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A meta-analysis of VEGF inhibitor efficacy in patients with liver metastases across cancer types

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - RAS has received fees for professional services from MetaOptima Technology Inc., F. Hoffmann-La Roche Ltd, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, AMGEN Inc., Bristol-Myers Squibb, Myriad Genetics, GlaxoSmithKline. MSC has served on advisory boards or as a consultant for Amgen, BMS, Eisai, Ideaya, MSD, Nektar, Novartis, Oncosec, Pierre-Fabre, Qbiotics, Regeneron, Roche, Merck and Sanofi, and received honoraria from BMS, MSD, and Novartis AMM has served on advisory boards for BMS, MSD, Novartis, Roche, Pierre-Fabre and QBiotics. GVL is consultant advisor for Agenus, Amgen, Array Biopharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, Hexal AG (Sandoz Company), Highlight Therapeutics S.L., Innovent Biologics USA, Merck Sharpe & Dohme, Novartis, OncoSec, PHMR Ltd, Pierre Fabre, Provectus, Qbiotics, Regeneron. IPS has served on advisory board fro MSD, and received honoraria from Roche, BMS and MSD. JWC, JB, SNL have no conflicts of interest.

INPLASY registration number: INPLASY202390034

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 September 2023 and was last updated on 11 September 2023.

INTRODUCTION

Review question / Objective In this study, we aimed to assess the efficacy of VEGFi in cancer patients with liver metastases in a meta-analysis including randomized-controlled clinical trials (RCTs) testing the efficacy of VEGFi, regardless of primary cancer site. We also compared VEGFi efficacy in patients with versus without liver metastases.

Rationale The liver is a common site of metastasis, and the presence of liver metastases is a poor prognostic factor in several cancers. Furthermore, in melanoma, non small cell lung cancer (NSCLC), and renal cell carcinoma (RCC), the presence of liver metastases have been associated with poorer response and survival in patients treated with immunotherapy.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is known to be resistant to chemotherapy. Nevertheless, in the last

decade, targeting angiogenesis with vascular endothelial growth factor (VEGF) inhibitors (VEGFi) has improved clinical outcomes in patients with advanced HCC. Also, immunotherapy as monotherapy for HCC has seen modest responses11, however, combination with VEGFi in recent years have demonstrated more robust responses10. HCC is characterized by an immunosuppressive, hypoxic and highly vascularized tumour microenvironment. In the presence of oxygen, hypoxia inducible factor-1a (HIF1a) is degraded, however, in a hypoxic microenvironment (e.g. in the context of an aggressive tumour), HIF1a binds to HIF1b, leading to transcription of target genes, including VEGF, which plays a key role in angiogenesis. High levels of VEGF in the plasma is a poor prognostic feature in several cancer types, and the blockade of the VEGF-VEGFR signalling pathway has demonstrated significant improvement of clinical outcomes in some cancers15 besides HCC8,9,10, including renal cell carcinoma (RCC) and colorectal cancer (CRC). Liver is the most common site of metastasis in CRC, with 25-50% of patients presenting with liver metastases at the time of diagnosis, and the addition of bevacizumab (VEGFi) to FOLFOX/CAPOX (5-fluorouracil (5-FU) or capecitabine in combination with oxaliplatin) or FOLFIRI/CAPIRI (5-FU or capecitabine in combination with irinotecan) has shown significant improvement in objective response rate (ORR) and survival in these patients. Whether this strategy is also effective in liver metastases in patients with other cancer types is unknown.

Condition being studied Stage IV solid organ malignancy with liver metastasis. Hepatocellular carcinoma was excluded.

METHODS

Search strategy Supplementary

Table 2. 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.

Participant or population Stage IV solid organ malignancy with liver metastasis. Hepatocellular carcinoma was excluded.

Intervention Backbone of systemic therapy (chemotherapy and/or immunotherapy and/or non-VEGFi targeted therapy) or best supportive care (BSC) with a VEGFi (tyrosine kinase inhibitors [TKI] [sunitinib, pazopanib, sorafenib, lenvatinib, vandetanib, regorafenib, cabozantinib, axitinib, cediranib, ponatinib, aflibercept, vatalanib, tivozanib, motesanib, linifanib, anlotinib, fruquintinib, nintedanib, apatinib] or monoclonal antibody [bevacizumab, ramucirumab, vanucizumab]).

Comparator Backbone of systemic therapy (chemotherapy and/or immunotherapy and/or non-VEGFi targeted therapy) or best supportive care without VEGFi.

Study designs to be included Published randomized clinical trial (RCTs) with reported progression-free survival (PFS) and/or overall survival (OS).

Eligibility criteria Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to April 30, 2023, based on the following criteria. Population, stage IV solid organ malignancy with liver metastasis. Hepatocellular carcinoma was excluded. Intervention, backbone of systemic therapy (chemotherapy and/or immunotherapy and/or non-VEGFi targeted therapy) or best supportive care (BSC) with a VEGFi (tyrosine kinase inhibitors [TKI] [sunitinib, pazopanib, sorafenib, lenvatinib, vandetanib, regorafenib, cabozantinib, axitinib, cediranib, ponatinib, aflibercept, vatalanib, tivozanib, motesanib, linifanib, anlotinib, fruquintinib, nintedanib, apatinib] or monoclonal antibody [bevacizumab, ramucirumab, vanucizumab]). Comparator, backbone of systemic therapy (chemotherapy and/or immunotherapy and/or non-VEGFi targeted therapy) or best supportive care without VEGFi. Outcome, progression-free survival (PFS) and/or overall survival (OS). Study design, published randomized clinical trial (RCTs).This meta-analysis followed the Preferred Reporting Items for PRISMA guidelines.

Information sources Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to April 30, 2023, based on the following criteria. We have included Published randomized clinical trials only.

Main outcome(s) The two primary outcomes of this study were the PFS and OS of the addition of VEGFi to a backbone of systemic therapy (chemotherapy and/or immunotherapy and/or non-VEGFi targeted therapy) or best supportive care, measured in terms of the PFS and/or OS differences compared with no VEGFi.

Additional outcome(s) PFS and/or OS in patients with vs without liver metastases.

Quality assessment / Risk of bias analysis We have used two main strategies to assess quality and to reduce the risk of bias.
1. We have included only "Published randomized clinical trial (RCTs)".
2. We have performed subgroup analyses considering the preplanned subgroups of patients: a) cancer type, “colorectal cancer” and “non-colorectal cancers”; b) backbone systemic therapy, “chemotherapy” and “non-chemotherapy”; c) VEGFi type, “bevacizumab” and “non-bevacizumab”; d) line of treatment, “first line” and “subsequent line”; e) liver metastases, “presence” and “absence”. Information extracted included: first author’s name, study name, journal and year of publication, study design, National Clinical Trials

(NCT) identification number, study phase, cancer type, number of patients, lines of treatment, study drugs and hazard ratios (HRs) with 95% CIs for OS and for PFS.

Strategy of data synthesis Selected studies are summarized including the total number of patients (patients with liver metastases) and the estimated effect (HR for PFS, OS or both). Pooled effects of the addition of VEGFi to standard therapy or BSC in patients with liver metastases across different cancer types were estimated using random effect model with inverse variance. Forest plots of pooled results were generated. All statistical analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing).

Subgroup analysis Preplanned subgroups of analysis included: a) cancer type, "colorectal cancer" and "non-colorectal cancers"; b) backbone systemic therapy, "chemotherapy" and "non-chemotherapy"; c) VEGFi type, "bevacizumab" and "non-bevacizumab"; d) line of treatment, "first line" and "subsequent line"; e) liver metastases, "presence" and "absence".

Sensitivity analysis Heterogeneity between studies was assessed by I2, a statistical metric that estimates the percentage of total variation across studies.
Subgroup analyses were performed considering the preplanned subgroups of patients as defined in the Outcomes subsection. Forest plots of pooled results were generated. All statistical analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing).

Language restriction English.

Country(ies) involved Australia.

Keywords Liver metastases, VEGF inhibitors, drug resistance.

Dissemination plans We are planning to publish this meta-analysis soon.

Contributions of each author
Author 1 - Jordan Conway - Conceived and designed the study. Extracted the data for the study. Analyzed the data. Wrote the manuscript. Revised the manuscript and approved the submission.
Author 2 - Jorja Braden - Conceived and designed the study. Extracted the data for the study. Analyzed the data. Wrote the manuscript. Revised the manuscript and approved the submission.
Author 3 - Serigne Lo - Analyzed the data. Revised the manuscript and approved the submission.
Author 4 - Richard Scolyer - Revised the manuscript and approved the submission.
Author 5 - Matteo Carlino - Revised the manuscript and approved the submission.
Author 6 - Alexander Menzies - Revised the manuscript and approved the submission.
Author 7 - Georgina Long - Conceived and designed the study. Wrote the manuscript. Revised the manuscript and approved the submission.
Author 8 - Ines Pires da Silva - Conceived and designed the study. Extracted the data for the study. Analyzed the data. Wrote the manuscript. Revised the manuscript and approved the submission.