#### Supplementary Appendix

- We used the search terms to search the MEDLINE via PubMed (1 Jan 2010 to 30 June 2021) as follows:
- #1 "neoplasms"[MeSH Terms] OR "cancer\*"[Title/Abstract] OR "carcinoma\*"[Title/Abstract] OR "oncol\*"[Title/Abstract] OR "tumor\*"[Title/Abstract]
- OR "tumour\*"[Title/Abstract] OR "adenocarcinoma\*"[Title/Abstract] NOT Leukemia[MeSH Terms] NOT Lymphoma[MeSH Terms] NOT "Multiple

Myeloma" [MeSH Terms]

#2 "random\*"[Title/Abstract]

#3 "Antineoplastic Agents"[MeSH Terms] OR "immunotherapy"[All Fields] OR "Immune Checkpoint Inhibitors"[All Fields] OR "target therapy"[All Fields] OR "hormone"[All Fields] OR "chemotherapy"[All Fields]

#4 "humans"[MeSH Terms]

#5"english"[Language]

#6 randomizedcontrolledtrial[Filter]

#7 2010/01/01:2021/06/30[Date - Publication]

#8 adjuvant[Title] OR neoadjuvant[Title]

#9 "placebo"[Title] OR "blind"[Title]

#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7 NOT #8 NOT #9

#### Supplementary Figure 2. The trend in PFS adjudicators from 2010 to 2021



#### Supplementary Figure 3. The trend in ORR adjudicators from 2010 to 2021



### Supplementary Figure 4a. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.25$ ).

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight RHR, 95% CI
Author(s) and Year     Novelio, 2018     Reichardt, 2012     Tainer, 2017     Flaherty, 2012     Johann, 7020     Oza, 2015     Shaw, 2020     Tolaney, 2020     Penson, 2020     Shaw, 2020     Shaw, 2020     Shaw, 2020     Shaw, 2017     McDermott, 2018     Ribas, 2015     Moore, 2021     Wick, 2017     Mir, 2016     Sequist, 2013     Lynch, 2010     Rini, 2020     Bardia, 2021     West, 2019     Cortes, 2011     Camidge, 2020     Socianski, 2018     Yon, 2013     Jotte, 2020     Socianski, 2018     Yon, 2013     Jotte, 2021     Vermo: Carl 2014     Zhrong, 2015     Grown, 2013     Monk, 2010     Kim, 2013     Mourzer, 2017     Colombo, 2012     Peters, 2017     Colombo, 2012     Pignata, 2021	Ratio of hazard ratios (95% CI)	Weight   RHR, 95% Cl     0.17%   0.47 (0.22, 1.02)     0.65%   0.64 (0.43, 0.06)     0.49%   0.71 (0.39, 1.29)     0.37%   0.72 (0.42, 1.22)     0.98%   0.73 (0.53, 1.02)     0.25%   0.74 (0.38, 1.41)     0.45%   0.75 (0.46, 1.28)     1.25%   0.76 (0.45, 1.28)     1.25%   0.76 (0.45, 1.28)     0.53%   0.82 (0.61, 1.12)     0.53%   0.82 (0.61, 1.11)     1.15%   0.82 (0.61, 1.11)     1.15%   0.82 (0.61, 1.11)     1.15%   0.82 (0.61, 1.11)     1.42%   0.83 (0.63, 1.09)     0.37%   0.81 (0.44, 1.66)     0.70%   0.88 (0.64, 1.14)     0.44%   0.86 (0.64, 1.27)     2.11%   0.87 (0.71, 1.09)     0.44%   0.88 (0.64, 1.26)     0.48 (0.89, 1.27)   2.17%     2.11%   0.87 (0.71, 1.09)     0.44%   0.88 (0.81, 1.27)     2.11%   0.87 (0.71, 1.09)     0.41%   0.89 (0.71, 1.10)     2.44%   0.8
Test for overall effect: Z = -3.36 (P = 0.00)		and a second
	Local overestimate Central overe	estimate
	0.25 0.5 1 2	4

### Supplementary Figure 4b. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.50$ ).

Author(s) and Year	Ratio	o of hazard ratios (9	5% CI)	Weight	RHR, 95% CI
Author(s) and Year     Novello, 2018     Reichard, 2012     Tamura, 2017     Flaherty, 2012     Monk, 2020     Johann, 2020     Oza, 2015     Shaw, 2020     Tolaney, 2020     Penson, 2020     Shaw, 2017     McDermott, 2018     Ribas, 2015     More, 2021     Wick, 2017     Mir, 2016     Sequist, 2013     Lynch, 2010     Rini, 2020     Bardia, 2021     Hauschild, 2012     Robson, 2017     West, 2019     Cortes, 2011     Camidge, 2020     Sociania, 2017     Vermorken, 2014     Zhou, 2021     Motzer, 2013     Dummer, 2018     Kaufman, 2015     Crown, 2013     Monk, 2010     Kim, 2013     Dummer, 2018     Kaufma, 2015     Currylidae, 2021     Peters, 2017     Peters, 2017     Riscia, 2017     Ravaud, 2015<	Ratio   Image: Control of the second	o of hazard ratios (9 o of hazard ratios (9) a of ha	5% Cl)	Weight 0.19% 0.68% 0.68% 0.31% 0.40% 0.42% 0	RHR, 95% CI 0.47 (0.25, 0.88) 0.65 (0.45, 0.94) 0.65 (0.45, 0.94) 0.71 (0.43, 1.25) 0.73 (0.56, 0.96) 0.74 (0.43, 1.25) 0.75 (0.51, 1.11) 0.76 (0.60, 0.96) 0.79 (0.55, 1.13) 0.80 (0.67, 0.95) 0.81 (0.52, 1.25) 0.82 (0.63, 1.25) 0.82 (0.64, 1.05) 0.82 (0.63, 1.25) 0.82 (0.64, 1.05) 0.82 (0.64, 1.05) 0.84 (0.53, 1.35) 0.84 (0.63, 1.33) 0.85 (0.72, 1.00) 0.85 (0.66, 1.10) 0.85 (0.66, 1.10) 0.86 (0.63, 1.23) 0.86 (0.63, 1.23) 0.86 (0.63, 1.23) 0.86 (0.63, 1.23) 0.90 (0.58, 1.71) 0.88 (0.74, 1.05) 0.88 (0.74, 1.05) 0.88 (0.74, 1.05) 0.88 (0.74, 1.13) 0.90 (0.58, 1.39) 0.90 (0.68, 1.17) 0.90 (0.68, 1.17) 0.90 (0.68, 1.17) 0.90 (0.68, 1.17) 0.90 (0.61, 1.13) 0.91 (0.77, 1.13) 0.93 (0.67, 1.13) 0.94 (0.60, 1.11) 0.94 (0.60, 1.11) 0.94 (0.61, 1.23) 0.99 (0.74, 1.28) 0.99 (0.74, 1.28) 0.99 (0.74, 1.28) 0.99 (0.74, 1.28) 0.99 (0.74, 1.28) 0.99 (0.74, 1.23) 0.99 (0.74, 1.24) 0.99 (0.74, 1.24)
	1.4.7 A				
	0.25 0.5	1	2 4		

### Supplementary Figure 4c. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.75$ ).

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight	RHR, 95% CI
Novello, 2018 Reichardt 2012		0.37%	0.47 [0.30, 0.73]
Tamura, 2017 Elaberty, 2012	i i i	0.81%	0.65 0.50, 0.84
Monk, 2020		0.67%	0.72 0.53, 0.98
Oza, 2015		0.50%	0.74 [0.51, 1.07]
Shaw, 2020 Tolaney, 2020		0.76%	0.75 0.57, 0.99
Finn, 2020	<b>⊢</b> -∎1	1.30%	0.76 0.65, 0.90
Shitara, 2018		1.59%	0.80 [0.71, 0.90]
Wu, 2015 Naumann, 2013		0.66%	0.81 [0.60, 1.10]
Shaw, 2017 McDormott 2018	· • • • • •	1.01%	0.82 0.66, 1.02
Ribas, 2015		1.26%	0.82 0.69, 0.98
Moore, 2021 Wick, 2017		1.11%	0.82 0.68, 1.01
Mir, 2016 Sequist 2013		0.59%	0.84 0.60, 1.18
Lynch, 2010	. ⊢∎-4'	1.62%	0.85 0.75, 0.96
Bardia, 2021		1.30%	0.85 0.72, 1.01
Hauschild, 2012 Robson, 2017		0.48%	0.86 0.58, 1.26
West, 2019	· • • •	1.56%	0.87 0.76, 0.98
Camidge, 2020		0.92%	0.88 0.69, 1.11
Socinski, 2018 Von, 2013		1.57%	0.88 0.77, 1.00
Jotte, 2020 Soria, 2017		1.58%	0.89 0.78, 1.01
Vermorken, 2014		0.66%	0.90 0.66, 1.22
Motzer, 2013		1.16%	0.91 [0.78, 1.06]
Dummer, 2018 Kaufman, 2015		1.14%	0.91 [0.75, 1.10]
Crown, 2013 Monk, 2010		1.27%	0.91 0.77, 1.08
Kim, 2013	H	1.64%	0.91 0.81, 1.03
Wotzer, 2019 Wu, 2014		0.95%	0.93 [0.81, 1.07]
Bergh, 2012 Peters, 2017	<u>⊢-</u>	1.29%	0.93 0.79, 1.11
Colombo, 2012 Bisi 2010		1.64%	0.94 0.84, 1.06
Curigliano, 2013		1.06%	0.97 0.78, 1.19
Yao, 2017 Soria, 2015		1.32%	0.97 0.82, 1.14
de, 2021 Pignata, 2021		0.78%	0.98 0.75, 1.29
Machiels, 2015	<u>}_</u>	1.42%	0.99 0.85, 1.15
Ravaud, 2015		1.20%	0.99 0.82, 1.19
Rini, 2011 Baselga, 2017		1.48%	0.99 0.86, 1.14
Litton, 2018 Hida 2017	_ <b></b>	1.18%	1.00 0.83, 1.20
Ruzsa, 2014	i	0.67%	1.00 0.74, 1.36
Rini, 2014		1.43%	1.00 0.88, 1.13
Tap, 2016 Blav, 2014		0.57%	1.00 [0.71, 1.41]
Verma, 2012	_ <b>+</b> #++,	1.64%	1.02 0.90, 1.14
Zhou, 2014		0.94%	1.02 0.81, 1.29
Blackwell, 2010		1.45%	1.03 [0.89, 1.18]
Choueiri, 2016 Shi, 2021		1.45%	1.04 0.90, 1.20
Demetri, 2016	<u> </u>	1.01%	1.05 0.85, 1.31
Hersh, 2015		1.40%	1.07 0.92, 1.24
Odogwu, 2018		1.01%	1.07 [0.86, 1.33]
Flaherty, 2012 Xu. 2021		0.90%	1.07 [0.84, 1.36]
Gianni, 2013 Gogas, 2021		1.20%	1.14 0.95, 1.37
Motzer, 2014	· · · · · · · · · · · · · · · · · · ·	1.52%	1.16 1.02, 1.33
Oza, 2015		0.69%	1.20 [0.90, 1.59]
Kim, 2014 Motzer, 2021		0.47%	1.20 0.81, 1.77
Vansteenkiste, 2015 Blay, 2015	·	0.83%	1.27 0.98, 1.64
Ueno, 2016		0.75%	1.30 0.98, 1.73
Rugo, 2017		0.26%	1.34 1.04, 1.73
Zhang, 2017 Kawai, 2015		1.29% 0.26%	1.46 [1.23, 1.73]
Heterogeneity: $Tau^2 = 0.01$ ; $Chi^2 = 204.82$ , df = 9	1 (P = 0.00); I <sup>2</sup> = 56% ♦	100.00%	0.95 [0.92, 0.98]
Test for overall effect: $\angle = -3.51$ (P = 0.00)	Local overestimate Control overest	timate	
	1 1 1 1	1	
	0.25 0.5 1 2	4	

## Supplementary Figure 4d. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.95$ ).

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight	RHR, 95% CI
Novello, 2018	H	0.87%	0.47 [0.38, 0.57]
Tamura, 2017		1.07%	0.65 [0.58, 0.73]
Flaherty, 2012 Monk 2020		0.95%	0.71 [0.60, 0.84]
Johann, 2020	HEH.	1.13%	0.73 0.67, 0.80
Shaw, 2020		1.05%	0.75 [0.66, 0.85]
Tolaney, 2020 Finn 2020		1.02%	0.76 0.66, 0.88
Penson, 2020	H H	1.07%	0.79 0.70, 0.89
Shitara, 2018 Wu, 2015		1.18%	0.80 [0.76, 0.84]
Naumann, 2013	i i i i i i i i i i i i i i i i i i i	1.03%	0.82 0.71, 0.93
McDermott, 2018		1.07%	0.82 [0.73, 0.92]
Ribas, 2015 Moore 2021	HEH.	1.15%	0.82 0.76, 0.89
Wick, 2017	HEH	1.16%	0.83 0.77, 0.89
Mir, 2016 Seguist, 2013		1.00%	0.84 [0.73, 0.98]
Lynch, 2010 Rini, 2020		1.18%	0.85 0.81, 0.90
Bardia, 2021	(HER )	1.15%	0.85 0.79, 0.92
Robson, 2017		0.93%	0.86 [0.72, 1.02]
West, 2019	HEN	1.18%	0.87 0.82 0.92
Camidge, 2020	r≣t, F≣ti	1.09%	0.88 [0.79, 0.98]
Socinski, 2018 Von. 2013		1.18%	0.88 [0.83, 0.93]
Jotte, 2020		1.18%	0.89 0.84, 0.94
Vermorken, 2014		1.02%	0.90 [0.78, 1.03]
Zhou, 2021 Motzer, 2013		1.12%	0.90 0.82, 0.98
Dummer, 2018	H <b>a</b> t	1.13%	0.91 0.83, 0.99
Crown, 2013		1.19%	0.91 [0.86, 0.95]
Monk, 2010		1.17%	0.91 0.86, 0.97
Motzer, 2019	HE	1.17%	0.93 0.87, 0.99
Wu, 2014 Berah, 2012	1-8-4 1-8-1	1.10%	0.93 [0.84, 1.03] 0.93 [0.86, 1.01]
Peters, 2017 Colombo, 2012	i <u>i i i i i i i i i i i i i i i i i i </u>	1.10%	0.94 0.85, 1.04
Rini, 2019		1.18%	0.94 [0.89, 0.99]
Curigliano, 2013 Yao, 2017		1.12%	0.97 [0.88, 1.06] 0.97 [0.90, 1.04]
Soria, 2015		1.18%	0.98 0.93, 1.03
Pignata, 2021		1.15%	0.98 [0.91, 1.05]
Machiels, 2015 Urruticoechea, 2017		1.16%	0.99 0.92, 1.06
Ravaud, 2015	H H	1.13%	0.99 0.91, 1.08
Baselga, 2017		0.71%	0.99 [0.93, 1.05]
Litton, 2018 Hida 2017	H	1.13%	1.00 0.92, 1.09
Ruzsa, 2014		1.02%	1.00 0.87, 1.15
Hutson, 2014 Rini, 2014		1.16%	1.00 [0.94, 1.07] 1.00 [0.94, 1.06]
Tap, 2016	, <del></del>	0.93%	1.00 0.84, 1.20
Verma, 2012		1.18%	1.02 0.96, 1.07
Dummer, 2017 Zhou, 2014		1.13%	1.02 [0.93, 1.11] 1.02 [0.92, 1.13]
Yuan, 2019 Blackwoll, 2010	HEH.	1.17%	1.03 0.96, 1.09
Choueiri, 2016	HEH	1.16%	1.04 [0.97, 1.11]
Shi, 2021 Demetri, 2016	H에서 H에서	1.15%	1.05 [0.97, 1.13] 1.05 [0.96, 1.16]
Shi, 2017	HE-	1.08%	1.07 0.95, 1.19
Keunchil, 2016		1.15%	1.07 [0.99, 1.16]
Odogwu, 2018 Flaherty, 2012	<b>⊨</b> =-1	1.10%	1.07 [0.97, 1.19]
Xu, 2021	i <del>, a</del> i	1.08%	1.08 0.96, 1.21
Gogas, 2021		1.14%	1.15 1.06, 1.25
Motzer, 2014 Choueiri, 2018		1.17%	1.16 [1.09, 1.24]
Oza, 2015 Kim 2014	·	1.05%	1.20 1.05, 1.36
Motzer, 2021		1.16%	1.21 1.13, 1.29
Vansteenkiste, 2015 Blav. 2015		1.07%	1.27 1.12, 1.43
Ueno, 2016	i i 🖬 i	1.03%	1.30 1.14, 1.49
Rugo, 2017		1.06%	1.34 [1.19, 1.51]
Zhang, 2017 Kawai, 2015		1.15% 0.65%	1.46 [1.35, 1.57] 1.86 [1.38, 2.50]
Heterogeneity: $Tau^2 = 0.03$ ; $Chi^2 = 968.06$ , df = Test for overall effect: $7 = -3.10$ (P = 0.00)	91 (P = 0.00); I <sup>2</sup> = 94%	100.00%	0.95 [0.91, 0.98]
	Local overestimate Central overesti	mate	
		٦	
		(i).	
	0.25 0.5 1 2	4	

### Supplementary Figure 5a. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.25$ ).

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight	RHR, 95% CI
Novello, 2018 Reichardt, 2012		0.17% 0.65%	0.47 [0.22, 1.02] 0.64 [0.43, 0.96]
Tamura, 2017 Flaherty, 2012		0.49% 0.29%	0.65 0.41, 1.02 0.71 0.39, 1.29
Monk, 2020 Johann, 2020		0.37% 0.98%	0.72 [0.42, 1.22] 0.73 [0.53, 1.02]
Oza, 2015 Shaw, 2020		0.25% 0.45%	0.74 [0.38, 1.41] 0.75 [0.46, 1.21]
Tolaney, 2020 Finn, 2020		0.39% 1.25%	0.76 [0.45, 1.28] 0.76 [0.57, 1.02]
Penson, 2020 Shitara, 2018		0.53% 2.26%	0.79 [0.51, 1.23] 0.80 [0.64, 0.99]
Wu, 2015 Naumann, 2013		0.37% 0.37%	0.81 [0.48, 1.38] 0.82 [0.48, 1.38]
Shaw, 2017 McDermott, 2018		0.71% 0.55%	0.82 [0.56, 1.19] 0.82 [0.53, 1.26]
Ribas, 2015 Moore, 2021		1.15%	0.82 0.61, 1.11
Wick, 2017 Mir, 2016		1.42%	0.83 [0.63, 1.09]
Sequist, 2013 Lynch, 2010		2.45%	0.85 [0.69, 1.04]
Rini, 2020 Bardia, 2021		1.04%	0.85 0.62, 1.16
Robson, 2017		0.24%	0.86 0.59, 1.27
Cortes, 2011		2.04%	0.87 [0.70, 1.09]
Socinski, 2018		2.15%	0.88 [0.71, 1.10]
Jotte, 2020		2.54%	0.89 0.71, 1.10
Vermorken, 2014		0.36%	0.90 0.52, 1.53
Motzer, 2013		1.43%	0.91 0.69, 1.19
Kaufman, 2015		3.60%	0.91 0.77, 1.07
Monk, 2010 Kim 2013		2.04%	0.91 0.73, 1.14
Motzer, 2019		1.74%	0.93 0.73, 1.18
Bergh, 2012 Beters 2017	<u></u>	1.26%	0.93 0.70, 1.25
Colombo, 2012 Rini, 2019		2.57%	0.94 0.77, 1.15
Curigliano, 2013 Yao, 2017	·	0.79%	0.97 0.67, 1.39
Soria, 2015 de. 2021		2.83%	0.98 0.81, 1.18
Pignata, 2021 Machiels, 2015		1.32% 1.57%	0.98 0.74, 1.30 0.99 0.76, 1.28
Urruticoechea, 2017 Ravaud, 2015	i i i i i i i i i i i i i i i i i i i	1.47%	0.99 0.76, 1.29 0.99 0.72, 1.36
Rini, 2011 Baselga, 2017		1.78% 0.14%	0.99 0.78, 1.26 0.99 0.41, 2.37
Litton, 2018 Hida, 2017		1.00% 0.31%	1.00 0.73, 1.38
Ruzsa, 2014 Hutson, 2014		0.37% 1.58%	1.00 [0.59, 1.69] 1.00 [0.77, 1.29]
Rini, 2014 Tap, 2016		2.22% 0.31%	1.00 [0.81, 1.24] 1.00 [0.56, 1.79]
Blay, 2014 Verma, 2012		0.16% 2.57%	1.01 [0.45, 2.28] 1.02 [0.83, 1.24]
Dummer, 2017 Zhou, 2014		0.97%	1.02 [0.73, 1.41] 1.02 [0.68, 1.52]
Yuan, 2019 Blackwell, 2010		1.67% 0.85%	1.03 [0.80, 1.31] 1.03 [0.73, 1.46]
Choueiri, 2016 Shi, 2021		1.67%	1.04 [0.81, 1.33] 1.05 [0.78, 1.40]
Shi, 2017		0.64%	1.07 [0.71, 1.59]
Keunchil, 2016 Colorente 2018	, <b></b> ,	1.11%	1.07 (0.79, 1.45)
Flaherty, 2012		0.60%	1.07 [0.74, 1.50]
Gianni, 2013 Gogas, 2021		1.07%	1.14 0.83, 1.55
Motzer, 2014 Choueiri 2018		1.92%	1.16 0.92, 1.47
Oza, 2015 Kim 2014		0.43%	1.20 0.73, 1.95
Motzer, 2021 Vansteenkiste, 2015		1.53%	1.21 0.93, 1.56
Blay, 2015 Ueno, 2016		0.83%	1.30 0.91, 1.85
Wu, 2020 Rugo, 2017		0.11% 0.55%	1.31 0.50, 3.44
Zhăng, 2017 Kawai, 2015		1.21% 0.12%	1.46 [1.09, 1.95] 1.86 [0.74, 4.69]
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 69.16$ , df = 91 Test for overall effect: Z = -3.36 (P = 0.00)	(P = 0.96); I <sup>2</sup> = 0% ♦	100.00%	0.95 [0.92, 0.98]
	Local overestimate Central overestima	te	
	0.25 0.5 1 2 4		

### Supplementary Figure 5b. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.50$ ).

Author(s) and Year	Ratio of odds ratios (95% CI)	Weight	ROR, 95% CI
Chawla, 2015	▲	0.07%	0.22 [0.02, 2.60]
Hauschild, 2012	→	0.46%	0.33 [0.13, 0.83]
Krug, 2014	<b>∢</b> →→→→	0.18%	0.39 [0.09, 1.73]
Machiels, 2016	▲ · · · · · · · · · · · · · · · · · · ·	0.03%	0.49 [0.01, 19.93]
Ropetz, 2019		0.23%	0.49 [0.13, 1.83]
Tap 2016		0.36%	0.59 [0.21 1.69]
Seguist, 2013		1.08%	0.66 [0.36, 1.21]
Cortes, 2011		0.96%	0.67 [0.35, 1.27]
Zhang, 2017	► <b>−−−</b> +1	1.84%	0.68 [0.43, 1.08]
Bardia, 2021		1.00%	0.69 [0.37, 1.30]
Merie, 2019 Sebestian, 2010		0.09%	0.74 [0.09, 6.02]
Motzer 2013		2.76%	0.76 [0.52 1.11]
Lynch, 2010	· · · · · · · · · · · · · · · · · · ·	3.00%	0.78 [0.54, 1.12]
Zhou, 2014	<b>⊢−−−−</b>	0.47%	0.80 [0.32, 2.01]
Kaufman, 2015	·····	3.29%	0.81 [0.57, 1.14]
Soria, 2017		1.94%	0.82 [0.52, 1.28]
Ruzsa, 2014 Schwartzentruber, 2011		0.16%	0.82 [0.18, 3.62]
Rini, 2011		2.13%	0.83 [0.54, 1.28]
Arrieta, 2020	· · · · · · · · · · · · · · · · · · ·	0.38%	0.84 [0.31, 2.32]
Hida, 2017	► <b></b>	0.57%	0.86 [0.37, 1.97]
de, 2021	<►	0.10%	0.87 [0.12, 6.23]
Bergn, 2012 Shitara, 2018		3.72%	0.88 [0.64, 1.22]
Gogas 2021		2.28%	0.88 [0.54, 1.43]
Sahin, 2021		0.87%	0.89 [0.45, 1.74]
Motzer, 2018	<b>⊢</b>	4.74%	0.89 [0.67, 1.19]
Tolaney, 2020	· · · · · · · · · · · · · · · · · · ·	0.59%	0.89 [0.39, 2.03]
Hironaka, 2016 Rugo, 2017		0.58%	0.90 [0.40, 2.05]
Wu 2014		1 64%	0.93 [0.29, 2.97]
Motzer, 2019		5.03%	0.96 [0.72, 1.27]
Ueno, 2016	H	0.60%	0.96 [0.43, 2.16]
Shi, 2021		2.16%	0.97 [0.63, 1.48]
Motzer, 2021		3.99%	0.98 [0.72, 1.34]
Penson 2020		1 20%	0.98 [0.75, 1.27]
Moore, 2021	ii	1.09%	1.01 [0.55, 1.84]
Baselga, 2017	<>	0.04%	1.02 [0.05, 21.84]
Hamberg, 2011	► <del>\</del>	0.53%	1.03 [0.44, 2.43]
Vermorken, 2014		0.74%	1.05 [0.51, 2.18]
Rini, 2019		5.20%	1.06 [0.80, 1.39]
Zhou, 2021	H	2.47%	1.06 [0.71, 1.58]
Colombo, 2012	<b>⊢</b>	2.08%	1.06 [0.69, 1.65]
Modest, 2019	· · · · · · · · · · · · · · · · · · ·	0.34%	1.07 [0.36, 3.17]
Blay, 2015 Show 2020		4.06%	1.10[0.81, 1.51]
Monk, 2020		0.82%	1.11 [0.56, 2.22]
Tamura, 2017	·	1.24%	1.14 [0.65, 2.00]
Choueiri, 2016	H	0.99%	1.15 [0.61, 2.17]
O'Brien, 2011		0.35%	1.16 [0.40, 3.37]
Dummer 2018		1.70%	1.17 [0.73, 1.87]
Von. 2013		2.23%	1.29 [0.85, 1.97]
Shaw, 2017		0.57%	1.33 [0.58, 3.06]
Joensuu, 2010	H	1.11%	1.38 [0.76, 2.51]
Odogwu, 2018 Soria, 2015		2.06%	1.39 [0.90, 2.16]
Sona, 2015 Xu, 2021		1.58%	1.40 [0.71, 2.76]
Choueiri, 2018		0.49%	1.46 [0.59, 3.59]
Machiels, 2015	· · · · · · · · · · · · · · · · · · ·	0.62%	1.53 [0.69, 3.39]
Sun, 2015	÷	1.89%	1.54 [0.98, 2.43]
Thomas, 2017 Motroe, 2014		0.33%	1.59 [0.53, 4.76]
Wu 2020		0.33%	1.86 [0.62 5.57]
Curigliano, 2013		0.27%	1.97 [0.59, 6.61]
Boku, 2019	⊢ <b>►</b>	0.20%	2.03 [0.50, 8.23]
Finn, 2020	· · · · · · · · · · · · · · · · · · ·	0.95%	2.15 [1.13, 4.11]
Selwert, 2014 Bleiberg, 2012	·····	0.26%	3.41 [0.99, 11.66]
Oza, 2015		0.05%	8.64 [0.57, 130.22]
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 65.78$ , $df = 73$ Test for overall effect: $Z = -0.00$ ( $P = 1.00$ )	¢ (P = 0.71); l <sup>∠</sup> = 0% ◆	100.00%	1.00 [0.94, 1.06]
	1		
	Central overestimate Local overestima	te	
	0.25 0.5 1 0 1		
	0.25 0.5 1 2 4		

### Supplementary Figure 5c. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.75$ ).

Author(s) and Year	Ratio of odds ratios (95% CI)	Weight	ROR, 95% CI
Chawla, 2015	<b>▲</b>	0.10%	0.22 [0.03, 1.60]
Hauschild, 2012	→→→ :	0.67%	0.33 [0.16, 0.66]
Krug, 2014	<b>← → → → →</b>	0.32%	0.39 [0.13, 1.14]
Machiels, 2016 Kopetz, 2019		0.06%	0.49 [0.03, 6.91]
Ross. 2010		0.07%	0.49 [0.05, 4.76]
Tap, 2016		0.61%	0.59 [0.28, 1.25]
Sequist, 2013	·	1.43%	0.66 [0.43, 1.02]
Cortes, 2011	<b></b>	1.31%	0.67 [0.42, 1.06]
Zhang, 2017 Baselia, 2021		2.01%	0.68 [0.49, 0.94]
Merle, 2019		0.13%	0.74 [0.14, 3.98]
Sebastian, 2010	<>	0.09%	0.75 [0.09, 5.93]
Motzer, 2013	<b>⊢_∎</b> (	2.47%	0.76 [0.58, 0.99]
Lynch, 2010	· · · · · · · · · · · · · · · · · · ·	2.57%	0.78 [0.61, 1.01]
Kaufman 2015		2.63%	0.80 [0.42, 1.54]
Soria, 2017	<b>⊢</b>	2.08%	0.82 [0.59, 1.12]
Ruzsa, 2014	H	0.31%	0.82 [0.27, 2.43]
Schwartzentruber, 2011	• • • • • • • • • • • • • • • • • • •	0.72%	0.82 [0.42, 1.60]
Rini, 2011 Arrista, 2020		2.18%	0.83 [0.62, 1.13]
Hida, 2017		0.85%	0.86 [0.47, 1.58]
de, 2021	<	0.18%	0.87 [0.21, 3.72]
Bergh, 2012	► <b>₩</b>	2.80%	0.88 [0.70, 1.11]
Shitara, 2018		1.91%	0.88 [0.62, 1.24]
Sabin 2021		2.25%	0.88 [0.66, 1.18]
Motzer, 2018		3.05%	0.89 [0.73, 1.10]
Tolaney, 2020	► • • • • • • • • • • • • • • • • • • •	0.93%	0.89 [0.50, 1.60]
Hironaka, 2016	► <u></u>	0.92%	0.90 [0.50, 1.61]
Rugo, 2017		0.51%	0.93 [0.41, 2.12]
Motzer, 2019		3.11%	0.96 [0.79, 1.17]
Ueno, 2016		0.94%	0.96 [0.54, 1.71]
Shi, 2021	⊢ <b></b>	2.20%	0.97 [0.71, 1.31]
Motzer, 2021		2.88%	0.98 [0.78, 1.22]
Socinski, 2012 Penson 2020		3.22%	0.98 [0.81, 1.18]
Moore, 2021	i i i i i i i i i i i i i i i i i i i	1.45%	1.01 [0.66, 1.54]
Baselga, 2017	<→	0.07%	1.02 [0.11, 9.92]
Hamberg, 2011	·	0.86%	1.03 [0.56, 1.89]
Vermorken, 2014 Mook 2010		1.12%	1.05 [0.63, 1.76]
Rini 2019		2.00%	1.05 [0.82, 1.35]
Zhou, 2021		2.35%	1.06 [0.80, 1.41]
Colombo, 2012	<b>→</b>	2.16%	1.06 [0.78, 1.45]
Modest, 2019	<u>⊢−−−−</u> +	0.58%	1.07 [0.50, 2.32]
Blay, 2015 Show, 2020		2.89%	1.10 [0.89, 1.38]
Monk, 2020		1.20%	1.11 [0.68, 1.82]
Tamura, 2017	· · · · · · · · · · · · · · · · · · ·	1.59%	1.14 [0.76, 1.70]
Choueiri, 2016	► <u></u>	1.35%	1.15 [0.74, 1.81]
O'Brien, 2011		0.60%	1.16 [0.54, 2.46]
Dummer 2018		1.90%	1.17 [0.84, 1.64]
Von, 2013	H	2.23%	1.29 [0.96, 1.74]
Shaw, 2017	<b>⊢</b>	0.91%	1.33 [0.74, 2.40]
Joensuu, 2010	P. <del>↓ _ ■</del> 4	1.44%	1.38 [0.90, 2.13]
Odogwu, 2018 Soria, 2015		2.15%	1.39 [1.02, 1.90]
Xu. 2021		1.85%	1.41 [0.99, 2.01]
Choueiri, 2018		0.79%	1.46 [0.77, 2.77]
Machiels, 2015	► <u>·</u>	0.96%	1.53 [0.87, 2.69]
Sun, 2015		2.05%	1.54 [1.12, 2.13]
Motzer 2014		0.93%	1.59 [0.73, 3.45]
Wu, 2020	► ► ►	0.57%	1.86 [0.86, 4.04]
Curigliano, 2013	·	0.42%	1.97 [0.78, 4.97]
Boku, 2019	<u>⊢;</u> →	0.37%	2.03 [0.76, 5.46]
Finn, 2020 Solwort 2014		1.26%	2.15 [1.34, 3.46]
Bleiberg, 2012		0.39%	4.04 [1.54. 10.57]
Oza, 2015	<u>⊢</u> ►	0.08%	8.64 [1.00, 74.28]
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 126.20, df =	73 (P = 0.00); I <sup>2</sup> = 37%	100.00%	1.01 [0.95, 1.08]
Test for overall effect: Z = 0.41 (P = 0.68)			
	Central overestimate Local overestima	ite	
	0.25 0.5 1 2 4		

### Supplementary Figure 5d. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Sensitivity analysis ( $\rho = 0.95$ ).

Author(s) and Year	Ratio of odds ratios (95% CI)	Weight	ROR, 95% CI
Chawla, 2015	4	0.28%	0.22 [0.05, 0.98]
Hauschild, 2012	<b>←→</b>	1.15%	0.33 [0.21, 0.51]
Krug, 2014 Machiels, 2016		0.98%	0.39 [0.23, 0.68]
Kopetz 2019		0.99%	0.49 [0.28, 0.85]
Ross, 2010		0.41%	0.49 [0.15, 1.56]
Tap, 2016		1.31%	0.59 [0.42, 0.85]
Sequist, 2013		1.53%	0.66 [0.53, 0.81]
Cortes, 2011 Zhang, 2017		1.50%	0.67 [0.53, 0.84]
Bardia, 2021	Hand 1	1.53%	0.69 [0.56, 0.86]
Merle, 2019	→ + + + + + + + + + + + + + + + + + + +	0.36%	0.74 [0.21, 2.60]
Sebastian, 2010		0.40%	0.75 [0.23, 2.45]
Lynch, 2010		1.64%	0.78 [0.70, 0.88]
Zhou, 2014	<b>—</b>	1.41%	0.80 [0.60, 1.07]
Kaufman, 2015	HE-	1.63%	0.81 [0.71, 0.92]
Soria, 2017 Ruzsa, 2014		1.61%	0.82 [0.71, 0.94]
Schwartzentruber, 2011	· · · · · · · · · · · · · · · · · · ·	1.35%	0.82 [0.59, 1.13]
Rini, 2011	F-8-4	1.62%	0.83 [0.73, 0.96]
Arrieta, 2020		1.32%	0.84 [0.60, 1.19]
de 2021		0.65%	0.87 [0.88, 2.01]
Bergh, 2012	HEH!	1.65%	0.88 [0.79, 0.97]
Shitara, 2018	⊢∎-i	1.60%	0.88 [0.75, 1.03]
Gogas, 2021		1.62%	0.88 [0.77, 1.01]
Motzer 2018		1.53%	0.89 [0.72, 1.10]
Tolaney, 2020		1.45%	0.89 [0.69, 1.16]
Hironaka, 2016	· · · · · · · · · · · · · · · · · · ·	1.46%	0.90 [0.69, 1.17]
Rugo, 2017		1.27%	0.93 [0.64, 1.35]
Motzer, 2019	HEH	1.66%	0.96 [0.88, 1.05]
Ueno, 2016	<b>⊢</b>	1.46%	0.96 [0.74, 1.25]
Shi, 2021 Motzer, 2021		1.62%	0.97 [0.84, 1.10]
Socinski 2012		1.65%	0.98 [0.89, 1.08]
Penson, 2020	, international de la construcción de la construcc	1.57%	0.98 [0.82, 1.18]
Moore, 2021	. <b></b>	1.54%	1.01 [0.82, 1.23]
Hamberg 2011		1 44%	1.02 [0.27, 3.90]
Vermorken, 2014	·	1.50%	1.05 [0.84, 1.33]
Monk, 2010	H <b>H</b> ■H	1.64%	1.05 [0.94, 1.18]
Rini, 2019 Zhou: 2021		1.66%	1.06 [0.97, 1.15]
Colombo, 2012	⊢∎−1	1.62%	1.06 [0.93, 1.22]
Modest, 2019	⊢ <del>;∎</del>	1.30%	1.07 [0.75, 1.54]
Blay, 2015		1.65%	1.10 [1.00, 1.22]
Monk, 2020		1.52%	1.11 [0.90, 1.39]
Tamura, 2017	<b>⊢</b> ∎1	1.57%	1.14 [0.95, 1.36]
Choueiri, 2016		1.53%	1.15 [0.93, 1.43]
Crown, 2013		1.60%	1.17 [1.00, 1.37]
Dummer, 2018	1 H B H	1.62%	1.23 [1.07, 1.40]
Von, 2013	( <b>⊢≣</b> →	1.62%	1.29 [1.13, 1.48]
Joensuu, 2010		1.45%	1.38 [1.10, 1.74]
Odogwu, 2018	·	1.62%	1.39 [1.21, 1.60]
Soria, 2015	· · · · · ·	1.47%	1.40 [1.09, 1.81]
Xu, 2021 Choueiri, 2018	; <b></b> -	1.60%	1.41 [1.21, 1.66]
Machiels, 2015		1.46%	1.53 [1.18, 1.98]
Sun, 2015	; <b>+=</b> +	1.61%	1.54 [1.33, 1.78]
Thomas, 2017 Motzer, 2014		1.32%	1.59 [1.12, 2.25]
Wu, 2020		1.32%	1.86 [1.32, 2.64]
Curigliano, 2013	· · · · · · · · · · · · · · · · · · ·	0.91%	1.97 [1.07, 3.61]
Boku, 2019		1.16%	2.03 [1.30, 3.17]
Seiwert, 2014		1.45%	3.41 [2.31, 5.03]
Bleiberg, 2012	<b>→</b>	1.17%	4.04 [2.61, 6.24]
Oza, 2015	; 🛏 🏲	0.25%	8.64 [1.81, 41.26]
Heterogeneity: Tau <sup>2</sup> = 0.11; Chi <sup>2</sup> = 529.63, df = 7	/3 (P = 0.00); I <sup>2</sup> = 93%	100.00%	1.03 [0.95, 1.13]
Test for overall effect: Z = 0.79 (P = 0.43)			
	Central overestimate Local overestima	ite	
	0.25 0.5 1 2 1		
	0.25 0.5 1 2 4		

<u>.</u>	weight RHR, 95
	0.00% 0.70 0.50
	2.45% 0.85 (0.67 1
	0.86% 1.03 [0.07, 1
	2.04% 0.01 (0.70 1
	2.04% 0.91 [0.70, 1
	2.04% 0.87 [0.67, 1
	1.78% 0.99 [0.75, 1
	1.26% 0.93 [0.67, 1
	0.64% 0.64 [0.41, 1
	0.60% 1.07 (0.66, 1
<u> </u>	0.24% 0.86 (0.40.1
	2 57% 0 94 10 75 1
	2.67% 0.04[0.70,1
	2.30% 1.02[0.01, 1
	1.06% 1.14 [0.60, 1
	0.82% 0.84 [0.56, 1
<b>-</b> ,	1.18% 0.91 [0.65, 1
<del>- : - 1</del>	1.42% 0.91 [0.66, 1
■I	2.54% 0.88 [0.70, 1
	2.55% 0.91 [0.72, 1
	2.21% 1.00 [0.78, 1
i	1.58% 1.00 [0.74, 1
	0.64% 0.93 [0.58 1
	0.16% 1.01 [0.40.2
	0.10% 1.01 [0.40, 2
	1.92% 1.16 [0.89, 1
■;-!	3.61% 0.91 [0.75, 1
<b>→→</b> ■→	0.83% 1.30 [0.86, 1
	1.57% 0.99 [0.73, 1
<u> </u>	0.37% 0.81 [0.44, 1
	2.84% 0.98 [0.78, 1
	0.72% 1.05 [0.68, 1
	1.55% 1.07 (0.79, 1
_ <b></b>	1.67% 1.04 10 78 1
•	0.91% 0.89 (0.60 1
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2 T T	1.2170 1.40 [1.04, 2
	1.00% 0.0770 70
	1.29% 0.97 [0.70, 1
	1.46% 0.99 [0.73, 1
<b>→</b>	0.31% 1.00 [0.51, 1
<b></b>	0.70% 0.86 [0.55, 1
-•·1	0.64% 0.94 [0.59, 1
·	0.71% 0.82 [0.53, 1
	0.64% 1.07 0.67 1
	142% 0.83 (0.61.1
	0 74% 1 07 10 70 1
	0.74% 1.07[0.70, 1
	0.91% 0.91[0.62, 1
	0.17% 0.47 [0.19, 1
<b>■</b>	2.14% 0.88 [0.68, 1
-1	2.26% 0.80 [0.62, 1
- <b>+</b>	1.00% 1.00 [0.69, 1
	1.74% 0.93 [0.70, 1
	1.67% 1.03 [0 77 1
	2.48% 0.94 10 75 1
	2.11% 0.87 [0.67 1
	104% 0.85 0.50 4
	0.53% 0.70 (0.47 4
	0.53% 0.79[0.47, 1
	2.19% 0.89 [0.69, 1
	1.24% 0.76 [0.55, 1
	0.11% 1.31 [0.43, 3
•	0.61% 0.88 [0.55, 1
<u> </u>	0.37% 0.72 [0.39, 1
	1.22% 1.05 [0.75, 1
<b>→</b> →	0.45% 0.75 [0.43, 1
	1.00% 1.15 [0.79, 1
	0.98% 0.90 (0.62, 1
	1 32% 0 98 [0 71 1
	0.54% 1.09 [0.65.1
	1 52% 1 21 (0 90 1
	1.53% 1.21 [0.69, 1
	1.19% 0.82 [0.59, 1
<b>→</b> →	1.25% 0.85 [0.61, 1
•	0.94 [0.91, 0
· ·	
1	
	1.11% 1.07 (0.75.1
	0.29% 0.71 0.36 1
	0 79% 0 07 10 64 4
	0.37% 0.97 [0.04, 1
· · ·	0.37% 0.82 [0.44, 1
••••••	0.36% 0.90 [0.48, 1
	0.23% 1.20 [0.55, 2
	0.37% 1.00 [0.55, 1
	0.64% 1.02 [0.64, 1
֥1	0.43% 1.20 [0.68. 2
<b>&gt;</b>	0.12% 1.86 [0.64.5
	1.04% 0.99 0 69
	0.52% 1.27 10.76
1 1 1	0.249/ 0.74 10.25
	1.140 0.0010 55
	0.45% 4.00 (0.75
	0.45% 1.30 [0.75, 2
<del></del>	0.31% 0.84 [0.43, 1
	0.31% 1.00 [0.52, 1
	0.49% 0.65 [0.38, 1
	0.14% 0.99 [0.36. 2
	0.55% 1.34 [0.81.2
	0.39% 1.17 [0.64 2
	0.55% 0.82 10 50 1
	0.30% 0.72 [0.50, 1
	0.39% 0.76 [0.42, 1
	0.46% 0.98 [0.57, 1
	0.97 [0.87, 1
+ + + + + + + + + + + + + +	
↓ ↓ ↓ ↓	100.00% 0.95 [0.91, 0
Central overestimate	100.00% 0.95 [0.91, 0
Central overestimate	100.00% 0.95 [0.91, (
Central overestimate	100.00% 0.95 [0.91, (
•	

#### Supplementary Figure 6a. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Subgroup analysis: trial phase.

#### Supplementary Figure 6b. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Subgroup analysis: trial phase.

suloi(s) una real	Natio of odda fatioa (55% of)		
nase 3			
ensuu, 2010		1.13% 1	.38 [0.60. 3
roch 2010		3.00% 0	78 10 47 1
101, 2010		3.00% 0.	05 10 05 4
5nk, 2010	,	3.28% 1.	.05 [0.65, 1
ortes, 2011		0.97% 0.	.67 [0.27, 1
chwartzentruber, 2011	<b>←</b>	0.44% 0	.82 [0.22, 3
ni 2011		2 13% 0	83 10 45 1
		2.740/ 0	00 [0.40, 1
irgn, 2012		3.71% 0.	.88 [0.56, 1
cinski, 2012	<b>⊢_</b> =	5.68% 0.	.98 [0.68, 1
auschild, 2012	<b>∢</b> →→→→	0.49% 0	.33 [0.09, 1
olombo, 2012		2.07% 1	.06 [0.58. 1
aquiet 2013		1.00% 0	66 10 28 1
Julia, 2015		1.00% 0.	00 [0.20, 1
own, 2013		1.77% 1.	.17 [0.60, 2
otzer, 2013		2.75% 0	.76 [0.45, 1
on, 2013	<u>⊢-!</u>	2.22% 1	.29 [0.71, 2
0 2014		1.63% 0	94 10 47 1
0, 2014		1.03% 0.	.54 [0.47, 1
otzer, 2014	► • • • • •	0.60% 1.	.68 [0.53, 5
aufman, 2015		3.33% 0	.81 [0.50, 1
av. 2015		4.05% 1	.10 [0.71. 1
achiels 2015		0.62% 1	53 10 49 4
0015		0.0270 1.	10 10 55 0
una, 2015		0.88% 1.	.40 [0.55, 3
noueiri, 2016	⊢;•I	0.99% 1	.15 [0.47, 2
oria, 2017		1.93% 0	.82 10.43. 1
ang. 2017		1.83% 0	68 10 35 1
40.0017		0.0070 0.	0010 07 1
ua, 2017		0.59% 0.	.00 [0.27, 2
naw, 2017	·→	0.57% 1.	.33 [0.41, 4
dogwu, 2018	<b>⊢</b> ••••••••••••••••••••••••••••••••••••	2.05% 1	.39 [0.75, 2
otzer, 2018		4.72% 0	.89 [0.59. 1
ummer 2018		2 204/ 4	23 10 69 1
Alimiter, 2010		2.2070 1.	a. 10.00, 2
ntara, 2018		1.66% 0.	.88 [0.44, 1
otzer, 2019		5.01% 0	.96 [0.65, 1
erle, 2019	<hr/>	0.10% 0.1	74 [0.05. 11
ni 2019		E 100/ 4	06 10 72 4
		3.13% 1.	10 10 00
spetz, 2019	• • • •	0.24% 0.	.49 [0.08, 3
anson, 2020	<b>→</b>	1.19% 0	.98 [0.44, 2
nn. 2020		0.98% 2	15 10.88. 5
0. 2020		0.229/ 4	96 10 40 9
u, 2020		0.33% 1.	.00 [0.40, 0
ank, 2020		0.82% 1.	.11 [0.42, 2
ni, 2021	<b>⊢</b>	2.15% 0.	.97 [0.53, 1
naw, 2020	······	1.50% 1	.11 [0.54, 2
0035 2021		2 27% 0	88 10 49 1
0004		D.400/ 4	00 10.40, 1
100, 2021		2.46% 1.	.06 [0.60, 1
J, 2021	<b>⊢_;_</b>	1.57% 1.	.41 [0.70, 2
otzer, 2021	<b>⊢</b>	3.97% 0	.98 [0.63, 1
oore. 2021		1.09% 1	01 10.43. 2
ardia 2021		1.00% 0	60 10 20 1
ubtotal (Q = 21.92, df = 44, p = 1.00; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ )	•	0	.98 [0.89, 1
nase 2			
055. 2010	4 · · · · · · · · · · · · · · · · · · ·	0.04% 0	49 [0.01 40
abastian 2010		0.05% 0.	75 10 02 24
Joastian, 2010		0.05% 0.	15 [0.02, 30
amberg, 2011	· · · · · · · · · · · · · · · · · · ·	0.53% 1.	.03 [0.31, 3
Brien, 2011	<u>⊢</u>	0.34% 1	.16 [0.26, 5
eiberg, 2012		0.21% 4.0	04 10.59 27
urieliene 2012		0.00% 1	07 10 29 10
Jingilano, 2013		0.29% 1.3	97 [0.36, 10
ermorken, 2014	, <b></b>	0.74% 1.	.05 [0.38, 2
uzsa, 2014	<→	0.18% 0.	.82 [0.10, 6
siwert, 2014	· · · · · · · · · · · · · · · · · · ·	0.26% 3.4	41 [0.60, 19
2014		0 18% 0	39 10 05 3
2014		0.1070 0.	00 10 00, 0
100, 2014		0.46% 0.	.ou [0.22, 2
za, 2015	<→	0.06% 8.6	4 [0.24, 310
un, 2015	H	1.88% 1	.54 [0.81, 2
nawla, 2015	• • • • • • • • • • • • • • • • • • •	0.08% 0	22 10.01 5
ronaka 2016		0.60% 0	90 10 28 1
1010KG, 2010	· · · · · · · · · · · · · · · · · · ·	0.56% 0.	00 [0.20, 2
ano, 2016		0.59% 0.	.96 [0.30, 3
ip, 2016	← → → → → → → → → → → → → → → → → → → →	0.36% 0	.59 [0.14, 2
achiels, 2016	<>	0.03% 0.6	49 [0.00, 90
amura, 2017		1 23% 1	14 10.51 3
2017		0.000 1	50 10 24 7
ionias, 2017		0.33% 1.	.59 [0.34, 7
iselga, 2017	<→	0.04% 1.0	JZ [0.02, 69
ugo, 2017	<→	0.29% 0	.93 [0.18, 4
houeiri, 2018		0.49% 1	46 [0.41. 5
2019		0.20% 0.	03 10 29 44
MU, 2013		0.20% 2.0	35 [0.28, 14
odest, 2019	<→	0.34% 1.	.07 [0.23, 4
rieta, 2020	← · · · · · · · · · · · · · · · · · · ·	0.38% 0	.84 [0.20, 3
planey, 2020		0.59% 0	89 10.28 2
2021		0.440/ 0.	97 10 00 10
. 2021	•	0.11% 0.	ar [0.06, 13
ihin, 2021		0.87% 0.	.89 [0.34, 2
ubtotal (Q = 10.76, df = 28, p = 1.00; $I^2 = 0.0\%$ , $\tau^2 = 0.00$ )	-	1.	.14 [0.88, 1
verall (Q = 33.74, df = 73, p = 1.00; $I^2$ = 0.0%, $\tau^2$ = 0.00) ast for Subgroup Differences: Q <sub>M</sub> = 1.06, df = 1, p = 0.30	•	100.00% 1.	.00 [0.91, 1
,	Central overestimate Local overestimate		
in the congresp content task, $a_{M} = r(a_{1}, a_{2} = r_{1})$	Central overestimate Local overestimate		

# Supplementary Figure 7a. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Subgroup analysis: cancer type.

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight RHR, 95% CI
Squamous cell carcinoma of the lung Soria, 2015	⊢ <b>∔</b> ⊣	2.84% 0.98 [0.78, 1.22]
Sarcoma Blay, 2014 Kawai, 2015 Tap, 2016		0.16% 1.01 [0.40, 2.57] 0.12% 1.86 [0.64, 5.38] 0.31% 1.00 [0.52, 1.95]
		$\begin{array}{c} 1.4 \left[0.70, 1.85\right]\\ 1.76\% & 0.99 \left(0.75, 1.31\right]\\ 1.94\% & 0.99 \left(0.76, 1.31\right)\\ 1.94\% & 0.91 \left(0.566, 1.339\right)\\ 1.55\% & 1.00 \left(0.74, 1.341\right)\\ 1.95\% & 0.96 \left(0.568, 1.428\right)\\ 1.95\% & 0.96 \left(0.568, 1.428\right)\\ 1.95\% & 0.96 \left(0.568, 1.428\right)\\ 1.95\% & 0.96 \left(0.569, 1.428\right)\\ 1.95\% & 0.96 \left(0.569, 1.428\right)\\ 1.95\% & 0.96 \left(0.569, 1.35\right)\\ 1.24\% & 0.94 \left(0.758, 1.99\right)\\ 1.24\left(0.389, 1.633\right)\\ 1.20 \left(0.99, 1.09\right)\\ \end{array}$
Prostate cancer Johann, 2020	<b>⊢_</b> ∎i	0.98% 0.73 [0.50, 1.07]
Pancretic cancer Von, 2013 Ueno, 2016 Subtotal (Q = 1.60, df = 1, p = 0.21; $I^2$ = 37.7%, $\tau^2$ = 0.03)		2.54% 0.88 [0.70, 1.12] 0.45% 1.30 [0.75, 2.27] 0.99 [0.70, 1.39]
$ \begin{array}{l} \textbf{Ovarian cancer} \\ \textbf{Monk, 2010} \\ \textbf{Colombo, 2012} \\ \textbf{Naumann, 2013} \\ \textbf{Oza, 2015} \\ \textbf{Penson, 200} \\ \textbf{Penson, 200} \\ \textbf{Portata, 2021} \\ \textbf{Moore, 2021} \\ \textbf{Subtotal (Q = 2.50, df = 7, p = 0.93; l^2 = 0.0\%, \tau^2 = 0.00) \\ \end{array} } $		$\begin{array}{c} 2.04\% \\ 0.91 \\ 0.70 \\ 0.47 \\ 0.42 \\ 0.41 \\ 0.43\% \\ 1.20 \\ 0.43\% \\ 0.72 \\ 0.42 \\ 0.43\% \\ 0.72 \\ 0.43\% \\ 0.72 \\ 0.43\% \\ 0.72 \\ 0.43\% \\ 0.71 \\ 0.43\% \\ 0.71 \\ 0.43\% \\ 0.71 \\ 0.43\% \\ 0.71 \\ 0.91 \\$
Non-small cell lung cancer Keurchil, 2013 Sequelt, 2013 Viti, 2014 Viti, 2017 Viti, 2017		$\begin{array}{c} 1.11\% \\ 2.45\% \\ 0.66\% \\ 0.66\% \\ 1.11\% \\ 0.66\% \\ 1.11\% \\ 0.66\% \\ 1.11\% \\ 0.66\% \\ 1.11\% \\ 0.11\% \\$
Neuroendocrine tumors Yao, 2017		1.29% 0.97 [0.70, 1.34]
Melanoma Falandi, 2012 Hauschld, 2012 Falandy, 2012 Falandy, 2012 Horsh, ac 2017 Durimer, 2018 Gogas, 2021		$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Subtotal (Q = 3.31, df = 7, p = 0.86; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ )	<b>•</b>	0.98 [0.85, 1.13]
de, 2021	H	0.46% 0.98 [0.57, 1.69]
Demetri, 2016	<b>⊢</b> •−−1	0.72% 1.05 [0.68, 1.63]
Finn, 2020	⊢	1.24% 0.76 [0.55, 1.06]
Head and Neck Cancer Vermorken, 2014 Ruzsa, 2014 Machiels, 2015 Subtotal ( $Q = 0.09$ , df = 2, $p = 0.96$ ; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ )		0.36% 0.90 [0.48, 1.66] 0.37% 1.00 [0.55, 1.83] 1.57% 0.99 [0.73, 1.33] 0.97 [0.76, 1.24]
Glioblastoma Wick 2017		1 42% 0 83 [0 61 1 13]
Gastrointestinal stromal tumours Reichardt, 2012 Blay, 2015 Mir, 2016		0.64% 0.64 [0.41, 1.02] 0.83% 1.30 [0.86, 1.95] 0.31% 0.84 [0.43, 1.64]
Subtotal (Q = 5.05, df = 2, p = 0.08; $i^2$ = 58.8%, $\tau^2$ = 0.09)		0.91 [0.58, 1.42]
Shitara, 2018	<b>⊢</b> •-••	2.26% 0.80 [0.62, 1.02]
Oza, 2015	·	0.24% 0.74 [0.35, 1.56]
Breakt Cancer Bergant Cancer Cortes, 2017 Bergh, 2012 Grown, 2013 Grown, 2013 Grown, 2014 Grown, 2014 Grown, 2014 Chang, 2017 Jaweiga, 2017 Jaweiga, 2017 Baseiga, 2017 Robson, 2017 Huton, 2018 Jaweiga, 2017 Huton, 2018 Jaweiga, 2017 Huton, 2018 Jaweiga, 2017 Huton, 2018 Jaweiga, 2017 Baseiga, 2017 Huton, 2018 Jaweiga, 2017 Baseiga, 2017 Jaweiga, 2017 J		$\begin{array}{c} 0.66\% \\ 0.076 \\$
Cycail (Q = 51.96, dt = 91, p = 1.00; l* = 0.0%, r* = 0.00) Test for Subgroup Differences: $Q_M = 10.85$ , dt = 17, p = 0.86	5	100.00% 0.95 [0.91, 0.98]
	Local overestimate Central overestimate	
	200723-C 20007 5c 2004 2017	
	0.25 0.5 1 2 4	

## Supplementary Figure 7b. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Subgroup analysis: cancer type.

Author(s) and Year	Ratio of odds ratios (95% CI)	Weight	ROR, 95% CI
Squamous cell carcinoma of the lung Soria, 2015		0.88%	1.40 [0.55, 3.62]
Small-cell lung cancer O'Brien, 2011	<b>&gt;</b>	0.34%	1.16 [0.26, 5.24]
Sarcoma		0.08%	0.22 (0.01 6.64)
Tap, 2016		0.36%	0.59 [0.14, 2.58]
Subtotal (Q = 0.30, df = 1, p = 0.59; I <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00)			0.50 [0.13, 1.91]
Renal cell cancer Rini, 2011 Motzer, 2013 Motzer, 2014 Chouser, 2016 Motzer, 2018		2.13% 2.75% 0.60% 0.99% 0.49% 4.72%	0.83 [0.45, 1.53] 0.76 [0.45, 1.30] 1.68 [0.53, 5.29] 1.15 [0.47, 2.81] 1.46 [0.41, 5.19] 0.89 [0.59, 1.34]
Motzer, 2019 Rini, 2019 Motzer, 2021		5.01% 5.19% 3.97%	0.96 0.65, 1.42 1.06 0.72, 1.56 0.98 0.63, 1.53
Subtotal (Q = 2.80, df = 8, p = 0.95; $I^2 = 0.0\%$ , $\tau^2 = 0.00$ )	+		0.96 [0.81, 1.14]
Pleural mesohelioma Krug, 2014	<b>∢</b> →→→	0.18%	0.39 [0.05, 3.11]
Pancretic cancer Von, 2013 Ueno, 2016		2.22% 0.59%	1.29 [0.71, 2.35] 0.96 [0.30, 3.02]
Subtotal (Q = 0.21, df = 1, p = 0.65; l <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00)			1.22 [0.72, 2.06]
Ovana cancer Monk, 2010 11 Celombo, 2010 Monk, 2020 Moore, 2021		3.28% 2.07% 1.19% 0.82% 1.09%	1.05 [0.65, 1.72] 1.06 [0.58, 1.97] 0.98 [0.44, 2.22] 1.11 [0.42, 2.96] 1.01 [0.43, 2.35]
Subtotal (Q = 0.05, df = 4, p = 1.00; $l^{c} = 0.0\%$ , $\tau^{c} = 0.00$ )	-		1.05 [0.77, 1.42]
Lynch, 2010 Sebastian, 2010 Sebastian, 2010 Sebastian, 2010 Sequist, 2013 Wu, 2014 Soria, 2017 Hida, 2017 Hida, 2017 Hida, 2017 Odogwu, 2018 Arrela, 2020 Shaw, 2020 Shaw, 2020 Shaw, 2020		$\begin{array}{c} 3.00\%\\ 0.04\%\\ 0.05\%\\ 1.09\%\\ 1.63\%\\ 0.46\%\\ 0.33\%\\ 0.33\%\\ 0.57\%\\ 2.05\%\\ 0.38\%\\ 0.33\%\\ 2.15\%\\ 1.50\%\\ 1.45\%\\ 2.46\%\end{array}$	$\begin{array}{c} 0.78 & [0.47, \ 1.30) \\ 0.49 & [0.01, \ 40.50) \\ 0.75 & [0.02, \ 36.36] \\ 0.88 & [0.68, \ 1.42] \\ 0.88 & [0.62, \ 1.54] \\ 0.80 & [0.22, \ 2.95] \\ 1.54 & [0.81, \ 2.94] \\ 0.80 & [0.22, \ 2.95] \\ 1.54 & [0.81, \ 2.94] \\ 0.80 & [0.22, \ 2.95] \\ 1.54 & [0.34, \ 7.49] \\ 0.86 & [0.27, \ 2.72] \\ 1.33 & [0.41, \ 4.31] \\ 1.59 & [0.54, \ 7.49] \\ 0.54 & [0.54, \ 2.72] \\ 1.30 & [0.54, \ 2.51] \\ 1.86 & [0.40, \ 8.77] \\ 1.86 & [0.40, \ 1.87] \\ 1.97 & [0.54, \ 1.87] \\ 1.97 & [0.54, \ 1.87] \\ 1.86 & [0.40, \ 1.87] \\ 1.86 & [0.50, \ 1.87] \\ \end{array}$
Subtotal (Q = 6.77, df = 17, p = 0.99; $l^2$ = 0.0%, $\tau^2$ = 0.00)	•		1.01 [0.85, 1.20]
Melanoma Schwartzentruber, 2011 Hauschild, 2012 Dummer, 2018 Gogas, 2021		0.44% 0.49% 2.20% 2.27%	0.82 [0.22, 3.08] 0.33 [0.09, 1.15] 1.23 [0.68, 2.23] 0.88 [0.49, 1.58]
Subtotal (Q = 0.53, df = 1, p = 0.47; l <sup>2</sup> = 0.0%, $\tau^2$ = 0.00)			0.91 [0.62, 1.34]
de, 2021	<→	0.11%	0.87 [0.06, 13.20]
Hepatocellular cancer Merie, 2019 Finn, 2020	← ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	0.10% 0.98%	0.74 [0.05, 11.48] 2.15 [0.88, 5.27]
Subtotal (Q = 1.73, df = 4, p = 0.79; $I^2 = 0.0\%$ , $\tau^2 = 0.00$ )			1.94 [0.83, 4.55]
Head and Neck Cancer Vermorken, 2014 Ruzsa, 2014 Machiels, 2015 Machiels, 2016		0.74% 0.18% 0.26% 0.62% 0.03%	1.05 [0.38, 2.95] 0.82 [0.10, 6.47] 3.41 [0.60, 19.41] 1.53 [0.49, 4.71] 0.49 [0.00, 90.11]
Subtotal (Q = 1.73, df = 4, p = 0.79; $I^2$ = 0.0%, $\tau^2$ = 0.00)			1.36 [0.71, 2.61]
Gastrointestinal stromal tumours Blay, 2015	F	4.05%	1.10 [0.71, 1.71]
Gastric and gastroesophageal junction cancer Hironaka, 2016 Boku, 2019 Boku, 2019 Sahim, 2021		0.58% 1.66% 0.20% 0.87%	0.90 [0.28, 2.89] 0.88 [0.44, 1.75] 2.03 [0.28, 14.69] 0.89 [0.34, 2.30]
Subtotal (Q = 0.64, df = 3, p = 0.89; $I^2 = 0.0\%$ , $\tau^2 = 0.00$ )			0.93 [0.57, 1.52]
Endometrial carcinoma Oza, 2015	← →	0.06%	8.64 [0.24, 310.13]
Golorectal cancer Bleiberg, 2012 Kopetz, 2019 Modest, 2019		0.21% 0.24% 0.34%	4.04 [0.59, 27.56] 0.49 [0.08, 3.03] 1.07 [0.23, 4.94]
Subtotal (Q = 2.48, df = 2, p = 0.29; l <sup>2</sup> = 9.9%, $\tau^2$ = 0.09)			1.22 [0.42, 3.50]
Breast cancer Joensuu, 2010 Cortes, 2011 Hamberg, 2011 Bergh, 2012		1.13% 0.97% 0.53% 3.71%	1.38 [0.60, 3.17] 0.67 [0.27, 1.64] 1.03 [0.31, 3.47] 0.88 [0.56, 1.39]
Curigliano, 2013 Kaufman, 2015 Zhaen, 2017		0.29%	1.97 [0.38, 10.15] 0.81 [0.50, 1.31] 0.68 [0.35, 1.20]
Tamura, 2017 Baselga, 2017		1.83% 1.23% 0.04%	1.14 0.51, 2.53 1.02 0.02, 69.43
Rugo, 2017 Tolaney, 2020		0.29% 0.59%	0.93 0.18, 4.80 0.89 0.28, 2.84
Bardia, 2021		1.00%	0.69 [0.29, 1.68]
Subtotal (Q = 5.97, df = 13, p = 0.95; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Overall (Q = 33.74, df = 73, p = 1.00; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ )	<b>•</b>	100.000	0.94 [0.76, 1.15]
Test for Subgroup Differences: $Q_M = 8.75$ , df = 16, p = 0.92	<b>T</b>	100.00%	1.00 [0.91, 1.09]
	Central overestimate Local overestimate		
	0.25 0.5 1 2 4		

## Supplementary Figure 8a. Comparison of treatment effect estimates (Hazard Ratio) between central reviewers and local investigators. Subgroup analysis: drug classification.

Author(s) and Year	Ratio of hazard ratios (95% CI)	Weight RHR, 95%
Target therapy	1945 • 20	
Keunchil, 2016		1.11% 1.07 [0.75, 1.5
Lynch 2010		2 45% 0.85 [0.67 1.0
Blackwell, 2010		0.86% 1.03 [0.69, 1.5
Rini, 2011	· — • — • ·	1.78% 0.99 [0.75, 1.3
Bergh, 2012	<b>⊢</b> =¦(	1.26% 0.93 [0.67, 1.3
Reichardt, 2012		0.64% 0.64 [0.41, 1.0
Flaherty, 2012	· · · · · · · · · · · · · · · · · · ·	0.60% 1.07 [0.66, 1.7
Hauschild, 2012 Elaberty, 2012		0.24% 0.86 [0.40, 1.8
Verma 2012		2 56% 1 02 10 81 1 1
Gianni, 2013		1.08% 1.14 [0.80, 1.6
Sequist, 2013		0.82% 0.84 [0.56, 1.3
Crown, 2013	· · · · · · · · · · · · · · · · · · ·	1.18% 0.91 [0.65, 1.3
Curigliano, 2013	<b>⊢</b>	0.79% 0.97 [0.64, 1.
Motzer, 2013		1.42% 0.91 [0.66, 1.
Rim, 2013 Pipi 2014		2.55% 0.91[0.72, 1.
Hutson 2014		158% 1.00 [0.76, 1.
Wu. 2014		0.64% 0.93 [0.58, 1.
Motzer, 2014		1.92% 1.16 0.89, 1.
Kim, 2014	<u>⊢−−−</u>	0.23% 1.20 [0.55, 2.
Ruzsa, 2014		0.37% 1.00 [0.55, 1.
Oza, 2015		0.43% 1.20 [0.68, 2.
Ravaud, 2015 Play, 2015		1.04% 0.99[0.69, 1.
Machiels 2015		1 57% 0 99 [0.36, 1.
Vansteenkiste 2015		0.52% 1.27 [0.76.2
Oza, 2015		0.24% 0.74 [0.35, 1.
Wu, 2015		0.37% 0.81 [0.44, 1.
Soria, 2015	<b>⊢</b>	2.84% 0.98 [0.78, 1.
Mir, 2016		0.31% 0.84 [0.43, 1.
Chouein, 2016	, <del>  • • •</del> ·	1.67% 1.04 [0.78, 1.
Tap, 2016 Soria, 2017		0.31% 1.00[0.52, 1.
Dummer 2017		0.97% 1.02 [0.70, 1
Baselga, 2017		0.14% 0.99 [0.36, 2.
Yao, 2017	H	1.29% 0.97 [0.70, 1.
Urruticoechea, 2017	▶ + + - 1	1.46% 0.99 [0.73, 1.
Hida, 2017		0.31% 1.00 [0.51, 1.
Robson, 2017		0.70% 0.86 [0.55, 1.
Shaw 2017		0.04% 0.94 [0.59, 1.
Rugo, 2017		0.55% 1.34 [0.81, 2.
Shi. 2017		0.64% 1.07 [0.67, 1,
Wick, 2017	i i i i i i i i i i i i i i i i i i i	1.42% 0.83 [0.61, 1.
Odogwu, 2018	<b>⊢</b>	0.74% 1.07 [0.70, 1.
Choueiri, 2018		0.39% 1.17 [0.64, 2.
Dummer, 2018		0.91% 0.91 [0.62, 1.
Novello, 2018		1.00% 1.00 [0.69.1
Rini 2020		1.04% 0.85 [0.59, 1
Penson, 2020		0.53% 0.79 [0.47, 1.
Tolaney, 2020		0.39% 0.76 [0.42, 1.
Wu, 2020		0.11% 1.31 [0.43, 3.
Camidge, 2020		0.61% 0.88 [0.55, 1.
Monk, 2020	<u>⊢</u>	0.37% 0.72 [0.39, 1.
Shaw, 2020 Biggata, 2021		0.45% 0.75[0.43, 1.
Fighala, 2021 Xii 2021		0.54% 1.08 [0.65.1
Moore, 2021		1.19% 0.82 [0.59, 1.
Bardia, 2021	ii	1.25% 0.85 [0.61, 1.
Subtotal (Q = 28.91, df = 61, p = 1.00; $\Gamma = 0.0\%$ , $\tau^{-} = 0.00$ )		0.95 [0.91, 1.
Immune checknoint inhibitor		
Ribas 2015		1 14% 0 82 10 58 1
Socioski 2018		2 14% 0 88 [0 68 1
McDermott 2018		0.55% 0.82 [0.50, 1
Shitara, 2018	·	2.26% 0.80 [0.62, 1,
Motzer, 2019	·	1.74% 0.93 [0.70, 1.
Rini, 2019	·	2.48% 0.94 [0.75, 1.
West, 2019	<u>}∎</u> ]	2.11% 0.87 [0.67, 1.
Jotte, 2020	· · · · · · · · · · · · · · · · · · ·	2.19% 0.89 [0.69, 1.
Finn, 2020		1.24% 0.76 [0.55, 1.
30gas, 2021 Zhou 2021		1.00% 1.15[0.79, 1.
Motzer, 2021		1.53% 1.21 [0.89 1
Subtotal (Q = 7.86, df = 11, p = 0.73; $I^2 = 0.0\%$ , $\tau^2 = 0.00$ )	◆:	0.90 [0.83, 0.
Chamatharany		
Linemotherapy		2.049/ 0.04 10 70 1
Cortes 2011		2.04% 0.91 [0.70, 1.
Colombo 2012		2.04% 0.87 [0.67, 1.
Naumann, 2013		0.37% 0.82 [0.44 1
/on, 2013		2.54% 0.88 [0.70, 1.
Blay, 2014	<b>⊢</b>	0.16% 1.01 [0.40, 2.
Vermorken, 2014		0.36% 0.90 [0.48, 1.
2hou, 2014	H	0.64% 1.02 [0.64, 1.
Kawai 2015		0.12% 4.96 0.64 5
Demetri 2016		0.12% 1.00 [0.64, 5.
Hersh, 2015		1.55% 1.07 [0.79 1
Jeno, 2016	h	0.45% 1.30 [0.75. 2.
Zhang, 2017	· · · · · · · · · · · · · · · · · · ·	1.21% 1.46 [1.04, 2.
Tamura, 2017		0.49% 0.65 [0.38, 1.
Yuan, 2019	, <b></b> ,	1.67% 1.03 [0.77, 1.
Shi, 2021		1.22% 1.05 [0.75, 1.
		0.40% 0.98[0.57, 1.
Subtotal (Q = 13.60, df = 17, p = 0.70; l <sup>2</sup> = 0.0%, $\tau^{2}$ = 0.00)	•	0.97 [0.89, 1.
Test for Subgroup Differences: $Q_M = 1.00$ ; $r = 0.0\%$ , $\tau = 0.00$ )	•	100.00% 0.95 [0.91, 0.
	Local overestimate Central overestimate	
	0.25 0.5 1 2 4	

-		
Target therapy		
Lunch 2010		2 0.0% 0 79 10 47 1 201
Lynch, 2010		3.00% 0.78 [0.47, 1.30]
Ross, 2010	<→	0.04% 0.49 [0.01, 40.50]
Sebastian, 2010	<→	0.05% 0.75 [0.02, 36.36]
Hamberg 2011		0 53% 1 03 [0 31 3 47]
Di-1 2014		0.0010 1.00 [0.01, 0.01]
Rini, 2011		2.13% 0.83 [0.45, 1.53]
Bergh 2012		3 71% 0 88 [0 56 1 39]
Heurschild 2012		0.40% 0.22 [0.00, 4.45]
Hauschild, 2012	<b>∢</b> →→→→	0.49% 0.33 [0.09, 1.15]
Seguist, 2013		1.09% 0.66 [0.28, 1.54]
0		4 778 4 47 10 00 0 001
Grown, 2013		1.77% 1.17 [0.60, 2.28]
Curigliano, 2013	<b>⊢</b>	0.29% 1.97 [0.38, 10.15]
Matras 2012		2 7E% 0 7E IO 4E 1 201
W01261, 2013		2.75% 0.70[0.45, 1.50]
Wu, 2014	<b>→</b>	1.63% 0.94 [0.47, 1.89]
Motzer 2014		0.60% 1.68 (0.53 5.29)
molzer, zora		0.00% 1.00[0.00, 0.20]
Ruzsa, 2014	$\leftarrow$	0.18% 0.82 [0.10, 6.47]
Seiwert 2014		0.26% 3.41 (0.60 19.41)
Di 0015		0.2010 0.41 [0.00, 10.41]
Blay, 2015		4.05% 1.10 [0.71, 1.71]
Machiels, 2015		0.62% 1.53 [0.49, 4.71]
0 0045		0.00% 0.04 (0.04.040.40)
Uza, 2015	• • • •	0.06% 8.64 [0.24, 310.13]
Soria, 2015		0.88% 1.40 [0.55, 3.62]
Chausid 2016		0.00% 1.15 (0.47 0.91)
Chouein, 2016		0.99% 1.15[0.47, 2.81]
Tap. 2016		0.36% 0.59 [0.14, 2.58]
Machiele 2016		0.03% 0.40 0.00 00.111
macineis, 2010	• • • • •	0.03% 0.49 [0.00, 90.11]
Soria, 2017		1.93% 0.82 [0.43, 1.54]
Bacolan 2017		0.04% 1.02 [0.02 60 43]
baseiya, 2017	• • • •	0.04% 1.02 [0.02, 69.43]
Hida, 2017	• • • • • • • • • • • • • • • • • • •	0.59% 0.86 [0.27, 2.72]
Show 2017		0 57% 1 22 [0 41 4 24]
Gliaw, 2017	· · · · · · · · · · · · · · · · · · ·	0.57% 1.33 [0.41, 4.31]
Rugo, 2017	<>	0.29% 0.93 [0.18, 4.80]
Odomini 2018		2 05% 1 20 10 75 2 501
Ou0ywu, 2010		2.00% 1.39[0.75, 2.59]
Choueiri, 2018	<b>→</b>	0.49% 1.46 [0.41, 5.19]
Dummer 2018		2 20% 1 23 10 68 2 231
Durinition, 2010		2.20% 1.23 [0.00, 2.23]
Kopetz, 2019		0.24% 0.49 [0.08, 3.03]
Modest 2019	A	0 34% 1 07 10 23 4 941
D		4.400 0.00 0.44
Penson, 2020		1.19% 0.98 [0.44, 2.22]
Tolaney 2020		0.59% 0.89 (0.28 2.84)
Tolandy, 2020		0.0010 0.00 [0.20, 2.04]
Wu, 2020		0.33% 1.86 [0.40, 8.77]
Monk 2020		0.82% 1.11[0.42 2.96]
Show 2020	· · · · · ·	1 50% 1 11 10 54 2 201
Snaw, 2020		1.50% 1.11[0.54, 2.29]
Xu, 2021		1.57% 1.41 [0.70, 2.87]
Sabia 2021		0.97% 0.90 (0.24 0.20)
Janin, 2021	· · · · · · · · · · · · · · · · · · ·	0.0176 0.03 [0.04, 2.00]
Moore, 2021	<b></b>	1.09% 1.01 [0.43, 2.35]
Bardia, 2021		1.00% 0.69 [0.29, 1.68]
Subtotal (0 = 10.12 df = 40 p = 1.00; $l^2 = 0.0\%$ $z^2 = 0.00$ )		1 00 10 97 1 141
Subtotal (Q = 19.13, d1 = 40, p = 1.00, 1 = 0.0%, t = 0.00)	-	1.00 [0.87, 1.14]
Immunotherapy		
Schwartzentruber, 2011	<b>4</b>	0.44% 0.82 [0.22, 3.08]
Keye 0044		0 40% 0 20 10 05 0 441
Riug, 2014		0.18% 0.39[0.03, 3.11]
Thomas, 2017	⊢; <b>→</b>	0.33% 1.59 [0.34, 7.49]
Subtotal (Q = 1.15, df = 2, p = 0.56; $I^2$ = 0.0%, $\tau^2$ = 0.00)		0.89 [0.36, 2.21]
Subtotal (Q = 1.15, df = 2, p = 0.56; l <sup>2</sup> = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor		0.89 [0.36, 2.21]
Subtotal (Q = 1.15, df = 2, p = 0.56; $t^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Matzer 2018		0.89 [0.36, 2.21]
Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Motzer, 2018		0.89 [0.36, 2.21]
Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Molzer, 2018 Shitara, 2018		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75]
Subtolal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2019 Ecku: 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69]
Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Motzer, 2018 Solitara, 2019 Boku, 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42]
Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2$ = 0.0%, $\tau^2$ = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Motzer, 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56]
Subtotal (Q = 1.15, df = 2, p = 0.56; l <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Rini, 2019 Anime, 2020		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.30% 0.44 [0.20 C_51]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Rini, 2019 Arrieta, 2020		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51]
Subtotal (Q = 1.15, df = 2, p = 0.56; i <sup>2</sup> = 0.0%, r <sup>2</sup> = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27]
Subtotal (Q = 1.15, df = 2, p = 0.56; i <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Rini, 2019 Rini, 2020 Finn, 2020 Finn, 2020		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.57, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 (0.49, 1.49)
Subtotal (Q = 1.15, df = 2, $p = 0.56$ ; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Motzer, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.05, 1.42] 5.19% 0.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.38, 5.27] 2.27% 0.88 [0.49, 1.56]
Subtotal (Q = 1.15, df = 2, p = 0.56; l <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00) Immune checkpoint inhibitor Motzer, 2018 Boku, 2019 Rini, 2019 Rini, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.52, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87]
Subtotal (Q = 1.15, df = 2, p = 0.56; i <sup>2</sup> = 0.0%, τ <sup>2</sup> = 0.00) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Rini, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 0.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53]
Subtotal (Q = 1.15, df = 2, $p = 0.56$ ; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtrait (Q = 4.16, df = 0, $p = 2.000$ , $i^2 = 2.000$ ,		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.01% 0.96 [0.72, 1.56] 0.38% 0.94 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.48, 1.58] 2.46% 1.06 [1.60, 1.87] 3.97% 0.98 [0.63, 1.53]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ )		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18]
Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.19% 0.69 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Rini, 2019 Rini, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Longenue 3010		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.65, 14.2] 5.01% 0.66 [0.72, 1.56] 0.38% 0.064 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.00 [0.84, 1.18]
$\begin{split} & \text{Subtotal} \left( Q = 1.15, df = 2, p = 0.56; i^2 = 0.0\%, \tau^2 = 0.00 \right) \\ & \textbf{Immune checkpoint inhibitor} \\ & \text{Motzer, 2018} \\ & \text{Shitara, 2018} \\ & \text{Soku, 2019} \\ & \text{Motzer, 2019} \\ & \text{Arrieta, 2020} \\ & \text{Finn, 2020} \\ & \text{Finn, 2020} \\ & \text{Gogas, 2021} \\ & \text{Zobust, 2021} \\ & \text{Motzer, 2021} \\ & \text{Subtotal} \left( Q = 4.16, df = 9, p = 0.90; i^2 = 0.0\%, \tau^2 = 0.00 \right) \\ & \textbf{Chemotherapy} \\ & \text{Joensul, 2010} \\ \end{split}$		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.55, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.88 [0.43, 1.53] 1.00 [0.84, 1.18] 1.135 1.38 [0.60, 3.17]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Rini, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuz, 2010 Monk, 2010 Cortes, 2011		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.01% 0.96 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97 [0.67 [0.27, 1.64]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 Cortes, 2011		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 0.67 [0.27, 1.64] 0.97% 0.67 [0.27, 1.64] 0.97% 0.67 [0.27, 1.64]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Rini, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cotries, 2011 O'Brien, 2011		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.65, 14.2] 5.01% 0.66 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.67 [0.27, 1.64] 0.34% 1.16 [0.26, 5.24]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Shitara, 2019 Motzer, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensus, 2010 Monk, 2010 Cortes, 2011 O'Brien, 2012		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.01% 0.96 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.44, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.98 [0.68, 1.72] 0.97% 0.98 [0.63, 1.72] 3.28% 1.05 [0.65, 1.72] 0.97% 0.98 [0.68, 1.72] 0.97% 0.98 [0.68, 1.42]
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Subtotal (Q = 1.15, df = 2, p = 0.56; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Contes, 2011 Subtotal (D = 4.16, df = 9, p = 0.90; $l^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Contes, 2011 Socianki, 2012 Biebierg, 2012 Colombo, 2012 Von, 2013 Vermorken, 2014 Kaufman, 2015		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.80, 1.87] 3.97% 0.88 [0.49, 1.58] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 105 [0.65, 1.72] 0.34% 1.16 [0.26, 5.24] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.42] 0.27% 1.06 [0.58, 1.72] 0.27% 0.08 [0.52, 1.23] 0.46% 0.00 [0.22, 2.95] 3.33% 0.81 [0.50, 1.31] 1.80%
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Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 Solinoski, 2012 Bibiberg, 2012 Colombo, 2012 Varmotken, 2014 Zhou, 2015		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.57, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.44, 1.58] 2.46% 1.06 [0.06, 1.87] 3.97% 0.98 [0.63, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.67 [0.27, 1.64] 0.34% 1.16 [0.26, 5.24] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.88, 1.42] 0.27% 1.06 [0.58, 1.97] 2.27% 1.05 [0.38, 2.95] 0.46% 0.80 [0.22, 2.95] 0.46% 0.80 [0.51, 1.31] 1.88% 1.54 [0.81, 2.94] 0.68% 0.22 [0.01, 5.54]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Shitara, 2019 Motzer, 2019 Rini, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensu, 2010 Monk, 2010 Cortes, 2011 O'Brien, 2011 Socinski, 2012 Bioberg, 2012 Colombo, 2012 Von, 2013 Vermorken, 2014 Kaufman, 2015 Shava, 2015 Chawaka, 2015		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.96 [0.65, 1.42] 5.01% 0.96 [0.72, 1.56] 0.38% 0.46 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.49, 1.58] 2.46% 1.06 [0.04, 1.87] 3.97% 0.98 [0.43, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.42] 5.07% 1.06 [0.58, 1.97] 2.27% 1.64 [0.58, 5.27] 0.27% 0.40 [0.59, 2.756] 2.07% 1.06 [0.58, 1.97] 3.28% 0.98 [0.68, 1.97] 3.29% 0.98 [0.68, 1.42] 5.04% 0.98 [0.68, 1.97] 3.29% 0.98 [0.62, 1.21] 1.88% 0.50 [0.22, 2.95] 3.33% 0.81 [0.50, 1.31] 1.88% 0.22 [0.01, 5.54] 0.68% 0.22 [0.1, 5.54] 0.68% 0.22 [0.01, 5.54] 0.68% 0
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Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 Solinbar, 2011 Solinba, 2012 Colombo, 2012 Von, 2013 Vermorken, 2014 Zhou, 2015 Sun, 2015 Hironaka, 2016		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.57, 1.42] 5.01% 0.66 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.44, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.88 [0.44, 1.58] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.67 [0.27, 1.64] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.88, 1.42] 5.68% 0.98 [0.88, 1.42] 5.24% 1.05 [0.35, 1.72] 0.27% 1.06 [0.58, 1.97] 2.27% 1.06 [0.58, 1.97] 2.27% 1.06 [0.58, 1.97] 2.27% 1.06 [0.58, 1.97] 3.33% 0.81 [0.20, 1.31] 1.88% 1.54 [0.81, 2.94] 0.68% 0.92 [0.21, 5.54] 0.68% 0.90 [0.22, 2.95] 3.33% 0.81 [0.20, 1.31] 1.88% 1.54 [0.81, 2.94] 0.68% 0.90 [0.22, 0.21] 0.58% 0.90 [0.28, 2.89]
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Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 Socinski, 2012 Biebarg, 2012 Colombo, 2012 Von, 2013 Vermorker, 2014 Zhou, 2015 Sun, 2015 Hironaka, 2015 Hironaka, 2016 Zhang, 2017 Mete, 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.09% 2.03 [0.28, 14.6] 5.01% 0.66 [0.55, 14.2] 5.19% 1.06 [0.72, 1.56] 0.38% 2.15 [0.88, 5.27] 2.27% 0.88 [0.44, 1.58] 2.45% 1.06 [0.60, 1.87] 3.97% 0.88 [0.44, 1.58] 1.00 [0.84, 1.18] 1.00 [0.84, 1.18] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.67 [0.27, 1.64] 5.68% 0.98 [0.68, 1.42] 5.68% 0.98 [0.68, 1.47] 0.27% 1.06 [0.58, 1.97] 0.27% 1.06 [0.58, 1.97] 0.28% 0.90 [0.23, 2.95] 0.33% 0.81 [0.50, 1.31] 1.88% 1.54 [0.81, 2.94] 0.68% 0.90 [0.22, 0.25] 0.58% 0.90 [0.23, 0.22] 1.33% 0.88 [0.50, 1.31] 1.83% 0.88 [0.50, 1.31] 1.83% 0.88 [0.50, 1.31] 1.83% 0.88 [0.50, 1.31] 1.83% 0.88 [0.55, 1.30] 1.23% 1.14 [0.51, 2.53] 0.08% 0.90 [0.23, 0.22] 1.23% 0.81 [0.50, 1.14] 0.59% 0.90 [0.23, 0.22] 1.23% 1.14 [0.51, 2.53] 0.05% 0.90 [0.23, 0.25] 1.23% 1.14 [0.51, 2.53] 0.05% 0.97 [0.57, 11.48] 0.55%
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Shitara, 2018 Doku, 2019 Arrieta, 2020 Finn, 2020 Gogas, 2021 Zhou, 2021 Motzer, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemcherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 O'Brien, 2011 Socinski, 2012 Bielieng, 2012 Colombo, 2012 Von, 2013 Vermorken, 2014 Zhou, 2015 Chawda, 2015 Chawda, 2015 Chawda, 2017 Tamura, 2017 Tamura, 2017 Meter, 2019		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.66 [0.72, 1.56] 0.38% 0.64 [0.20, 3.51] 0.98% 2.15 [0.88, 5.27] 2.27% 0.88 [0.44, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.88 [0.40, 1.56] 2.46% 1.06 [0.60, 1.87] 3.97% 0.98 [0.43, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.08 [0.68, 1.97] 2.27% 1.64 [0.56, 2.756] 2.07% 1.66 [0.58, 1.97] 2.27% 1.60 [0.28, 1.97] 3.33% 0.81 [0.50, 1.31] 1.88% 1.54 [0.81, 2.94] 0.68% 0.22 [0.01, 5.54] 0.59% 0.96 [0.33, 3.02] 1.83% 0.59 [0.58, 1.30] 1.23% 1.14 [0.51, 2.53] 0.59% 0.96 [0.33, 3.02] 1.23% 1.14 [0.51, 2.53] 0.10% 0.74 [0.05, 1.14] 2.15% 0.97 [0.53, 1.30] 1.23% 1.14 [0.51, 2.53] 0.10% 0.74 [0.05, 1.14] 0.58% 0.90 [0.22, 2.55] 1.30]
Subtotal (Q = 1.15, df = 2, p = 0.56; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Immune checkpoint inhibitor Motzer, 2018 Shitara, 2018 Boku, 2019 Motzer, 2019 Arrieta, 2020 Gogas, 2021 Zhou, 2021 Subtotal (Q = 4.16, df = 9, p = 0.90; $i^2 = 0.0\%$ , $\tau^2 = 0.00$ ) Chemotherapy Joensuu, 2010 Monk, 2010 Cortes, 2011 Socinski, 2012 Bioblerg, 2012 Diologanta, 2014 Zhou, 2014 Xaufman, 2015 Sun, 2015 Hironaka, 2016 Ueno, 2017 Tamura, 2017 Tamura, 2017 Marker, 2019 Shi, 2021		0.89 [0.36, 2.21] 4.72% 0.89 [0.59, 1.34] 1.66% 0.88 [0.44, 1.75] 0.20% 2.03 [0.28, 14.69] 5.01% 0.86 [0.65, 1.42] 5.19% 1.06 [0.72, 1.56] 0.38% 0.84 [0.44, 1.58] 0.38% 0.84 [0.44, 1.58] 2.46% 1.06 [0.60, 1.87] 3.97% 0.88 [0.44, 1.53] 1.00 [0.84, 1.18] 1.13% 1.38 [0.60, 3.17] 3.28% 1.05 [0.65, 1.72] 0.97% 0.67 [0.27, 1.64] 0.34% 1.16 [0.26, 5.24] 5.68% 0.89 [0.68, 1.42] 0.21% 1.05 [0.58, 1.57] 0.27% 1.05 [0.58, 1.57] 0.27% 1.05 [0.58, 1.57] 0.27% 1.05 [0.58, 1.57] 0.27% 1.05 [0.58, 1.57] 0.24% 0.80 [0.22, 2.55] 0.46% 0.80 [0.22, 2.55] 0.46% 0.80 [0.22, 2.55] 0.46% 0.96 [0.30, 3.02] 1.83% 0.86 [0.35, 1.30] 1.23% 1.14 [0.51, 2.53] 0.58% 0.90 [0.28, 2.89] 0.59% 0.96 [0.30, 3.02] 1.83% 0.86 [0.35, 1.30] 1.24% 0.14 [0.51, 2.53] 0.074 [0.07, 11.48] 2.15% 0.87 [0.53, 1.76] 0.15% 0.87 [0.53, 1.76]

Local overestimate ٦ 4

2

Central overestimate

0.5

17

1

0.25

Subtotal (Q = 9.22, df = 19, p = 0.97;  $i^2$  = 0.0%,  $\tau^2$  = 0.00)

 $\begin{array}{l} \mbox{Overall (Q = 33.74, df = 73, p = 1.00; l^2 = 0.0\%, \tau^2 = 0.00)} \\ \mbox{Test for Subgroup Differences: } Q_M = 0.08, df = 3, p = 0.99 \end{array}$ 

#### Supplementary Figure 8b. Comparison of treatment effect estimates (Odds Ratio) between central reviewers and local investigators. Subgroup analysis: drug classification. Author(s) and Year Ratio of odds ratios (95% CI)

1.01 [0.86, 1.19]

100.00% 1.00 [0.91, 1.09]

Weight ROR, 95% CI

Supplementary Table 1. Adjudicators of open-label trials of anticancer drugs (n = 1,197)

157 (13.1)
134 (11.2)
291 (24.3)
528 (44.1)
87 (7.3)
141 (11.8)
158 (13.2)
301 (25.2)
536 (44.8)
61 (5.1)

Abbreviations: ORR, objective response rate; PFS, progression-free survival.

Supplementary Table 2. Effect of correlation between central and local adjudications (sensitivity analysis).					
RHR (95%CI)	Tau <sup>2</sup>	$ ^2$	P value for heterogeneity		
0.95 (0.91 to 0.98)	0.00	0%	>0.99		
0.95 (0.92 to 0.98)	0.00	0%	0.96		
0.95 (0.92 to 0.97)	0.00	7.0%	0.18		
0.95 (0.92 to 0.98)	0.01	56.0%	< .0001		
0.95 (0.91 to 0.98)	0.03	94.0%	< .0001		
ROR (95%CI)	Tau <sup>2</sup>	l <sup>2</sup>	P value for heterogeneity		
1.00 (0.91 to 1.09)	0.00	0%	>0.99		
1.00 (0.93 to 1.08)	0.00	0%	>0.99		
1.00 (0.94 to 1.06)	0.00	0%	0.71		
1.01 (0.95 to 1.08)	0.02	37.0%	< .0001		
1.03 (0.95 to 1.13)	0.11	93.0%	< .0001		
	ntary Table 2. Effect of correct   RHR (95%CI)   0.95 (0.91 to 0.98)   0.95 (0.92 to 0.98)   0.95 (0.92 to 0.97)   0.95 (0.92 to 0.98)   0.95 (0.92 to 0.98)   0.95 (0.91 to 0.98)   ROR (95%CI)   1.00 (0.91 to 1.09)   1.00 (0.93 to 1.08)   1.01 (0.95 to 1.08)   1.03 (0.95 to 1.13)	ntary Table 2. Effect of correlation betweenRHR (95%Cl)Tau2 $0.95 (0.91 to 0.98)$ $0.00$ $0.95 (0.92 to 0.98)$ $0.00$ $0.95 (0.92 to 0.97)$ $0.00$ $0.95 (0.92 to 0.98)$ $0.01$ $0.95 (0.92 to 0.98)$ $0.01$ $0.95 (0.91 to 0.98)$ $0.03$ ROR (95%Cl)Tau2 $1.00 (0.91 to 1.09)$ $0.00$ $1.00 (0.93 to 1.08)$ $0.00$ $1.00 (0.94 to 1.06)$ $0.02$ $1.03 (0.95 to 1.13)$ $0.11$	ntary Table 2. Effect of correlation between central and localRHR (95%Cl)Tau2 $l^2$ 0.95 (0.91 to 0.98)0.000%0.95 (0.92 to 0.98)0.000%0.95 (0.92 to 0.97)0.007.0%0.95 (0.92 to 0.98)0.0156.0%0.95 (0.91 to 0.98)0.0394.0%ROR (95%Cl)Tau2 $l^2$ 1.00 (0.91 to 1.09)0.000.000%1.00 (0.94 to 1.08)0.000.01 (0.95 to 1.08)0.020.02 (0.95 to 1.13)0.1193.0%		

Abbreviations: ORR, objective response rate; PFS, progression-free survival; RHR, ratios of hazard ratio; ROR, ratios of odds ratio.

A p is correlation coefficients between central and local adjudications in each trial.

A  $\rho$  of 0 indicates no dependency and a r of 0.95 indicates almost complete dependency.