	Stintzing et al, 2019 (25)	164	CMS R package	29.00 (26.70 to 31.40)	14.9	
	Guinney et al, 2015 (15)	46	CMS R package	38.90 (27.00 to ND)	9.5	
	Lam et al, 2020 (32)	43	NanoString	40.00 (34.00 to 51.00)	11.4	
	Lenz et al, 2019 (19)	242	NanoString	40.30 (36.10 to 43.10)	14.5	
	Morris et al, 2020 (22)	111	NanoString	46.00 (36.60 to 53.80)	11.5	
	Piskol et al, 2018 (PROCURED cohort) (9)	47	NanoString	46.00 (32.00 to 67.00)	6.4	
	Okita et al, 2018 (chemotherapy cohort) (23)	53	CMS R package	48.10 (34.80 to 65.60)	7.5	
3	Okita et al, 2018 (anti-EGFR cohort) (23)	27	CMS R package	13.40 (5.80 to 15.40)	15.3	21.89 (15.92 to 27.85)
	Mooi et al, 2018 (21)	28	CMS R package	17.60 (11.30 to 24.60)	14.5	
	Stintzing et al, 2019 (25)	65	CMS R package	18.60 (15.40 to 21.70)	16.8	
	Guinney et al, 2015 (15)	10	CMS R package	20.00 (11.70 to ND)	13.2	
	Morris et al, 2020 (22)	25	NanoString	22.30 (16.90 to 35.20)	11.9	
	Lenz et al, 2019 (19)	68	NanoString	24.30 (16.40 to 29.00)	14.6	
	Okita et al, 2018 (chemotherapy cohort) (23)	69	CMS R package	38.70 (30.60 to 45.60)	13.8	

(continued)

Supplementary Table 6 (continued)

CMS	Study	N	Classification method	Median OS in months (95% CI)	Weight (%)	Pooled median OS in months (95% CI)
4	Piskol et al, 2018 (DARECK cohort) (9)	29	NanoString	13.10 (9.00 to NA)	11.1	26.79 (21.07 to 32.50)
	Okita et al, 2018 (anti-EGFR cohort) (23)	23	CMS R package	17.00 (13.20 to 24.90)	10.3	
	Mooi et al, 2018 (21)	54	CMS R package	21.40 (15.80 to 23.10)	11.1	
	Stintzing et al, 2019 (25)	148	CMS R package	24.80 (22.60 to 27.10)	11.6	
	Piskol et al, 2018 (PROCURED cohort) (9)	25	NanoString	27.00 (19.00 to NA)	9.6	
	Guinney et al, 2015 (15)	41	CMS R package	28.00 (22.00 to 52.00)	5.6	
	Lam et al, 2020 (32)	55	NanoString	28.00 (21.00 to 33.00)	10.4	
	Lenz et al, 2019 (19)	167	NanoString	31.40 (26.30 to 36.90)	10.7	
	Morris et al, 2020 (22)	178	NanoString	37.10 (33.20 to 44.30)	10.5	
	Okita et al, 2018 (chemotherapy cohort) (23)	50	CMS R package	44.00 (33.00 to 50.50)	9.1	

Abbreviations: CMS, consensus molecular subtypes; N, number of patients included in the cohort; OS, overall survival; 95% CI, 95% confidence interval; ND, not determined

Supplementary Table 7. Sensitivity analyses to explore heterogeneity in the pooled median overall survival per CMS in metastatic colorectal cancer.

	Original values		Adjusted values sensitivity analyses		Excluded studies
Meta-analyses	Months (95% CI)	Heterogeneity	Months (95% CI)	Heterogeneity	Reference
CMS1	11.20 (7.69 to 14.71)	I^2 = 72.8%, P < 0.001	11.44 (7.61 to 15.27)	I^2 = 50.4%, P = 0.06	Piskol 2019 (9); Stintzing 2019 (25)
CMS2	36.39 (30.44 to 42.33)	I^2 = 87.1%, P < 0.001	37.87 (31.23 to 44.52)	I^2 = 78.5%, P < 0.001	Mooi 2018 (21); Lenz 2019 (19)
CMS3	21.89 (15.92 to 27.85)	I^2 = 81.4%, P < 0.001	18.77 (15.80 to 21.75)	I^2 = 29.1%, P = 0.22	Okita 2018 (23)
CMS4	26.79 (21.07 to 32.50)	I^2 = 89.0%, P < 0.001	28.00 (23.75 to 32.25)	I^2 = 75.4%, P < 0.001	Okita 2018 (2x) (23); Piskol 2019 (9)

Abbreviations: 95% CI, 95% confidence interval; CMS, consensus molecular subtypes; HR, Hazard ratio; RFS, relapse-free survival; PFS, progression- free survival; OS, overall survival

Supplementary Table 8. Distribution of CMS labels in the local versus metastatic setting with studies using classification methods with only 3 classes excluded[a].

		CMS1		CMS2		CMS3		CMS4		Unknown	
	N	n	%	n	%	n	%	n	%	n	%
Local	11	2076	18.7	4077	36.7	1079	9.7	2968	26.8	894	8.1
Metastatic	16	378	10.6	1227	34.3	462	12.9	1245	34.8	261	7.3

Pearson's Chi-squared test: X-squared = 201.15, df = 4, P value < 0.001

Abbreviations: CMS, consensus molecular subtypes; N, Number of studies; n, number of patients

[a]Immunohistochemistry, De Sousa subtypes and Roepman subtypes

Supplementary Table 9. CMS classification method for each study included in the prognostic meta-analyses

Setting	CMS4 versus CMS1		CMS3 versus CMS1		CMS2 versus CMS1	
Local OS	Li et al., 2020 (8)	Immunohistochemistry	Jary et al., 2020 (6)	CMS R package	Budinska et al., 2013 (2)	Budinska classification
	Roepman et al., 2014 (10)	Roepman classification			Piskol et al., 2019 AVANT cohort (9)	NanoString
	Piskol et al., 2019 AVANT cohort (9)	NanoString			Jary et al., 2020 (6)	CMS R package
	Jary et al., 2020 (6)	CMS R package				
Local RFS	Li et al., 2020 (8)	Immunohistochemistry	Shinto et al., 2020 (11)	CMS R package	Shinto et al., 2020 (11)	CMS R package
	Song et al., 2016 Discovery cohort (12)	Sadanandam classification	Williams et al., 2018 (13)	CMS R package	Williams et al., 2018 (13)	CMS R package
	Song et al., 2016 Validation cohort (12)	Sadanandam classification	Dienstmann et al., 2019 (3)	CMS R package	Budinska et al., 2013 (2)	Budinska classification
	Dienstmann et al., 2019 (3)	CMS R package			Dienstmann et al., 2019 (3)	CMS R package
	Piskol et al., 2019 AVANT cohort (9)	NanoString			Piskol et al., 2019 AVANT cohort (9)	NanoString
Local SAR	Piskol et al., 2019 AVANT cohort (9)	NanoString			Budinska et al., 2013 (2)	Budinska classification
Metastatic OS	Lenz et al., 2019 (19)	NanoString	Lenz et al., 2019 (19)	NanoString	Lenz et al., 2019 (19)	NanoString
	Mooi et al., 2018 (21)	CMS R package	Mooi et al., 2018 (21)	CMS R package	Mooi et al., 2018 (21)	CMS R package
	Piskol et al., 2019 DARECK cohort (9)	NanoString	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Piskol et al., 2019 (9) DARECK cohort	NanoString
	Piskol et al., 2019 PROCURED cohort (9)	NanoString	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package	Piskol et al., 2019 (9) PROCURED cohort	NanoString
	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Del Rio et al., 2017 (17)	CMS R package	Okita et al., 2018 (23) chemotherapy cohort	CMS R package
	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package			Okita et al., 2018 (23) anti-EGFR cohort	CMS R package
	Del Rio et al., 2017 (17)	CMS R package			Del Rio et al., 2017 (17)	CMS R package
					Lee et al., 2019 (33)	Multinomial elastic net classifier
Metastatic PFS	Lenz et al., 2019 (19)	NanoString	Lenz et al., 2019 (19)	NanoString	Lenz et al., 2019 (19)	NanoString
	Mooi et al., 2018 (21)	CMS R package	Mooi et al., 2018 (21)	CMS R package	Mooi et al., 2018 (21)	CMS R package
	Piskol et al., 2019 DARECK cohort (9)	NanoString	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Piskol et al., 2019 (9) DARECK cohort	NanoString
	Piskol et al., 2019 (9) PROCURED cohort	NanoString	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package	Piskol et al., 2019 (9) PROCURED cohort	NanoString
	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Del Rio et al., 2017 (17)	CMS R package	Okita et al., 2018 chemotherapy cohort (23)	CMS R package
	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package			Okita et al., 2018 anti-EGFR cohort (23)	CMS R package
	Del Rio et al., 2017 (17)	CMS R package			Del Rio et al., 2017 (17)	CMS R package

(continued)

Supplementary Table 9 (continued)

Setting	CMS4 versus CMS2		CMS3 versus CMS2		CMS4 versus CMS3	
Local OS	Budinska et al., 2013 (Subgroup D) (2)	Budinska classification	Budinska et al., 2013 (2)	Budinska classification		
	Budinska et al., 2013 (Subgroup E) (2)	Budinska classification				
	Piskol et al., 2019 AVANT cohort (9)	NanoString				
Local RFS	Shinto et al., 2020 (11)	CMS R package	Shinto et al., 2020 (11)	CMS R package	Shinto et al., 2020 (11)	CMS R package
	Song et al., 2016 (12) Discovery cohort	Sadanandam classification	Williams et al., 2018 (13)	CMS R package	Williams et al., 2018 (13)	CMS R package
	Song et al., 2016 (12) Validation cohort	Sadanandam classification	Budinska et al., 2013 (2)	Budinska classification	Song et al., 2016 (12) Discovery cohort	Sadanandam classification
	Williams et al., 2018 (13)	CMS R package	Dienstmann et al., 2019 (3)	CMS R package	Song et al., 2016 (12) Validation cohort	Sadanandam classification
	Budinska et al., 2013 (2) (Subgroup D)	Budinska classification			Dienstmann et al., 2019 (3)	CMS R package
	Budinska et al., 2013 (2) (Subgroup E)	Budinska classification				
	Dienstmann et al., 2019 (3)	CMS R package				
	Piskol et al., 2019 (9) AVANT cohort	NanoString				
Local SAR	Budinska et al., 2013 (2) (Subgroup D)	Budinska classification	Budinska et al., 2013 (2)	Budinska classification		
	Budinska et al., 2013 (2) (Subgroup E)	Budinska classification				
	Piskol et al., 2019 (9) AVANT cohort	NanoString				
Metastatic OS	Schlicker et al., 2020 (24)	CMS R package	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Okita et al., 2018 (23) chemotherapy cohort	CMS R package
	Piskol et al., 2019 (9) DARECK cohort	NanoString	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package
	Piskol et al., 2019 (9) PROCURED cohort	NanoString	Del Rio et al., 2017 (17)	CMS R package	Del Rio et al., 2017 (17)	CMS R package
	Okita et al., 2018 (23) chemotherapy cohort	CMS R package				
	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package				
	Del Rio et al., 2017 (17)	CMS R package				
Metastatic PFS	Piskol et al., 2019 (9) DARECK cohort	NanoString	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Okita et al., 2018 (23) chemotherapy cohort	CMS R package
	Piskol et al., 2019 (9) PROCURED cohort	NanoString	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package
	Okita et al., 2018 (23) chemotherapy cohort	CMS R package	Del Rio et al., 2017 (17)	CMS R package	Del Rio et al., 2017 (17)	CMS R package
	Okita et al., 2018 (23) anti-EGFR cohort	CMS R package				
	Del Rio et al., 2017 (17)	CMS R package				

Abbreviations: CMS, consensus molecular subtypes; OS, overall survival; PFS, progression free survival; RFS, relapse free survival; SAR, survival after relapse

Supplementary Table 10. Sensitivity analyses for phenotypic (immunohistochemical) versus RNA-based CMS labeling in the prognostic meta-analyses

Meta-analyses	Original values	Adjusted values sensitivity analyses	Excluded study
	HR (95% CI)	HR (95% CI)	Reference
CMS4 versus CMS1			
OS local	3.28 (1.27 to 8.47), P = 0.01	2.72 (0.98 to 7.52), P = 0.05	Li et al., 2020 (8)
RFS local	1.84 (1.35 to 2.51), P < 0.001	1.83 (1.30 to 2.59), P < 0.001	Li et al., 2020 (8)

Abbreviations: CMS, consensus molecular subtypes; HR, hazard ratio; OS, overall survival; RFS, relapse free survival

Supplementary Table 11. Subgroup analyses of single group versus consensus transcriptomic profiling in the prognostic meta-analyses[a].

Subgroup analyses				
Meta-analyses	Original values	Subgroups	Values subgroup analyses	Difference between subgroups
	HR (95% CI)		HR (95% CI)	P value
CMS4 versus 1	1.84 (1.35 to 2.51), P < 0.001	Sadanandam labels (n=2)	2.44 (1.82 to 3.28), P < 0.001	0.003
RFS local		CMS labels (n=3)	1.41 (1.15 to 1.72), P < 0.001	
CMS4 versus 2	1.46 (1.29 to 1.64), P < 0.001	Sadanandam labels (n=2)	1.42 (1.12 to 1.82), P = 0.005	0.76
RFS local		Budinska labels (n=2)	1.64 (1.19 to 2.26), P = 0.002	
		CMS labels (n=4)	1.44 (1.20 to 1.74), P < 0.001	
CMS4 versus 3	1.23 (0.82 to 1.84), P = 0.32	Sadanandam labels (n=2)	1.11 (0.71 to 1.75), P = 0.64	0.94
RFS local		CMS labels (n=3)	1.18 (0.33 to 4.24), P = 0.80	

[a]Among single group classifications, only Roepman, Budinska and Sadanandam labels were used as surrogates for the CMSs.

Supplementary Table 12. Sensitivity analyses of single group versus consensus transcriptomic profiling in the prognostic meta-analyses[a].

Meta-analyses	Original values HR (95% CI)	Adjusted values sensitivity analyses HR (95% CI)	Excluded classification Reference
CMS4 versus 1			
OS local	3.28 (1.27 to 8.47), P = 0.01	2.79 (0.95 to 8.20), P = 0.003	Roepman et al., 2014 (10)
CMS2 versus 1			
OS local	0.92 (0.70 to 1.21), P = 0.54	0.98 (0.73 to 1.32), P = 0.88	Budinska et al., 2013 (2)
CMS2 versus 1			
RFS local	0.97 (0.82 to 1.15), P = 0.74	0.96 (0.80 to 1.15), P = 0.68	Budinska et al., 2013 (2)
CMS3 versus 2			
RFS local	0.96 (0.77 to 1.21), P = 0.74	0.97 (0.76 to 1.24), P = 0.81	Budinska et al., 2013 (2)
CMS4 versus 2			
OS local	2.60 (1.93 to 3.50), P < 0.001	3.33 (2.00 to 5.00), P < 0.001	Budinska et al., 2013 (2)
CMS4 versus 2			
SAR local	1.97 (1.41 to 2.74), P < 0.001	2.00 (1.25 to 3.33), P = 0.009	Budinska et al., 2013 (2)

[a]Among single group classifications, only Roepman, Budinska and Sadanandam labels were used as surrogates for the CMSs.

Supplementary Table 13. Subgroup analyses for differences between RNA-based CMS classification methods for the meta-analyses into pairwise CMS comparison.

Meta-analyses	Original values	Subgroups	Values subgroup analyses	Difference between subgroups
	HR (95% CI)	Method (number of cohorts n)	HR (95% CI)	P value
CMS4 versus CMS1	0.45 (0.32 to 0.62), P < 0.001	NanoString-based labels (n=3)	0.42 (0.29 to 0.60), P < 0.001	0.69
OS metastastic		CMS R package labels (n=4)	0.48 (0.26 to 0.88), P = 0.02	
CMS4 versus CMS1	0.53 (0.38 to 0.75), P < 0.001	NanoString-based labels (n=3)	0.53 (0.38 to 0.72), P < 0.001	0.86
PFS metastatic		CMS R package labels (n=4)	0.49 (0.21 to 1.11), P = 0.09	
CMS2 versus CMS1	0.33 (0.23 to 0.48), P < 0.001	NanoString-based labels (n=3)	0.29 (0.12 to 0.74), P = 0.01	0.90
OS metastatic		CMS R package labels (n=4)	0.34 (0.23 to 0.51), P < 0.001	
		CMS elastic net labels (n=1)	0.39 (0.18 to 0.86), P = 0.02	
CMS2 versus CMS1	0.53 (0.35 to 0.81), P = 0.003	NanoString-based labels (n=3)	0.35 (0.14 to 0.88), P = 0.03	0.18
PFS metastatic		CMS R package labels (n=4)	0.71 (0.45 to 1.10), P = 0.12	
CMS4 versus CMS2	1.41 (1.07 to 1.86), P = 0.02	NanoString-based labels (n=2)	1.53 (0.97 to 2.39), P = 0.07	0.84
OS metastatic		CMS R package labels (n=4)	1.43 (0.91 to 2.23), P = 0.12	
CMS4 versus CMS2	0.96 (0.72 to 1.29), P = 0.80	NanoString-based labels (n=2)	1.25 (0.86 to 1.82), P = 0.25	0.11
PFS metastatic		CMS R package labels (n=3)	0.82 (0.58 to 1.16), P = 0.26	

Abbreviations: CMS, consensus molecular subtype; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Supplementary Table 14. Subgroup analyses for differences between RNA-based CMS classification methods for meta-analyses into mOS times per CMS.

Meta-analyses	Original values	Subgroups	Values subgroup analyses	Difference between subgroups
	Months (95% CI)	Method (number of cohorts n)	HR (95% CI)	P value
CMS1	11.20 (7.69 to 14.71)	NanoString-based labels (n=4)	10.51 (4.81 to 16.20)	0.71
mOS metastatic		CMS R package labels (n=5)	11.91 (6.99 to 16.83)	
CMS1	36.39 (30.44 to 42.33)	NanoString-based labels (n=4)	41.14 (38.09 to 44.19)	0.01
mOS metastatic		CMS R package labels (n=5)	31.20 (24.15 to 38.26)	
CMS1	21.89 (15.92 to 27.85)	NanoString-based labels (n=2)	23.70 (18.27 to 29.13)	0.66
mOS metastatic		CMS R package labels (n=5)	21.44 (13.03 to 29.85)	
CMS1	26.79 (21.07 to 32.50)	NanoString-based labels (n=5)	27.18 (19.09 to 35.28)	0.91
mOS metastatic		CMS R package labels (n=5)	26.47 (17.34 to 35.61)	

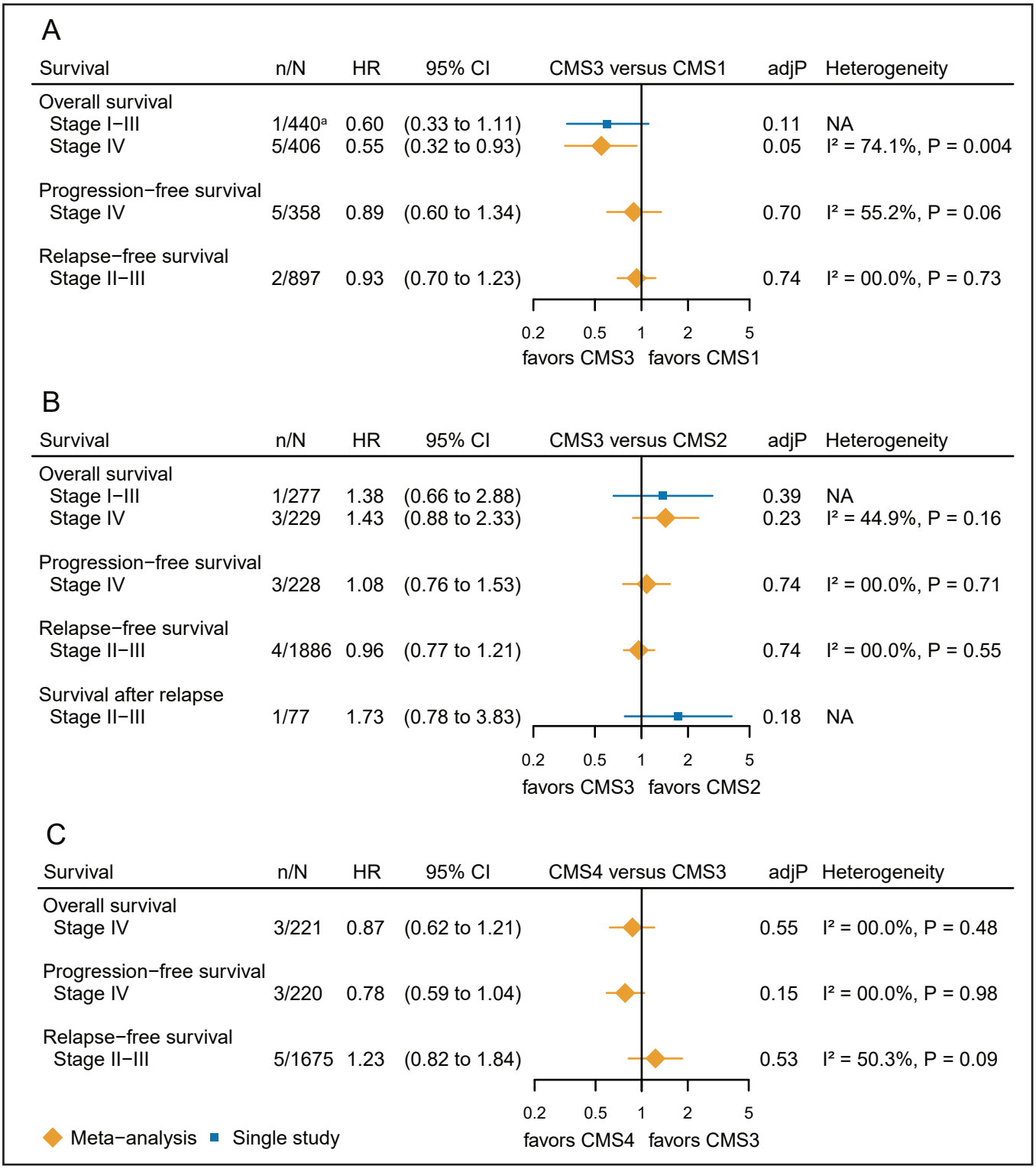
Abbreviations: CMS, consensus molecular subtype; HR, hazard ratio; mOS, medium overall survival

Supplementary Table 15. Sensitivity analyses for differences between RNA-based CMS classification methods when subgroup analyses were not feasible.

Meta-analyses	Original values	Adjusted values sensitivity analyses	Excluded study
	HR (95% CI)	HR (95% CI)	Reference (classifier)
CMS4 versus CMS1 OS local	3.28 (1.27 to 8.47), P = 0.01	3.27 (0.84 to 12.69), P = 0.09	Piskol et al., 2019 (9) (NanoString classifier)
CMS4 versus CMS1 RFS local	1.84 (1.35 to 2.51), P < 0.001	1.96 (1.34 to 2.85), P < 0.001	Piskol et al., 2019 (9) (NanoString classifier)
CMS3 versus CMS1 OS metastastic	0.55 (0.32 to 0.93), P = 0.03	0.45 (0.32 to 0.62), P < 0.001	Lenz et al., 2019 (19) (NanoString classifier)
CMS3 versus CMS1 PFS metastatic	0.89 (0.60 to 1.34), P = 0.59	0.75 (0.51 to 1.09), P = 0.14	Lenz et al., 2019 (19) (NanoString classifier)
CMS2 versus CMS1 OS local	0.92 (0.70 to 1.21), P = 0.54	0.89 (0.66 to 1.19), P = 0.43	Piskol et al., 2019 (9) (NanoString classifier)
CMS2 versus CMS1 OS metastatic	0.33 (0.23 to 0.48), P < 0.001	0.32 (0.22 to 0.48), P < 0.001	Lee et al., 2020 (33) (CMS elastic net classifier)
CMS2 versus CMS1 RFS local	0.97 (0.82 to 1.15), P = 0.74	0.98 (0.82 to 1.18), P = 0.85	Piskol et al., 2019 (9) (NanoString classifier)
CMS4 versus CMS2 OS local	2.60 (1.93 to 3.50), P < 0.001	2.17 (1.47 to 3.21), P < 0.001	Piskol et al., 2019 (9) (NanoString classifier)
CMS4 versus CMS2 RFS local	1.46 (1.29 to 1.64), P < 0.001	1.46 (1.29 to 1.67), P < 0.001	Piskol et al., 2019 (9) (NanoString classifier)
CMS4 versus CMS2 SAR local	1.97 (1.41 to 2.74), P < 0.001	1.95 (1.27 to 3.00), P = 0.002	Piskol et al., 2019 (9) (NanoString classifier)

Abbreviations: CMS, consensus molecular subtype; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SAR, survival after relapse

Supplementary Figure 1. Forest plots of pooled and single hazard ratios (HRs) for different survival outcomes per consensus molecular subtype (CMS) comparison in colorectal cancer. (A) CMS3 versus CMS1, (B) CMS3 versus CMS2 and (C) CMS4 versus CMS3. Number of cohorts (n) and total number of included patients (N) per meta-analysis indicated with n/N, with overall adjP for the random-effect model. As several studies described more cohorts, the number of cohorts n does not reflect the number of studies. Heterogeneity depicted as I^2 index and Cochran's Q-test P value.



Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; adjP, adjusted *P* value; NA, not applicable.

[a]Estimate

Supplementary Figure 2. Data and weight information for the meta-analyses on the prognostic value of the consensus molecular subtypes. As several studies described more cohorts, the number of cohorts k does not reflect the number of studies. Heterogeneity depicted as I^2 index and Cochran's Q-test.

CMS4 vs CMS1 Overall Survival Stage I-III

	HR	95%-CI	%W
Roepman et al., 2014	5.71	(1.82 to 17.90)	22.4
Piskol et al., 2019	3.85	(2.02 to 7.33)	28.7
Jary et al., 2020	1.18	(0.82 to 1.71)	31.5
Li et al., 2020	7.86	(1.63 to 37.90)	17.3

Number of cohorts combined: k = 4

	HR	95%-CI	z	P value
Random effects model	3.28	(1.27 to 8.47)	2.45	0.01

Quantifying heterogeneity:
I^2 = 83.0% (56.6% to 93.3%); H = 2.43 (1.52 to 3.88)

Test of heterogeneity:

Q	d.f.	P value
17.66	3	< 0.001

CMS4 vs CMS1 Overall Survival Stage IV

	HR	95%-CI	%W
Lenz et al., 2019	0.73	(0.54 to 0.99)	24.3
Mooi et al., 2018	0.59	(0.35 to 0.99)	17.6
Piskol et al., 2019 DARECK	0.33	(0.15 to 0.72)	11.2
Piskol et al., 2019 PROCURED	0.34	(0.14 to 0.82)	9.5
Okita et al., 2018 chemotherapy group	0.42	(0.23 to 0.77)	15.1
Okita et al., 2018 anti-EGFR	0.22	(0.09 to 0.56)	8.9
Del Rio et al., 2017 (biocolon, regp, cosival)	0.36	(0.18 to 0.71)	13.4

Number of cohorts combined: k = 7

	HR	95%-CI	z	P value
Random effects model	0.45	(0.32 to 0.62)	-4.77	< 0.001

Quantifying heterogeneity:
I^2 = 49.7% (0.0% to 78.7%); H = 1.41 (1.00 to 2.17)

Test of heterogeneity:

Q	d.f.	P value
11.92	6	0.06

CMS4 vs CMS1 Progression-Free Survival Stage IV

	HR	95%-CI	%W
Lenz et al., 2019	0.92	(0.68 to 1.24)	22.4
Mooi et al., 2018	0.53	(0.25 to 1.12)	11.9
Piskol et al., 2019 DARECK	0.33	(0.16 to 0.66)	12.8
Piskol et al., 2019 PROCURED	0.31	(0.13 to 0.74)	9.9
Okita et al., 2018 chemotherapy group	0.59	(0.35 to 1.00)	16.3
Okita et al., 2018 anti-EGFR	0.42	(0.21 to 0.84)	12.9
Del Rio et al., 2017 (biocolon, regp, cosival)	0.54	(0.28 to 1.03)	13.9

Number of cohorts combined: k = 7

	HR	95%-CI	z	P value
Random effects model	0.53	(0.38 to 0.75)	-3.62	< 0.001

Quantifying heterogeneity:
I^2 = 57.1% (0.5% to 81.5%); H = 1.53 (1.00 to 2.32)

Test of heterogeneity:

Q	d.f.	P value
13.98	6	0.03

CMS4 vs CMS1 Relapse-Free Survival Stage II-III

	HR	95%-CI	%W
Song et al., 2016 (Discovery cohort)	2.44	(1.58 to 3.76)	21.7
Song et al., 2016 (Validation cohort)	2.44	(1.62 to 3.66)	22.8
Dienstmann et al., 2019	1.38	(1.11 to 1.72)	31.6
Piskol et al., 2019 (AVANT cohort)	1.43	(0.80 to 2.56)	6.1
Li et al., 2020	2.05	(0.77 to 5.46)	7.9

Number of cohorts combined: k = 5

	HR	95%-CI	z	P value
Random effects model	1.84	(1.35 to 2.51)	3.88	< 0.001

Quantifying heterogeneity:
I^2 = 58.6% (0.0% to 84.6%); H = 1.55 (1.00 to 2.55)

Test of heterogeneity:

Q	d.f.	P value
9.65	4	0.047

CMS4 vs CMS2 Overall Survival Stage I-III

	HR	95%-CI	%W
Budinska et al., 2013 (subgroup)	2.16	(1.36 to 3.43)	41.3
Budinska et al., 2013 (subgroup)	2.20	(1.06 to 4.58)	16.5
Piskol et al., 2019 (AVANT)	3.33	(2.11 to 5.27)	42.2

Number of cohorts combined: k = 3

	HR	95%-CI	z	P value
Random effects model	2.60	(1.93 to 3.50)	6.30	< 0.001

Quantifying heterogeneity:
I^2 = 0.0% (0.0% to 89.2%); H = 1.00 (1.00 to 3.05)

Test of heterogeneity:

Q	d.f.	P value
1.93	2	0.38

CMS4 vs CMS2 Overall Survival Stage IV

	HR	95%-CI	%W
Schlicker et al., 2020	5.20	(1.65 to 16.35)	5.3
Piskol et al., 2019 (DARECK)	1.67	(0.83 to 3.35)	12.5
Piskol et al., 2019 (PROCURED)	1.43	(0.79 to 2.58)	16.0
Okita et al., 2018 (chemotherapy group)	1.32	(1.03 to 1.70)	39.2
Okita et al., 2018 (anti-EGFR group)	1.36	(0.66 to 2.78)	11.9
Del Rio et al., 2017 (biocolon, regp, cosival)	0.94	(0.51 to 1.73)	15.1

Number of cohorts combined: k = 6

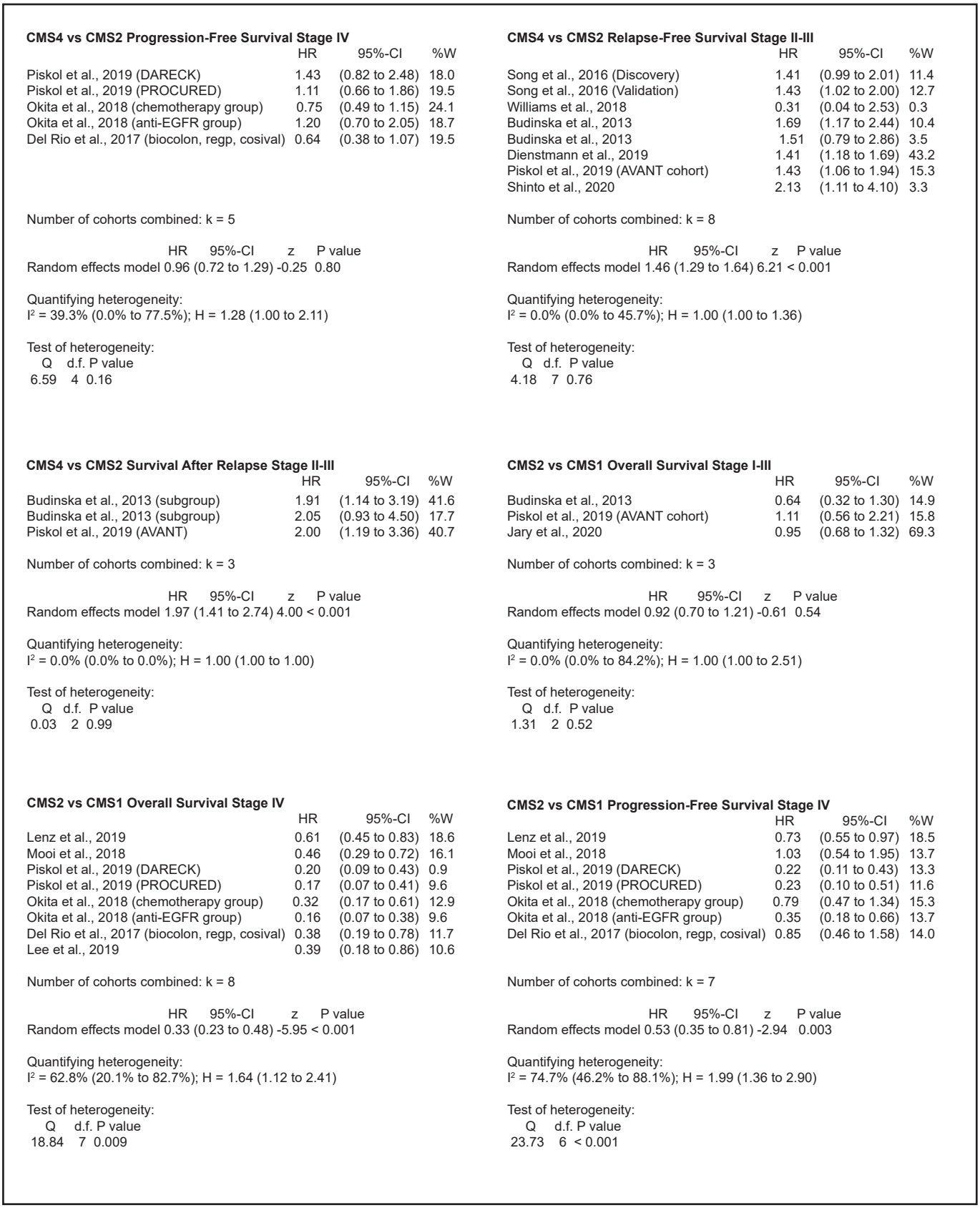
	HR	95%-CI	z	P value
Random effects model	1.41	(1.07 to 1.86)	2.44	0.01

Quantifying heterogeneity:
I^2 = 29.3% (0.0% to 71.1%); H = 1.19 (1.00 to 1.86)

Test of heterogeneity:

Q	d.f.	P value
7.08	5	0.22

Supplementary Figure 2 (continued)



Supplementary Figure 2 (continued)

CMS2 vs CMS1 Relapse-Free Survival Stage II-III

	HR	95%-CI	%W
Williams et al., 2018	0.31	(0.02 to 4.78)	0.4
Budinska et al., 2013	1.06	(0.58 to 1.94)	8.1
Dienstmann et al., 2019	0.98	(0.81 to 1.19)	76.5
Piskol et al., 2019 (AVANT cohort)	0.91	(0.58 to 1.42)	15.0

Number of cohorts combined: k = 4

	HR	95%-CI	z	P value
Random effects model	0.97	(0.82 to 1.15)	-0.34	0.74

Quantifying heterogeneity:
I^2 = 0.0% (0.0% to 45.4%); H = 1.00 (1.00 to 1.35)

Test of heterogeneity:

Q	d.f.	P value
0.84	3	0.84

CMS3 vs CMS1 Overall Survival Stage IV

	HR	95%-CI	%W
Lenz et al., 2019	1.19	(0.81 to 1.75)	24.3
Mooi et al., 2018	0.55	(0.31 to 0.97)	21.1
Okita et al., 2018 (chemotherapy group)	0.47	(0.26 to 0.84)	20.9
Okita et al., 2018 (anti-EGFR group)	0.37	(0.15 to 0.89)	15.9
Del Rio et al., 2017 (biocolon, regp, cosival)	0.33	(0.16 to 0.70)	17.8

Number of cohorts combined: k = 5

	HR	95%-CI	z	P value
Random effects model	0.55	(0.32 to 0.93)	-2.21	0.03

Quantifying heterogeneity:
I^2 = 74.1% (35.7% to 89.6%); H = 1.96 (1.25 to 3.10)

Test of heterogeneity:

Q	d.f.	P value
15.44	4	0.004

CMS3 vs CMS1 Progression-Free Survival Stage IV

	HR	95%-CI	%W
Lenz et al., 2019	1.33	(0.92 to 1.91)	28.9
Mooi et al., 2018	1.53	(0.61 to 3.85)	12.6
Okita et al., 2018 (chemotherapy group)	0.78	(0.46 to 1.31)	23.2
Okita et al., 2018 (anti-EGFR group)	0.50	(0.25 to 1.01)	17.6
Del Rio et al., 2017 (biocolon, regp, cosival)	0.68	(0.34 to 1.37)	17.7

Number of cohorts combined: k = 5

	HR	95%-CI	z	P value
Random effects model	0.89	(0.60 to 1.34)	-0.55	0.59

Quantifying heterogeneity:
I^2 = 55.2% (0.0% to 83.4%); H = 1.49 (1.00 to 2.46)

Test of heterogeneity:

Q	d.f.	P value
8.93	4	0.06

CMS3 vs CMS1 Relapse-Free Survival Stage II-III

	HR	95%-CI	%W
Williams et al., 2018	0.57	(0.04 to 8.58)	1.1
Dienstmann et al., 2019	0.93	(0.70 to 1.24)	98.9

Number of cohorts combined: k = 2

	HR	95%-CI	z	P value
Random effects model	0.93	(0.70 to 1.23)	-0.54	0.59

Quantifying heterogeneity:
I^2 = 0.0%; H = 1.00

Test of heterogeneity:

Q	d.f.	P value
0.12	1	0.72

CMS3 vs CMS2 Overall Survival Stage IV

	HR	95%-CI	%W
Okita et al., 2018 (chemotherapy group)	1.47	(0.88 to 2.47)	40.4
Okita et al., 2018 (anti-EGFR group)	2.27	(1.12 to 4.59)	29.1
Del Rio et al., 2017 (biocolon, regp, cosival)	0.88	(0.45 to 1.73)	30.5

Number of cohorts combined: k = 3

	HR	95%-CI	z	P value
Random effects model	1.43	(0.88 to 2.33)	1.43	0.15

Quantifying heterogeneity:
I^2 = 44.9% (0.0% to 83.6%); H = 1.35 (1.00 to 2.47)

Test of heterogeneity:

Q	d.f.	P value
3.63	2	0.16

CMS3 vs CMS2 Progression-Free Survival Stage IV

	HR	95%-CI	%W
Okita et al., 2018 (chemotherapy group)	0.99	(0.54 to 1.81)	29.9
Okita et al., 2018 (anti-EGFR group)	1.46	(0.86 to 2.47)	38.1
Del Rio et al., 2017 (biocolon, regp, cosival)	0.81	(0.45 to 1.45)	32.0

Number of cohorts combined: k = 3

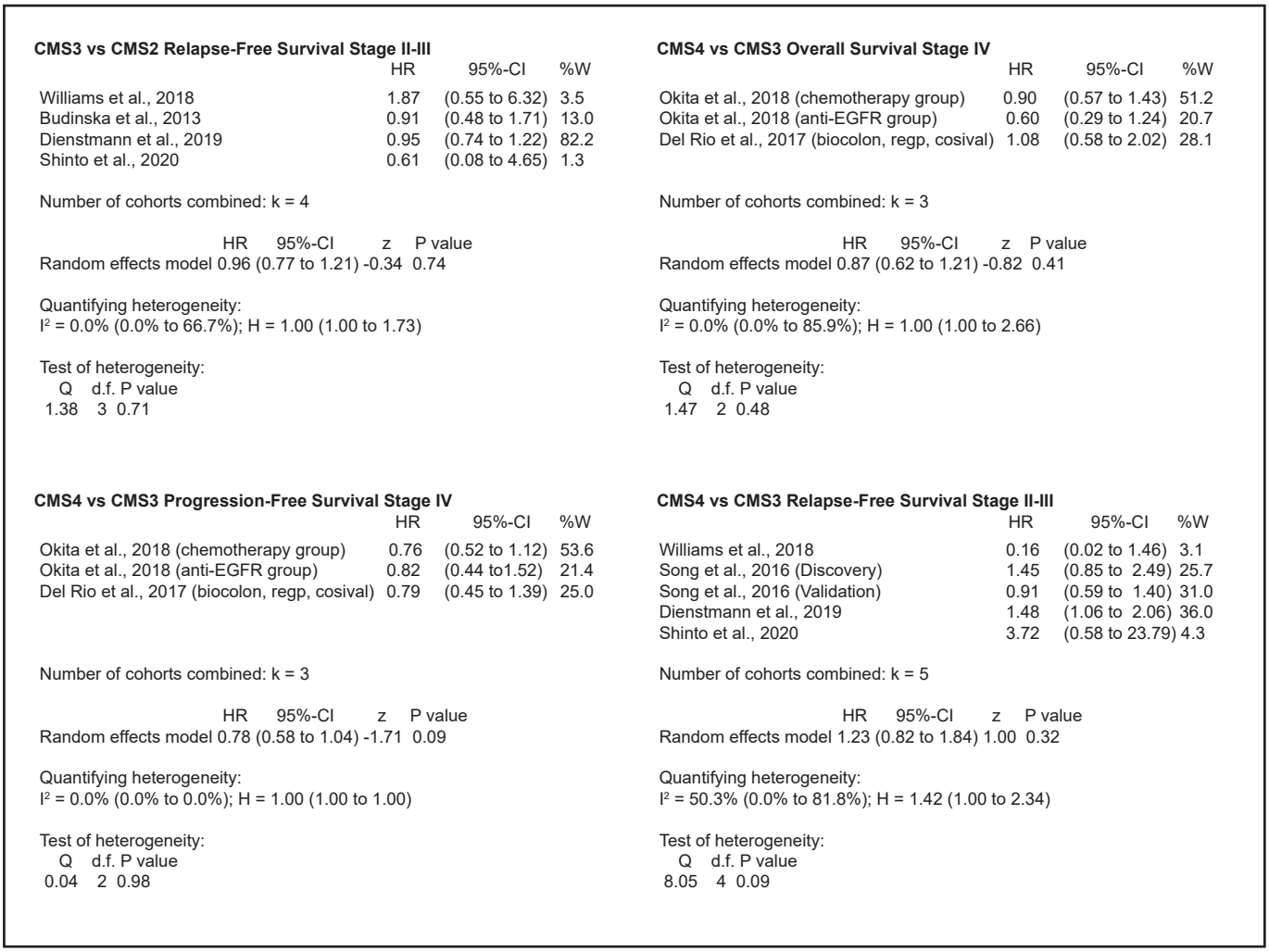
	HR	95%-CI	z	P value
Random effects model	1.08	(0.76 to 1.53)	0.41	0.68

Quantifying heterogeneity:
I^2 = 12.3% (0.0% to 90.9%); H = 1.07 (1.00 to 3.31)

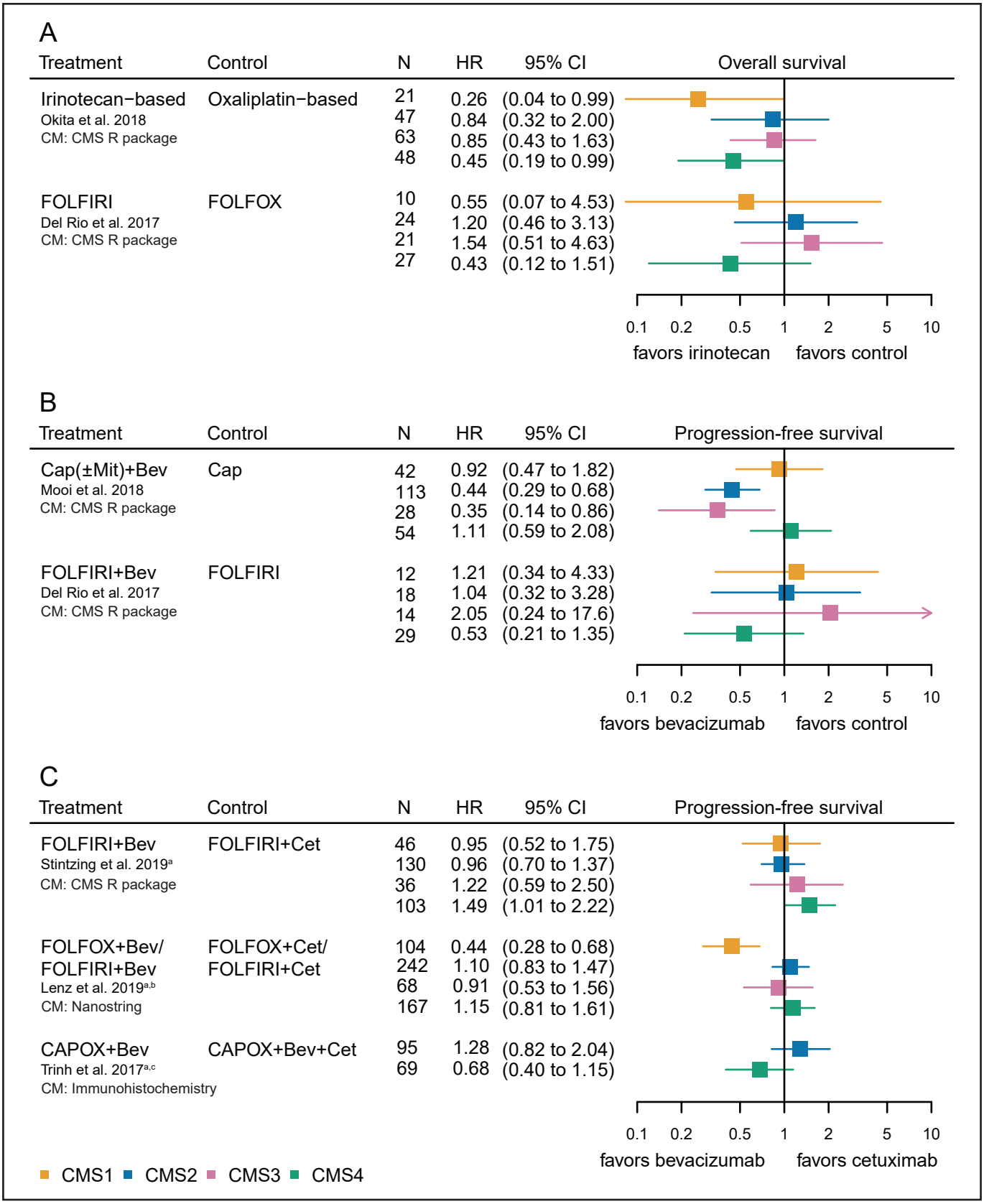
Test of heterogeneity:

Q	d.f.	P value
2.28	2	0.32

Supplementary Figure 2 (continued)



Supplementary Figure 3. Forest plots of hazard ratios (HRs) for the predictive value of the consensus molecular subtypes (CMSs) for first-line systemic therapy in metastatic colorectal cancer. (A) Overall survival for an irinotecan backbone versus control. (B) Progression-free survival for the addition of bevacizumab versus control. (C) Progression-free survival for the addition of bevacizumab versus cetuximab.



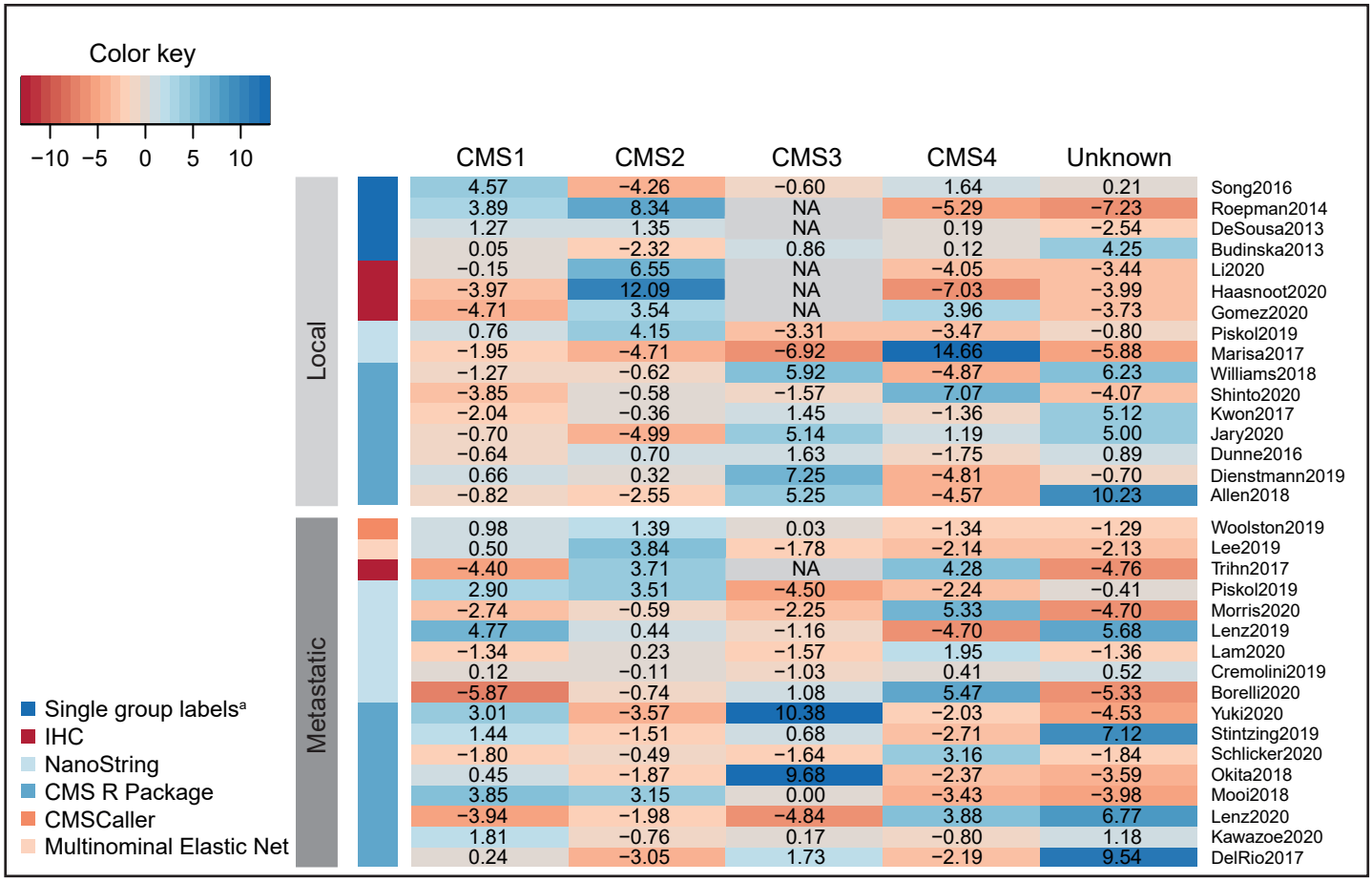
Abbreviations: Bev, bevacizumab; Cap, capecitabine; CAPOX, capecitabine and oxaliplatin; Cet, cetuximab; CM, classification method; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin and irinotecan; IRI, irinotecan; Mit, mitomycin; N, number of patients.

[a]KRAS wildtype population

[b]75.2% FOLFOX / 24.8% FOLFIRI

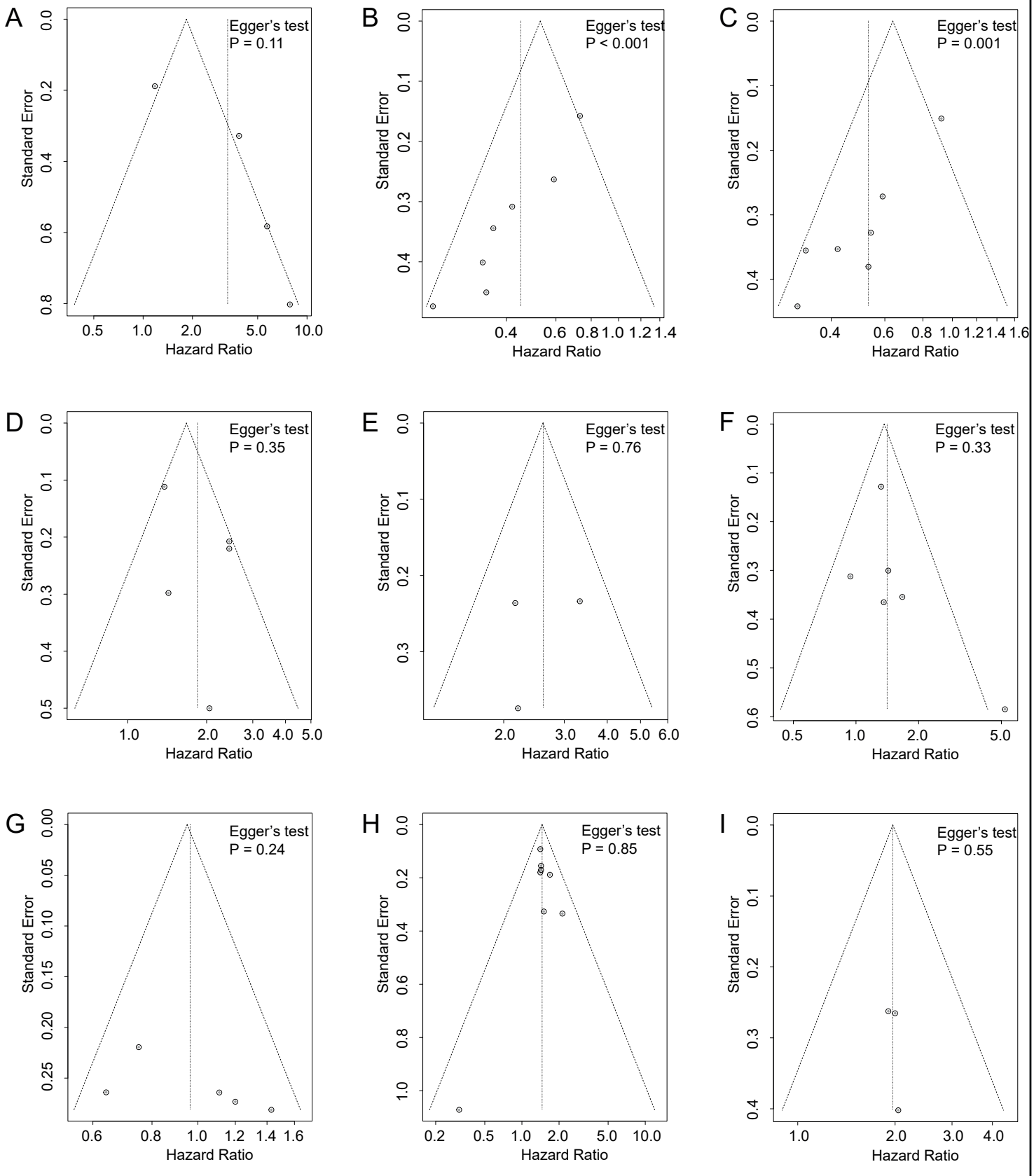
[c]Immunohistochemistry classification CMS2/3 depicted as CMS2

Supplementary Figure 4. Pearson residuals from the chi-square analysis into the distribution of the consensus molecular subtype (CMS) labels per individual study, stratified by stage.

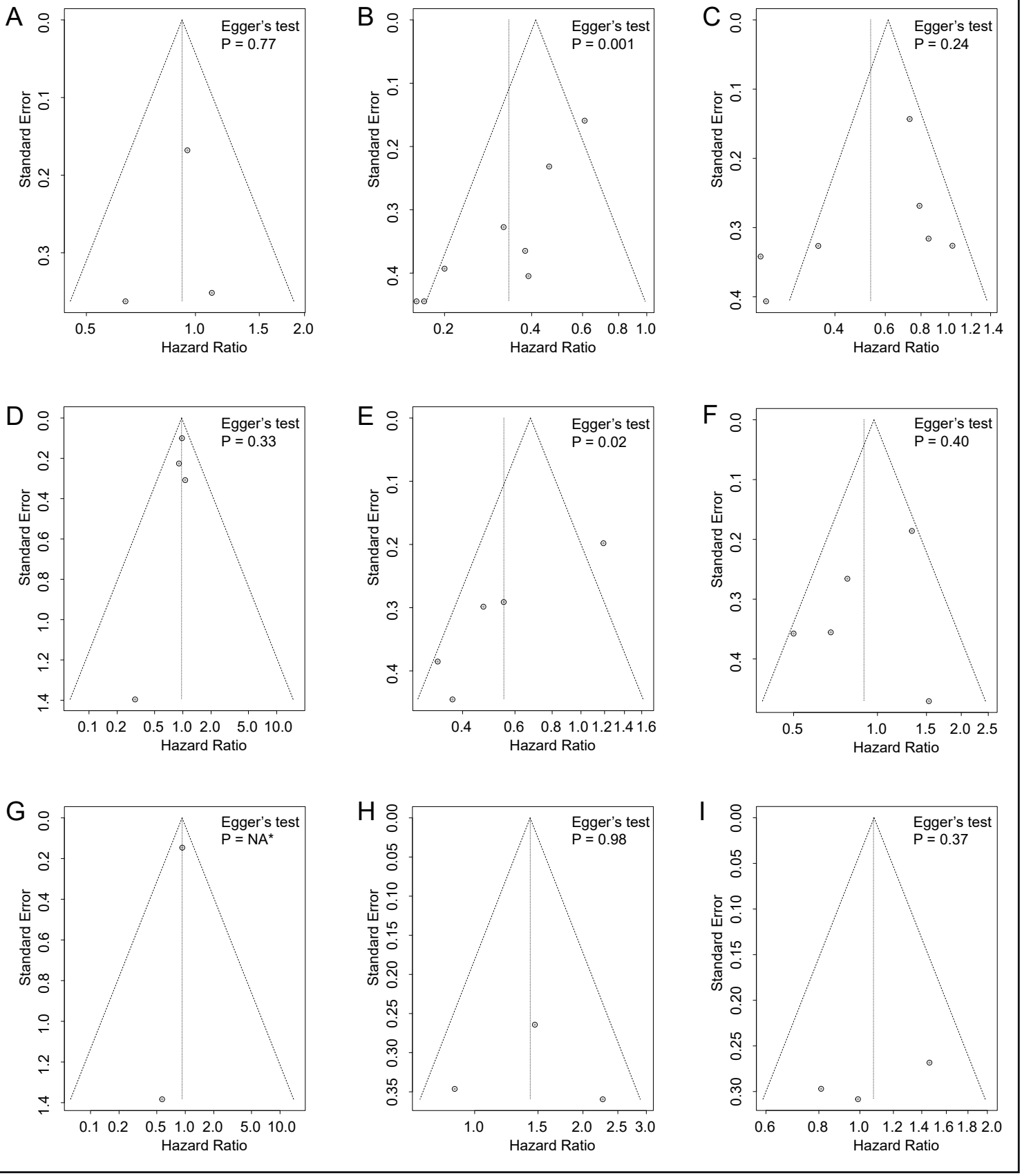


Abbreviations: IHC, immunohistochemistry; NA, no CMS3 labels available within the classification method used.
[a]Single group transcriptomic labels (Budinska, De Sousa, Roepman and Sadanandam).

Supplementary Figure 5. Funnel plots, including Egger's test p-values, for CMS4 versus CMS1 OS local (A), OS metastatic (B), PFS metastatic (C), RFS local (D); CMS4 versus CMS2 OS local (E), OS metastatic (F), PFS metastatic (G), RFS local (H), SAR local (I). Dashed vertical line indicates pooled effect size of each meta-analysis.

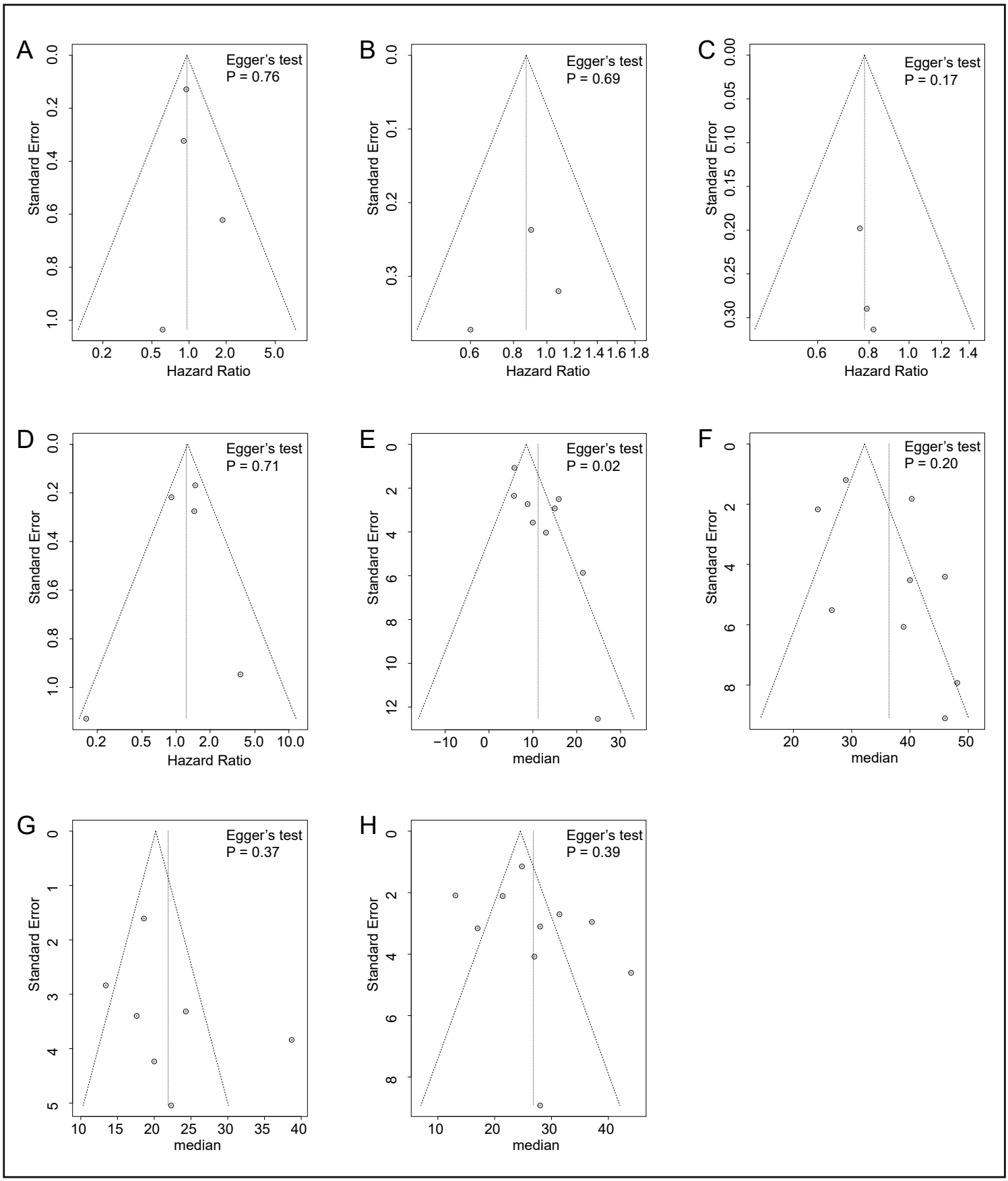


Supplementary Figure 6. Funnel plots, including Egger's test p-values, for CMS2 versus CMS1 OS local (A), OS metastatic (B), PFS metastatic (C), RFS local (D); CMS3 versus CMS1 OS metastatic (E), PFS metastatic (F), RFS local (G); CMS3 versus CMS2 OS metastatic (H), PFS metastatic (I). Dashed vertical line indicates pooled effect size of each meta-analysis.



Abbreviations: NA, not available.
*Egger's test P value not available since only two studies included.

Supplementary Figure 7. Funnel plots, including Egger's test p-values, for CMS3 versus CMS2 RFS local (A); CMS4 versus CMS3 OS metastatic (B), PFS metastatic (C), RFS local (D); CMS1 mOS metastatic (E), CMS2 mOS metastatic (F), CMS3 mOS metastatic (G), CMS4 mOS metastatic (H). Dashed vertical line indicates pooled effect size of each meta-analysis.



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