Supplementary Material

Supplementary Table S1. VEGF inhibitors.

Name of VEGFi	Agent type	Target
Sunitinib	TKI	VEGFR-1,-2, and -3, PDGFR, c-Kit, Flt-3, CSFR1, glial cell-derived neurotrophic factor receptor
Pazopanib	TKI	VEGFR-1,-2,-3, PDGFR-a and -ß, c-Kit
Sorafenib	TKI	VEGFR-2, VEGFR-3, PDGFR-ß, c-KIT, FLT-3, CRAF, BRAF and mutant BRAF,
Lenvatinib	TKI	VEGFR-1,-2, and -3, FGFR-1, FGFR-2,-3, and -4, PDGFRa, RET, and c-KIT
Vandetanib	TKI	VEGFR-2, EGFR
Regorafenib	TKI	VEGFR-1,-2, and -3, TIE-2, c-KIT, RET, RAF1, BRAF, and BRAFV600E, FDGFR, FGFR
Cabozantinib	TKI	VEGFR-1,-2 and -3, c-KIT, TRKB, Flt-3, AXL, RET, MET, and TIE-2
Axitinib	TKI	VEGFR-1,-2, and -3
Cediranib	TKI	VEGFR-1,-2, and -3
Ponatinib	TKI	VEGFR, BCR-ABL
Aflibercept	Soluble decoy receptor	VEGF A-D, PIGF
Vatalanib	TKI	VEGFR, PDGFR, c-KIT
Tivozanib	TKI	VEGFR-1,-2, and -3, PDGFR-ß
Motesanib	TKI	VEGFR, PDGFR
Linifanib	TKI	VEGFR
Anlotinib	TKI	VEGFR, FGFR, and PDGFR
Fruquintinib	TKI	VEGFR-1,-2, and -3
Nintedanib	TKI	VEGFR, FGFR, and PDGFR
Apatinib	TKI	VEGFR-2, c-KIT, c-SRC
Bevacizumab	Monoclonal antibody	VEGF
Ramucirumab	Monoclonal antibody	VEGFR-2

Vanucizumab	Monoclonal antibody	VEGF, angiopoietin-2

Supplementary Table S2. Search Strategy.

Database	Keywords	Number of studies
Ovid Medline		
1	Neoplasms/	497186
2	exp Carcinoma/	723044
3	exp Neoplasm Metastasis/	221165
4	(Neoplas* or cancer* or tumour* or tumor* or malignan* or carcinoma* or adenocarcinoma* or stage four cancer* or metast*).mp.	4876470
5	Sunitinib/	4133
6	Angiogenesis Inhibitors/	28867
7	Sorafenib/	6224
8	Bevacizumab/	14127
9	Axitinib/	716
10	Response*.mp.	3499677
11	disease-free survival/ or progression-free survival/ or response evaluation criteria in solid tumors/	89668
12	(disease?free survival* or progression?free survival* or response evaluation criteria in solid tumo?r* or RECIST or Overall survival*).mp.	236936
13	Randomized Controlled Trials as Topic/	162013
14	randomi?ed controlled trial.pt.	592772
15	(Stage 4 cancer* or advance* cancer* or Metast*).mp.	703445
16	control* trial.kw.	302
17	(sunitinib or pazopanib or vendetanib or lenvatanib or regorafenib or cabozantinib or cediranib or ponatanib or aflibercept or vatalanib or tivozanib or ramucirumab or motesanib).tw.	14697

18	1 or 2 or 3 or 4 or 15	4877863
19	5 or 6 or 7 or 8 or 9 or 17	52148
20	5 or 7 or 8 or 9 or 17	33872
21	10 or 11 or 12	3712762
22	13 or 14 or 16	749128
23	18 and 19 and 21 and 22	2062
24	18 and 20 and 21 and 22	1900
25	limit 24 to (humans and clinical trial, all and "therapy (maximizes sensitivity)" and medline)	1415
COCHRANE CENTRAL		
1	exp Neoplasms/	89556
2	(cancer or onco* or tumour or tumor).mp.	229437
3	exp Neoplasm Metastasis/	5568
4	(stage four cancer* or metast* or advanc* canc* or stage 4 cancer*).mp.	59226
5	exp Sunitinib/	357
6	exp Sorafenib/	541
7	exp Bevacizumab/	2223
8	exp Axitinib/	110
9	(disease?free survival* or progression?free survival* or response evaluation criteria in solid tumo?r* or RECIST or Overall survival* or DFS or PFS or OS).mp.	67468
10	1 or 2 or 3 or 4	255360
11	(sunitinib or pazopanib or vendetanib or lenvatanib or regorafenib or cabozantinib or cediranib or ponatanib or aflibercept or vatalanib or tivozanib or ramucirumab or motesanib or anlotinib or fruquitinib).tw.	4571

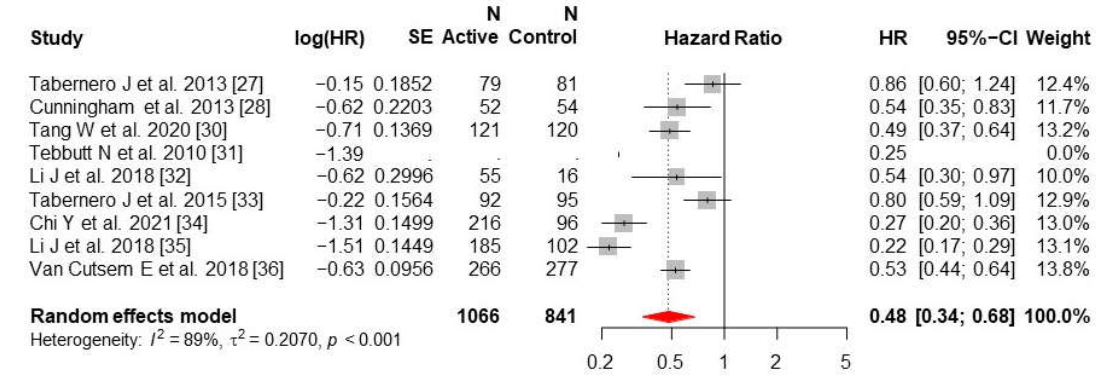
12	9 and 10 and 11	2511
13	limit 12 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)	453
EMBASE		
1	exp malignant neoplasm/	4073600
2	exp metastasis/	809335
3	(stage four cancer* or advanc* canc* or stage 4 cancer*).mp.	173583
4	exp sunitinib/	27348
5	exp sorafenib/	37394
6	exp bevacizumab/	72775
7	exp axitinib/	7085
8	exp pazopanib/	10590
9	exp regorafenib/	6617
10	exp cabozantinib/	6655
11	exp aflibercept/	8859
12	exp ramucirumab/	4532
13	exp motesanib/	838
14	exp linifanib/	602
15	(vendetanib or lenvatanib or cediranib or ponatanib or vatalanib or tivozanib).tw.	1247
16	exp disease free survival/	111754
17	exp overall survival/	465372
18	exp progression free survival/	166293
19	(disease?free survival* or progression?free survival* or response evaluation criteria in solid tumo?r* or RECIST or Overall survival* or DFS or PFS or OS).mp.	675343
20	response evaluation criteria in solid tumors/	18365

21	1 or 2 or 3	4166621
22	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	130727
23	16 or 17 or 18 or 19 or 20	733941
23	21 and 22 and 23	43832
24	limit 24 to (human and (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) and "therapy (maximizes sensitivity)" and article and journal)	4856

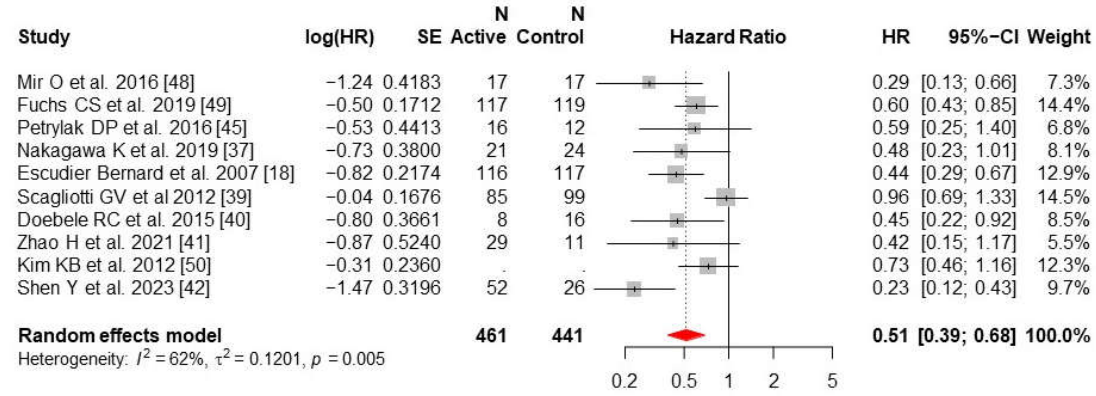
Supplementary Table S3. RCT quality assessment.

Trial	Randomization	Blinding	Withdrawals and dropouts	Total Jadad Scale
Escudier *et al.* JCO 2010 (AVOREN)[43]	2	2	1	**5**
Rini *et al.* JCO 2010 (CALGB 90206)[44]	2	0	1	**3**
Van Cutsem *et al.* JCO 2009[47]	2	2	1	**5**
Mir *et al.* Lancet Oncology 2016 (PAZOGIST)[48]	2	0	1	**3**
Fuchs *et al.* Lancet Oncology 2019 (RAINFALL)[49]	2	2	1	**5**
Petrylak *et al.* JCO 2016[45]	2	0	1	**3**
Petrylak *et al.* Lancet Oncology 2020 (RANGE)[46]	2	2	1	**5**
Nakagawa *et al.* Lancet Oncology 2019 (RELAY)[37]	2	2	1	**5**
Tabernero *et al.* Clinical Cancer Research 2013 (RESPECT)[27]	2	2	1	**5**
Escudier *et al.* NEJM 2007 (TARGET)[18]	2	2	1	**5**
Sandler *et al.* NEJM 2006. (NCT00021060)[38]	2	0	1	**3**
Scagliotti *et al.* JCO 2012	2	2	1	**5**
Cunningham *et al.* Lancet Oncology 2013 (AVEX)[28]	2	0	1	**3**
Tabernero *et al.* EJC 2014 (VELOUR)[29]	2	2	1	**5**
Tang *et al.* JCO 2020 (BECOME)[30]	2	0	1	**3**
Tebbutt *et al.* JCO 2010 (MAX)[31]	2	0	1	**3**
Li *et al.* Future Oncology 2018[32]	2	2	1	**5**
Tabernero *et al.* Lancet Oncology 2015 (RAISE)[33]	2	2	1	**5**
Chi *et al.* The Oncologist 2021 (ALTER0703)[34]	2	2	1	**5**
Doebele *et al.* Cancer 2015[40]	2	0	1	**3**
Li *et al.* Jama 2018 (FRESCO)[35]	2	2	1	**5**
Van Cutsem *et al.* Annals of Oncology 2018 (LUME-Colon 1)[36]	2	2	0	**4**
Zhao *et al.* Journal of Thoracic Oncology 2021 (CTONG1706)[41]	2	2	1	**5**
Kim *et al.* JCO 2012 (BEAM)[50]	2	2	1	**5**
Shen *et al.* Journal of Cancer Research and Clinical Oncology 2023 (ALTER 0303)[42]	2	2	0	**4**

A

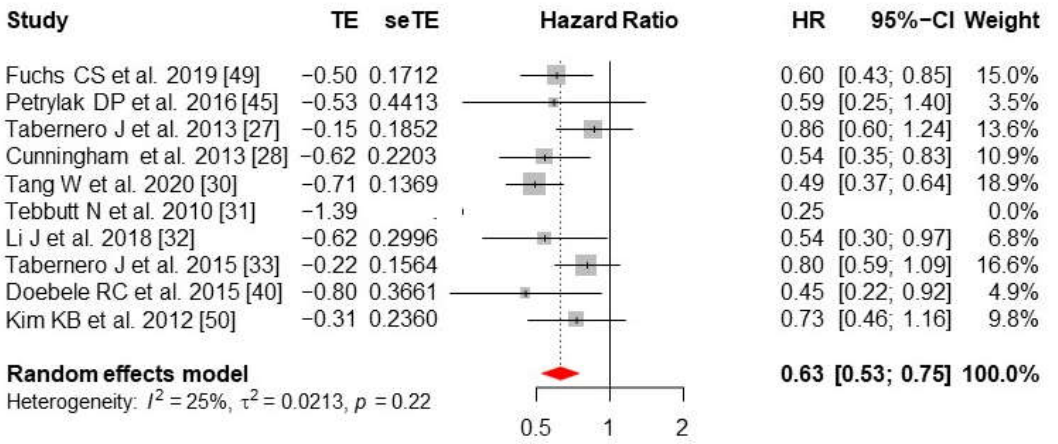


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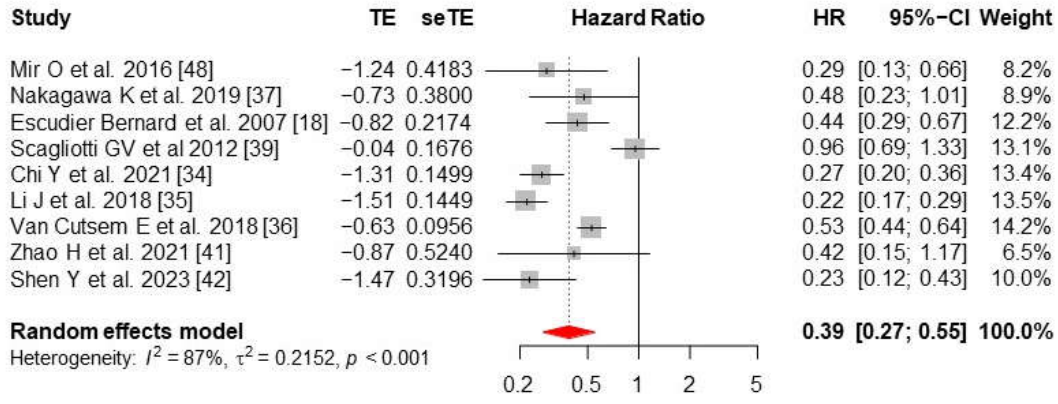


Supplementary Figure S1. The addition of VEGFi to a backbone of systemic therapy or BSC was associated with superior PFS in patients with liver metastases from "*colorectal*" and "*non-colorectal*" cancers. Forest plot and pooled HRs for PFS comparing the backbone systemic therapy or BSC with versus without VEGFi in patients with liver metastases from "*colorectal cancer*" (HR = 0.48; 95% CI, 0.34 - 0.68; high heterogeneity: I^2 = 89%, p < 0.001) **(A)** and with liver metastases from "*non-colorectal cancer*" (GIST, gastric or junctional adenocarcinoma, urothelial carcinoma, non-small cell lung cancer, renal cell carcinoma, melanoma) (HR = 0.51; 95% CI, 0.39 - 0.68; high heterogeneity: I^2 = 62%, p = 0.005) **(B)**.

A



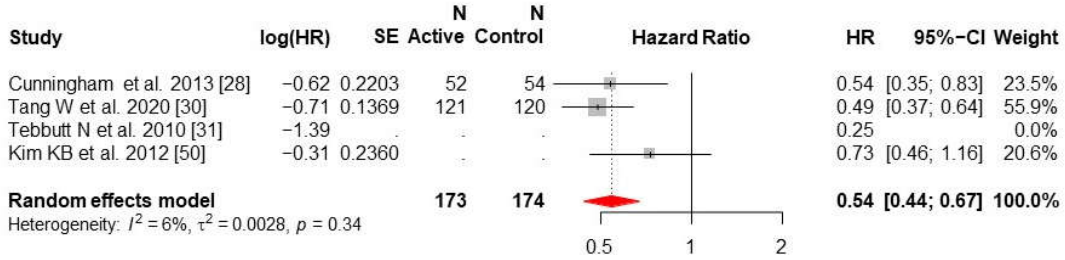
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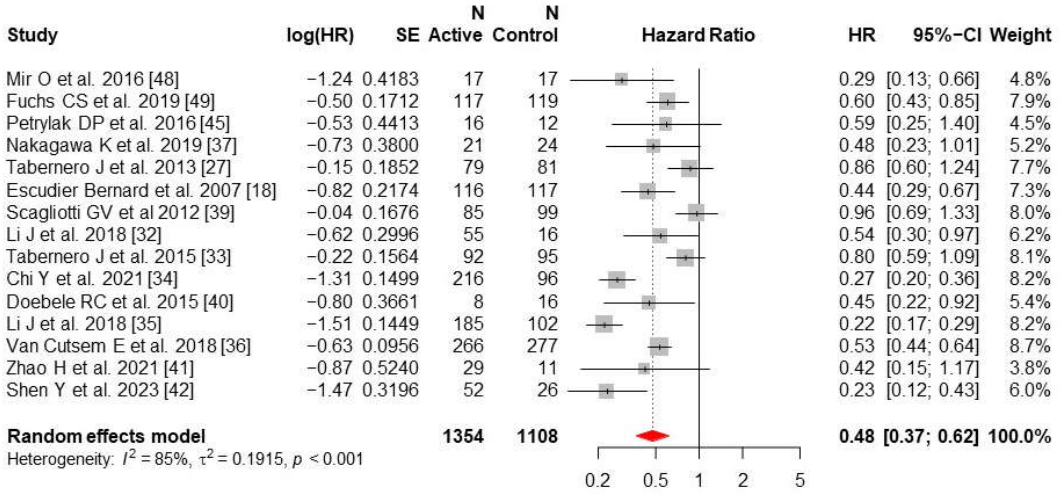
Supplementary Figure S2. The addition of VEGFi to "*chemotherapy*" and "*non-chemotherapy*" was associated with superior PFS in patients with liver metastases across cancers. Forest plot and pooled HRs for PFS comparing "*chemotherapy*" with versus without VEGFi in patients with liver metastases across cancers (HR = 0.63; 95% CI, 0.53 – 0.75; low heterogeneity: I^2 = 25, p =

0.22) **(A)** and "*non-chemotherapy*" (non-VEGFi targeted therapy or BSC) with versus without VEGFi in patients with liver metastases across cancers (HR = 0.39; 95% CI, 0.27 - 0.55; high heterogeneity: I^2 = 87%, p < 0.001) **(B)**.

A



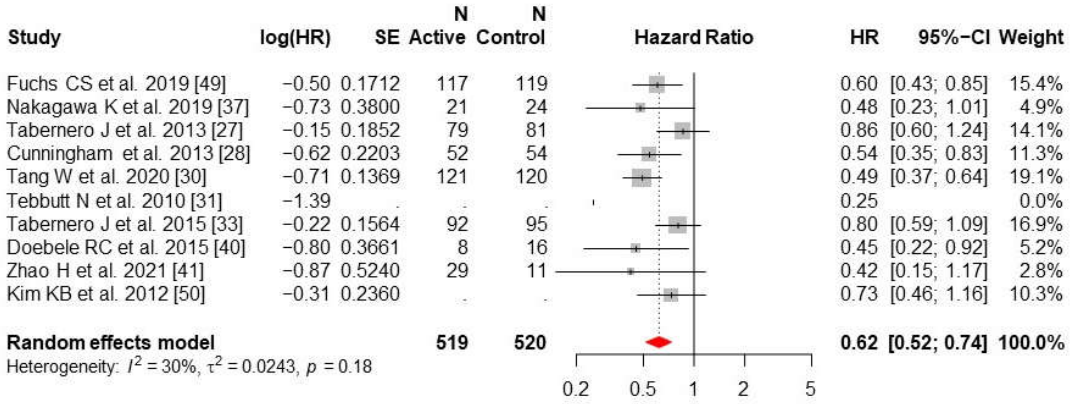
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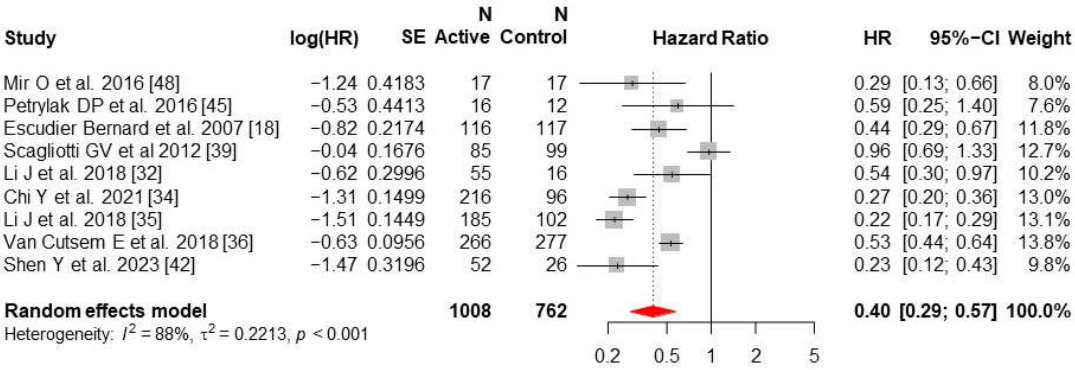
Supplementary Figure S3. The addition of VEGFi ("*bevacizumab*" and "*non-bevacizumab*") to a backbone of systemic therapy or BSC was associated with superior PFS in patients with liver metastases across cancers. Forest plot and pooled HRs for PFS comparing a backbone of systemic therapy with versus without VEGFi ("*bevacizumab*") in patients with liver metastases across cancers (HR = 0.54; 95% CI, 0.44 – 0.67; low heterogeneity: I^2 = 6%, p = 0.34) **(A)** and with versus without VEGFi ("*non-bevacizumab*" [pazopanib, ramucirumab,

sorafenib, sunitinib, aflibercept, anlotinib, fruquintinib, nintedanib, apatinib) in patients with liver metastases across cancers (HR = 0.48; 95% CI, 0.37 – 0.62; high heterogeneity: I^2 = 85%, p < 0.001) **(B)**.

A



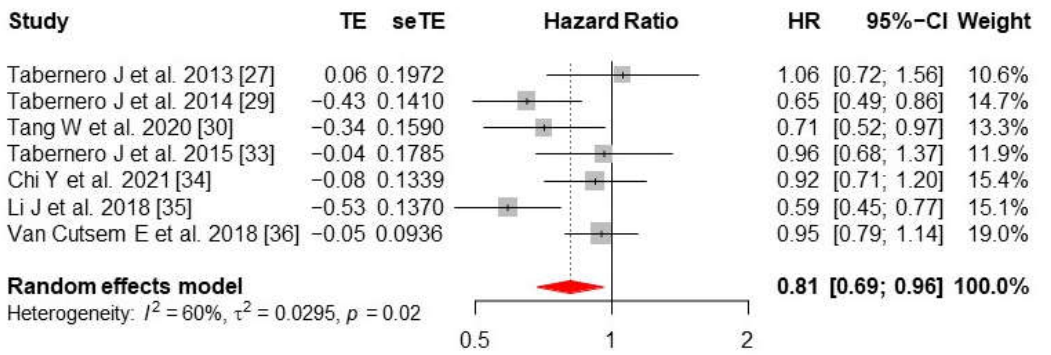
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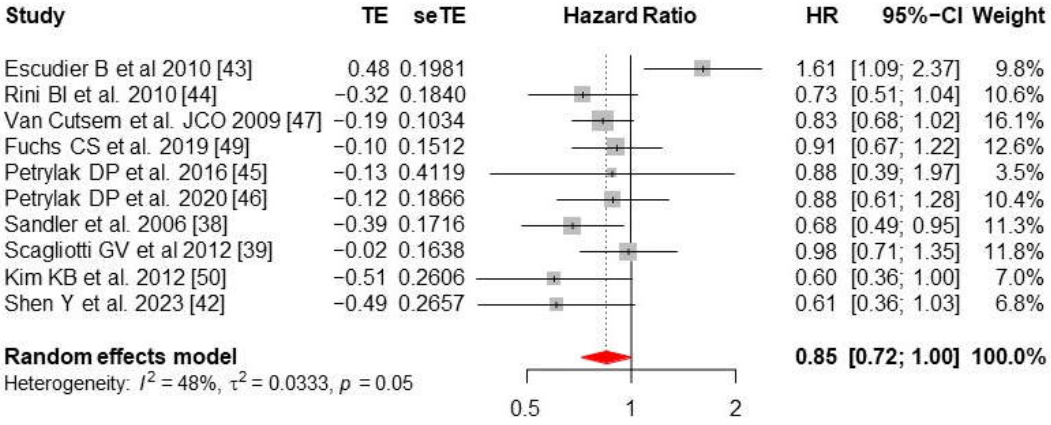
Supplementary Figure S4. The addition of VEGFi to a backbone of systemic therapy or BSC as "*1st line" and "subsequent line" of treatment* was associated with superior PFS in patients with liver metastases across cancers. Forest plot and pooled HRs for PFS comparing a backbone of systemic therapy with versus without VEGFi as "*1st line treatment*" in patients with liver metastases across

cancers (HR = 0.62; 95% CI, 0.52 – 0.74; low heterogeneity: I^2 = 30%, p = 0.18) **(A)** and as "*subsequent line treatment*" in patients with liver metastases across cancers (HR = 0.40; 95% CI, 0.29 – 0.57; high heterogeneity: I^2 = 88%, p < 0.001) **(B)**.

A



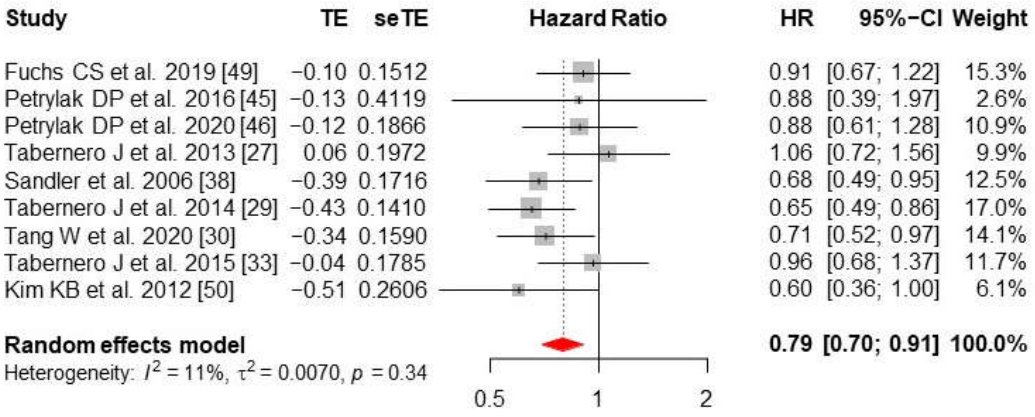
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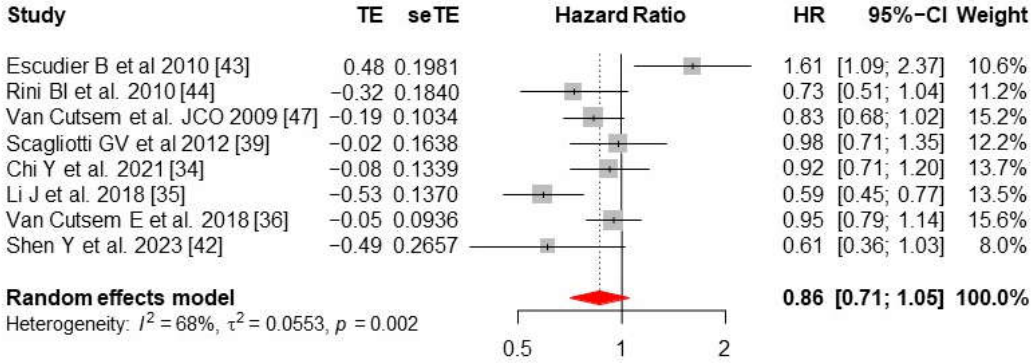
Supplementary Figure S5. The addition of VEGFi to a backbone of systemic therapy or BSC was associated with superior OS in patients with liver metastases from "*colorectal*" and "*non-colorectal*" cancers. Forest plot and pooled HRs for OS comparing the backbone systemic therapy or BSC with versus without VEGFi in patients with liver metastases from "*colorectal cancer*" (HR = 0.81; 95% CI, 0.69 - 0.96; moderate heterogeneity: I^2 = 60%, p = 0.02) **(A)** and with liver metastases from "*non-colorectal cancer*" (GIST, gastric or junctional

adenocarcinoma, urothelial carcinoma, non-small cell lung cancer, renal cell carcinoma, melanoma) (HR = 0.85; 95%CI, 0.72 – 1.00; moderate heterogeneity: I^2 = 48%, p = 0.05) **(B)**.

A



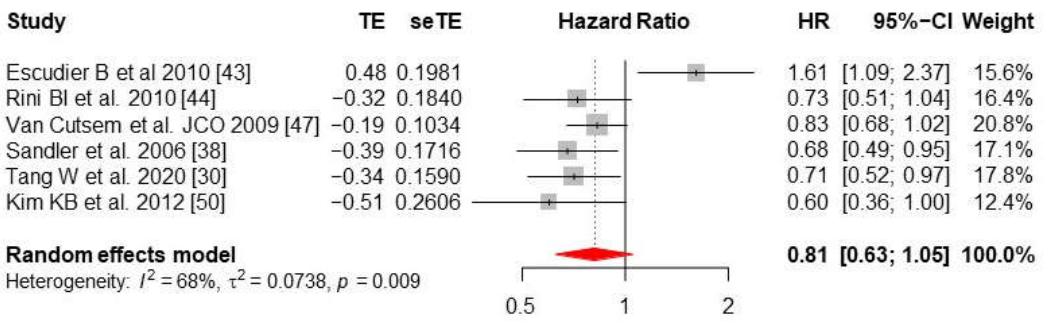
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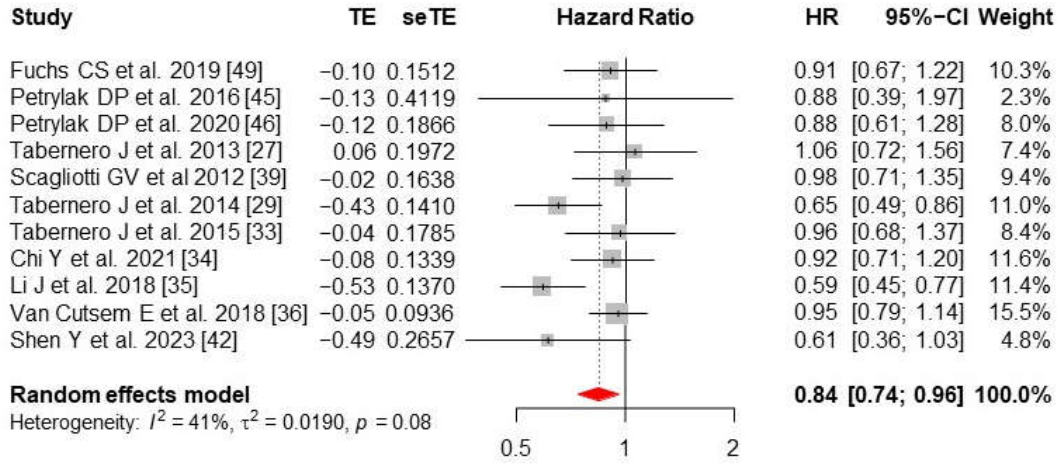
Supplementary Figure S6. The addition of VEGFi to "*chemotherapy*" and "*non-chemotherapy*" was associated with superior OS in patients with liver metastases across cancers. Forest plot and pooled HRs for OS comparing "*chemotherapy*" with versus without VEGFi in patients with liver metastases across cancers (HR = 0.79; 95% CI, 0.70 – 0.91; low heterogeneity: I^2 = 11%, p = 0.34) **(A)** and "*non-*

chemotherapy" (targeted therapy or BSC) with versus without VEGFi in patients with liver metastases across cancers (HR = 0.86; 95% CI, 0.71 - 1.05; high heterogeneity: I^2 = 68%, p = 0.002) **(B)**.

A



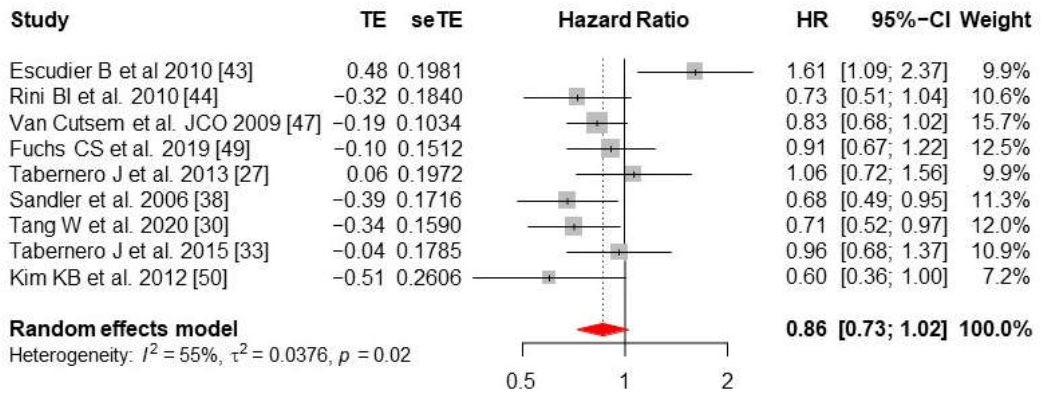
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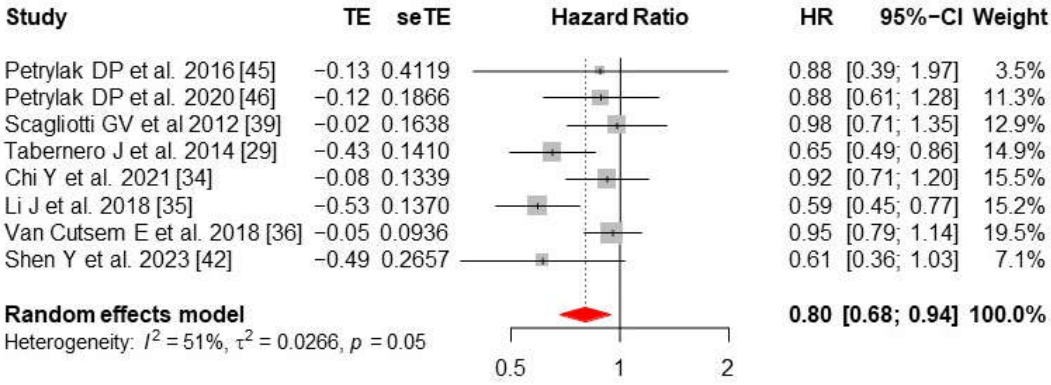
Supplementary Figure S7. The addition of VEGFi ("*bevacizumab*" and "*non-bevacizumab*") to a backbone of systemic therapy or BSC was associated with superior OS in patients with liver metastases across cancers. Forest plot and pooled HRs for OS comparing a backbone of systemic therapy with versus without VEGFi ("*bevacizumab*") in patients with liver metastases across cancers (HR = 0.81; 95% CI, 0.63 – 1.05; high heterogeneity: I^2 = 68%, p = 0.009) **(A)** and

with versus without VEGFi ("*non-bevacizumab*" [pazopanib, ramucirumab, sorafenib, sunitinib, aflibercept, anlotinib, fruquintinib, nintedanib, apatinib) in patients with liver metastases across cancers (HR = 0.84; 95% CI, 0.74 – 0.96; moderate heterogeneity, I^2 = 41%, p = 0.08) **(B)**.

A



B



Supplementary Figure S8. The addition of VEGFi to a backbone of systemic therapy or BSC as *1st or subsequent line of treatment* was associated with superior OS in patients with liver metastases across cancers. Forest plot and pooled HRs for OS comparing a backbone of systemic therapy with versus without VEGFi as "*1st line treatment*" in patients with liver metastases across

cancers (HR = 0.86; 95% CI, 0.73 – 1.02; moderate heterogeneity: I^2 = 55%, p = 0.02) **(A)** and as "*subsequent line treatment*" in patients with liver metastases across cancers (HR = 0.80; 95% CI, 0.68 – 0.94; moderate heterogeneity: I^2 = 51%, p = 0.05) **(B)**.