VEGF inhibitors (VEGFi) activity in liver metastases (mets) regardless of primary cancer type: meta-analysis and systematic review.

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Background

- Liver metastasis is a poor prognostic factor[1,2,3,4] in several cancers and is associated with poor response to immunotherapy in melanoma and lung cancer[1,2,3].
- VEGF inhibitors (VEGFi) have activity in hepatocellular carcinoma (HCC) and is hypothesized to be due the hypoxic microenvironment[5,6,7]. In the presence of oxygen, HIF1α is degraded, but in a hypoxic microenvironment, HIF1α binds to HIF1β, leading to the transcription of target genes, including VEGF, which plays a key role in angiogenesis[8].
- The effect of VEGFi in liver metastases across different cancer types is unknown.

Objectives

To assess the efficacy of VEGFi in liver metastases utilizing randomized-controlled clinical trials (RCTs) testing the efficacy of VEGFi, regardless of primary cancer site.

Methods

- Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to January 1, 2022.
- All RCTs that compared a backbone of systemic therapy (chemotherapy and/or immunotherapy and/or targeted therapy) or best supportive care (BSC) with vs without VEGFi in patients with liver metastases from any cancer were selected.

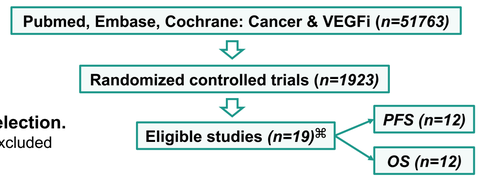


Figure 1. Study Selection.
⌘HCC trials were excluded

Table 1. List of selected RCTs

Study	Cancer type	Systemic therapy or BSC	VEGFi
AVOREN, CALGB 90206	Renal Cell Carcinoma (ca)	Immunotherapy (IT)	Bevacizumab
RELAY	Non-small cell lung cancer	Targeted therapy (TT)	Ramucirumab
RESPECT	Colorectal ca	Chemotherapy (chemo)	Sorafenib
Van Cutsem, JCO 2009	Pancreatic ca	Chemo + TT	Bevacizumab
PAZOGIST	GIST	BSC	Pazopanib
RAINFALL*; Petrylak, JCO 2016; RANGE*****	Gastric ca*; Colorectal ca**; Urothelial ca***	Chemo	Ramucirumab
TARGET	Renal Cell ca	BSC	Sorafenib
IMpower150‡; NCT00021060‡‡	Non-small cell lung cancer	Chemo + IT‡; Chemo‡‡	Bevacizumab
Scagliotti, JCO 2012	Non-small cell lung cancer	TT	Sunitinib
AVEX, BECOME, MAX	Colorectal ca	Chemo	Bevacizumab
VELOUR‡; Li, Future oncology 2018‡; RAISE‡‡	Colorectal ca	Chemo	Aflibercept‡; Ramucirumab‡‡

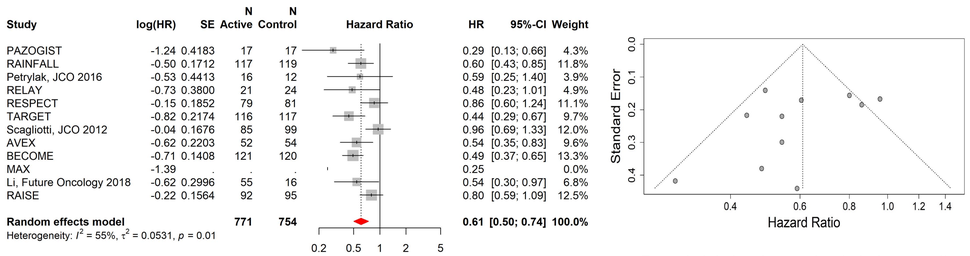
- Study design, cancer type, number of patients, lines of treatment, study drugs and hazard ratios (HRs) with 95% CIs for overall survival (OS) and progression-free survival (PFS) were extracted.
- Statistical Analysis:
  - Pooled effects of VEGFi in patients with liver metastases across different cancer types were estimated using random effect model with inverse variance.
  - Heterogeneity between studies was assessed by I^2 statistics.
  - Sensitivity analyses were performed considering prespecified subgroups of trials.

Results

Table 2. Breakdown of the 19 selected RCTs by cancer type, backbone systemic therapy, VEGFi type and line of treatment.

19 RCTs included in this meta-analysis → n=3170 patients with liver metastases	
Cancer type	Colorectal cancer (8), Non-small cell lung cancer (4), Renal cell cancer & urothelial cancer (4), Pancreatic cancer (1), GIST (1) and Gastric cancer (1).
Backbone systemic therapy	Chemotherapy (11), Targeted therapy (2), Immunotherapy (2), Chemotherapy + Immunotherapy (1), Chemotherapy + Targeted therapy (1); And Best supportive care (BSC; 2)
VEGFi type	Bevacizumab (8), Ramucirumab (5), Aflibercept (2), Sorafenib (2), Pazopanib (1), Sunitinib (1)
Line of treatment	First line (8), post 1st line (11)

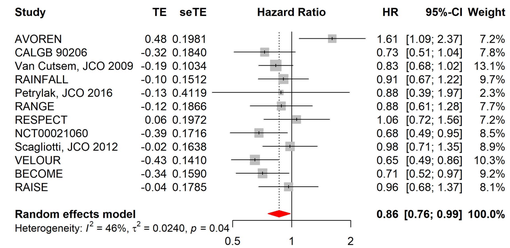
Figure 2. The addition of VEGFi to a backbone of systemic therapy or BSC was associated with superior PFS.



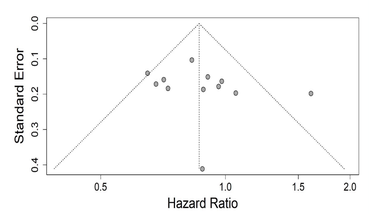
Forest plot and pooled HRs for PFS (HR = 0.61; 95% CI, 0.50-0.74; p < 0.0001).

Funnel plot showing moderate heterogeneity between studies for PFS (I^2 = 55%)

Figure 3. The addition of VEGFi to a backbone of systemic therapy or BSC was associated with superior OS.

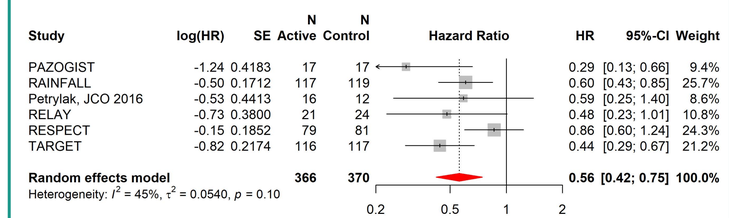


Forest plot and pooled HRs for OS (HR = 0.86; 95%CI, 0.76-0.99; p = 0.0334).

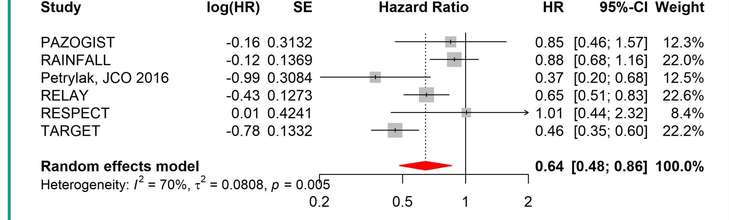


Funnel plot showing moderate heterogeneity between studies for OS (I^2 = 46%).

Figure 4. In the subset of RCTs with data on patients without liver metastases, the benefit with VEGFi was more pronounced in patients with liver metastases vs those without liver metastases for PFS.



Forest plot and pooled HRs for PFS in patients with liver metastases (HR = 0.56; 95% CI, 0.42-0.75).



Forest plot and pooled HRs for PFS in patients without liver metastases (HR = 0.64; 95% CI, 0.48-0.86).

Conclusions

- The addition of VEGFi to standard management improved progression-free survival and overall survival in patients with liver metastases across different cancer types and warrants further investigation.
- The benefit of the addition of VEGFi to standard management for liver metastases was seen independent of: a) *cancer type*, "colorectal cancer" vs "non-colorectal cancers"; b) *backbone systemic therapy*, "chemotherapy" vs "non-chemotherapy"; c) *VEGFi type*, "bevacizumab" vs "non-bevacizumab"; d) *line of treatment*, "first line" vs "post 1st line" (*data not shown*).
- VEGFi added to immunotherapy may be effective in patients with resistant liver metastases and translational studies are ongoing to address this.

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