

VEGF-A blockade overcomes liver metastases resistance to chemoimmunotherapy in patients with advanced non-squamous NSCLC

Matthieu Roulleaux-Dugage ^{1,2,3}, Andrey Yurchenko,⁴ Sergey Nikolaev,⁴ Barzin Nabet ⁵, Stéphanie Cognac ⁶, Céline Anquetil,⁶ Minu K Srivastava,⁷ Velimir Gayevskiy,^{7,8} Virginia McNally,⁹ Laura Mezquita ^{10,11}, Jean-Luc Perfettini,¹² Severine Mouraud,¹³ Christophe Massard,³ Benjamin Besse,¹⁴ Yohann Loriot,^{3,14} Aurelien Marabelle ^{3,13}, Nathalie Chaput,¹ Edouard Auclin²

To cite: Roulleaux-Dugage M, Yurchenko A, Nikolaev S, *et al.* VEGF-A blockade overcomes liver metastases resistance to chemoimmunotherapy in patients with advanced non-squamous NSCLC. *Journal for ImmunoTherapy of Cancer* 2026;**14**:e014991. doi:10.1136/jitc-2026-014991

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/jitc-2026-014991>).

MR-D and AY contributed equally.

Accepted 05 May 2026



© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to

Dr Edouard Auclin;
edouard.auclin@aphp.fr

ABSTRACT

Purpose Liver metastases (LMs) confer resistance to immune checkpoint blockade in advanced non-squamous non-small cell lung cancer (ns-NSCLC), likely through an immunosuppressive tumor microenvironment (TME). We hypothesized that vascular endothelial growth factor (VEGF)-A blockade, by remodeling the immunosuppressive TME, could restore the benefit of chemoimmunotherapy in LM+ patients. Here, we report the first comparative analysis of chemoimmunotherapy with and without bevacizumab specifically in this population.

Experimental design Data were analyzed from the phase III IMpower130 and IMpower150 trials in treatment-naïve, EGFR/ALK-wild-type patients with ns-NSCLC. Treatment arms included chemotherapy (CT), CT plus atezolizumab (CT+immunotherapy (IT)), CT plus bevacizumab (CT+antiangiogenic (AA)), and CT+IT+AA, with LM as a stratification factor. Survival outcomes were assessed by Kaplan-Meier estimates and multivariate Cox regression analyses. Bulk and single-cell RNA sequencing data were used to characterize the LM TME.

Results Among 1,713 patients, 236 (13.8%) presented with LMs. In IMpower130, LM+ patients derived no overall survival (OS) benefit from CT plus IT (CT+IT) compared with CT alone (HR for OS: 1.05; 95% CI 0.63 to 1.73). In contrast, in IMpower150, the addition of bevacizumab to CT+IT (CT+IT+AA) significantly improved progression-free survival (PFS; HR: 0.49) and OS (HR: 0.52) in LM+ patients—an effect not observed in patients without LM. Baseline transcriptomic exploratory analyses from IMpower150 revealed a myeloid-enriched, lymphocyte-depleted TME. Single-cell RNA sequencing further demonstrated VEGF-A/VEGFR-1/2 crosstalk between macrophages and endothelial cells, as well as an autocrine VEGF-A/VEGFR-1 loop within macrophages.

Conclusion The addition of bevacizumab to chemoimmunotherapy was associated with improved survival in ns-NSCLC specifically in patients with LMs. These hypothesis-generating findings suggest that the benefit may stem from disruption of VEGF-A-driven immunosuppressive signaling in the liver, but require prospective confirmation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Liver metastases (LMs) confer resistance to immune checkpoint blockade in advanced non-squamous non-small cell lung cancer (ns-NSCLC), but no strategy had been shown to overcome this resistance.

WHAT THIS STUDY ADDS

⇒ Adding bevacizumab to chemoimmunotherapy significantly improves survival in LM+ patients—an effect absent in LM− patients—alongside a myeloid-enriched, lymphocyte-depleted tumor microenvironment with prominent vascular endothelial growth factor-A signaling as a potential mechanism.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These hypothesis-generating findings suggest that chemotherapy+atezolizumab+bevacizumab may represent a relevant first-line option to consider in patients with LM+ ns-NSCLC, and that LM status warrants prospective evaluation as a candidate predictive biomarker in immunotherapy trials.

INTRODUCTION

The advent of immunotherapy (IT), particularly immune checkpoint blockers (ICBs), has revolutionized the treatment landscape for metastatic and advanced non-small cell lung cancer (aNSCLC). The combination of ICBs with chemotherapy (CT) has emerged as a standard of care for aNSCLC, regardless of programmed death-ligand 1 (PD-L1) expression levels,^{1–3} whereas anti-PD-(L)1 monotherapy can be considered for cancers with high PD-L1 expression.^{4–6}

The rationale for combining ICBs with anti-vascular endothelial growth factor (VEGF) agents, such as bevacizumab, lies in their

Table 1 Patients' baseline characteristics

	IMpower130				IMpower150			
	Whole sample n=675	LM- patients n=575	LM+ patients n=100	P value	Whole sample n=1038	LM- patients n=902	LM+ patients n=136	P value
Age—median (min–max)	64 (18–86)	64 (18–85)	64.1 (38–86)	0.923	63 (31–89)	63 (31–89)	62.8 (43–83)	0.744
≤65	359 (53.2%)	307 (53.4%)	52 (52%)		614 (59.2%)	533 (59.1%)	81 (59.6%)	
>65	316 (46.8%)	268 (46.6%)	48 (48%)		424 (40.8%)	369 (40.9%)	55 (40.4%)	
Sex				0.504				0.538
Female	277 (41%)	239 (41.6%)	38 (38%)		395 (38.1%)	340 (37.7%)	55 (40.4%)	
Male	398 (59%)	336 (58.4%)	62 (62%)		643 (61.9%)	562 (62.3%)	81 (59.6%)	
Smoking status				0.338				0.433
Current	144 (21.3%)	128 (22.3%)	16 (16%)		261 (25.1%)	222 (24.6%)	39 (28.7%)	
Previous	467 (69.2%)	392 (68.2%)	75 (75%)		625 (60.2%)	544 (60.3%)	81 (59.6%)	
Never	64 (9.5%)	55 (9.6%)	9 (9%)		152 (14.6%)	136 (15.1%)	16 (11.8%)	
Treatment				0.525				0.753
CT	228 (33.8%)	197 (34.3%)	31 (31%)		–	–	–	
CT+AA	–	–	–		336 (32.4%)	289 (32%)	47 (34.6%)	
CT+IT	447 (66.2%)	378 (65.7%)	69 (69%)		348 (33.5%)	306 (33.9%)	42 (30.9%)	
CT+IT+AA	–	–	–		354 (34.1%)	307 (34%)	47 (34.6%)	
ECOG performance status				0.308				0.263
0	277 (41.1%)	242 (42.2%)	35 (35%)		437 (42.3%)	386 (43%)	51 (37.8%)	
1	396 (58.8%)	331 (57.7%)	65 (65%)		595 (57.7%)	511 (57%)	84 (62.2%)	
Number of metastatic sites				<0.001				<0.001
≤3	512 (75.9%)	474 (82.4%)	38 (38%)		1001 (96.4%)	884 (98.0%)	117 (86.0%)	
>3	163 (24.1%)	101 (17.6%)	62 (62%)		27 (3.6%)	18 (2.0%)	19 (14.0%)	
Brain metastasis	67 (9.9%)	58 (10.1%)	9 (9%)	0.737	5 (0.5%)	4 (0.4%)	1 (0.7%)	0.505
Albumin—median (min–max)	38.6 (17.6–51)	38.8 (22.5–51)	37.6 (17.6–48)	0.026	38.7 (15–50)	38.8 (15–50)	38.2 (23–50)	0.274
Lung Immune Prognostic Index				0.011				0.001
Good	301 (49%)	270 (51.5%)	31 (34.4%)		474 (48.8%)	432 (51%)	42 (33.6%)	
Intermediate	234 (38.1%)	190 (36.3%)	44 (48.9%)		398 (40.9%)	331 (39.1%)	67 (53.6%)	
Poor	79 (12.9%)	64 (12.2%)	15 (16.7%)		100 (10.3%)	84 (9.9%)	16 (12.8%)	
KRAS mutation	79 (11.7%)	73 (12.7%)	6 (6%)	0.055	112 (10.8%)	94 (10.4%)	18 (13.2%)	0.324
PD-L1 TPS				0.201				0.078
<1%	451 (66.8%)	380 (66.1%)	71 (71%)		740 (71.3%)	632 (70.1%)	108 (79.4%)	
1–49%	131 (19.4%)	118 (20.5%)	13 (13%)		163 (15.7%)	147 (16.3%)	16 (11.8%)	
≥50%	93 (13.8%)	77 (13.4%)	16 (16%)		135 (13%)	123 (13.6%)	12 (8.8%)	

*All KRAS mutations are included in that subgroup, and not specifically KRAS G12C mutations.

AA, antiangiogenic; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IT, immunotherapy; LM, liver metastases; PD-L1, programmed death-ligand 1; TPS, Tumor proportion score.

complementary mechanisms of action. VEGF enhances tumor immunosuppression by promoting the recruitment, proliferation, and activation of regulatory T cells (Tregs), while hindering effector T cell (Teff) infiltration and antitumor activity.⁷ Bevacizumab, by blocking VEGF, can counteract these immunosuppressive effects and potentiate the efficacy of ICBs. The benefits of combining ICBs with anti-VEGF agents have been demonstrated in

various tumor types, including renal cell carcinomas, endometrial cancers or hepatocellular carcinoma.⁸ In the context of non-squamous advanced NSCLC (ns-aNSCLC) the IMpower150 trial showed that the addition of atezolizumab (an anti-PD-L1 antibody) to bevacizumab and CT significantly improves progression-free survival (PFS) and overall survival (OS) compared with CT and bevacizumab alone.² IMpower130 also demonstrated a benefit

of adding atezolizumab to CT in a similar cohort,⁹ while the effect of the addition of bevacizumab in this setting remains unclear.

Liver metastasis (LM), a common complication in aNSCLC, poses unique challenges due to its immunosuppressive microenvironment and has been constantly associated with little to no response to anti-PD-1 treatments in aNSCLC and other tumor types.¹⁰ Macrophage-mediated CD8+ T cell apoptosis,¹¹ increased Treg infiltration,¹² and elevated glycolysis are known to contribute to immune escape in LMs.¹³ Moreover, the distinct microvascular architecture of the liver, with liver sinusoidal endothelial cells promoting metastasis development, further complicates therapeutic efforts.¹⁴

To address these challenges and gain a deeper understanding of LM in ns-aNSCLC, we conducted a prespecified survival analysis in IMpower130 and IMpower150 trials to evaluate the prognostic and predictive value of LM in first-line treatment of ns-aNSCLC, and explored the relationship between LM's specific microenvironment and response to treatment.

METHODS

Trial designs and patients

IMpower130 and IMpower150 were two open-label, randomized phase III trials that evaluated chemoimmunotherapy combinations involving atezolizumab (anti-PDL-1) in CT-naïve adults with advanced ns-NSCLC (online supplemental figure 1). In both trials, the presence of LM was a stratification factor. In IMpower130, patients were randomized in a 2:1 proportion to CT plus atezolizumab or placebo. In IMpower150, patients were randomly assigned to CT or CT plus bevacizumab or CT plus bevacizumab plus atezolizumab in a 1:1:1 ratio. In both trials, eligible patients had Eastern Cooperative Oncology Group performance status 0 or 1 and any PD-L1 status. Both trials were positive and the addition of atezolizumab to first-line CT with or without bevacizumab for lung adenocarcinoma (LUAD) improves PFS and OS.^{2,9} Patients with *EGFR/ALK* genomic alterations were accepted in these trials but were excluded from this analysis due to the lack of efficiency of immunotherapeutic approaches in that population.

Statistical analysis

Data from the two studies were available on the VIVLI platform (<https://www.vivli.org>). Demographic and survival outcomes were summarized for the wild-type population (ie, patients with no known *EGFR/ALK* alterations). OS was calculated from the date of first treatment administration until death due to any cause. PFS was calculated from the date of first treatment administration until disease progression or death due to any cause.

Patient characteristics were compared using the χ^2 or Fisher's exact test for categorical variables and the unpaired t-test, Wilcoxon signed-rank test, or analysis of variance for continuous variables. Survival analysis

was performed using the Kaplan-Meier method and the log-rank test. All p values less than 0.05 were considered statistically significant.

A Cox proportional hazards regression model was used to evaluate factors independently associated with OS and PFS. Variables were included in the final multivariate model based on their clinical relevance and statistical significance in univariate analysis (cut-off, $p=0.10$). The predictive value of clinical features on survival benefit was assessed with an interaction term. A two-sided p value <0.05 was considered significant for interaction testing. Statistical analyses were performed with R software.

Analysis of bulk RNA-seq data

Whole-transcriptomes for IMpower150 originated from formalin-fixed paraffin-embedded (FFPE) tissue that was macrodissected for tumor area. RNA was extracted using the Qiagen miRNeasy FFPE kit. Libraries were generated using the Illumina TruSeq Stranded Total RNA method and sequenced on the Illumina NovaSeq 6000 (50bp paired-end sequencing and 80M total read depth). Reads were aligned to the human reference genome (NCBI Build 38) using GSNAP V.2013-10-10. The GenomicAlignments Bioconductor package was used to determine the number of reads mapped to the exons of each RefSeq gene (Ensembl 77). Raw counts were normalized for gene length using transcript-per-million (TPM) normalization and log2 transformed.

There are very few studies with publicly available RNA-seq from metastatic samples from the liver. We retrieved TPM values for LUAD tumors and associated clinical data from a recently published META-PRISM cohort from Institut Gustave Roussy.¹⁵ The final dataset of metastatic samples ($n=165$) included $n=19$ from LM, $n=95$ from lung metastasis, $n=14$ from lymph node metastasis, $n=10$ from pleura metastasis and $n=27$ from other more rare localizations (skin, adrenal gland, bones, breast, scapula, etc). TPMs of transcripts were additionally processed according to Zaitsev *et al* (2022) to reduce batch and RNA quality-related biases: mitochondrial, ribosomal and non-coding transcripts were removed, and TPM values were summed up by gene and then renormalized to 1M.

Unsupervised clustering of samples was performed based on $\log_2(\text{TPM}+1)$ values with Pearson correlation between samples and visualized with UMAP version realized in uwot R package (<https://github.com/jlmelville/uwot>).

Deconvolution of tumor microenvironment (TME) in metastatic samples was performed with CIBERSORTx algorithm ensuring deconvolution of the major cell types on two hierarchical levels: major cell types (epithelial, fibroblasts, immune, endothelial) and immune cells only (LM22 signature).¹⁶

Analysis of scRNA-seq dataset

We retrieved preprocessed single-cell RNA sequencing (scRNA-seq) counts and associated clinical information of the previously published dataset of primary and

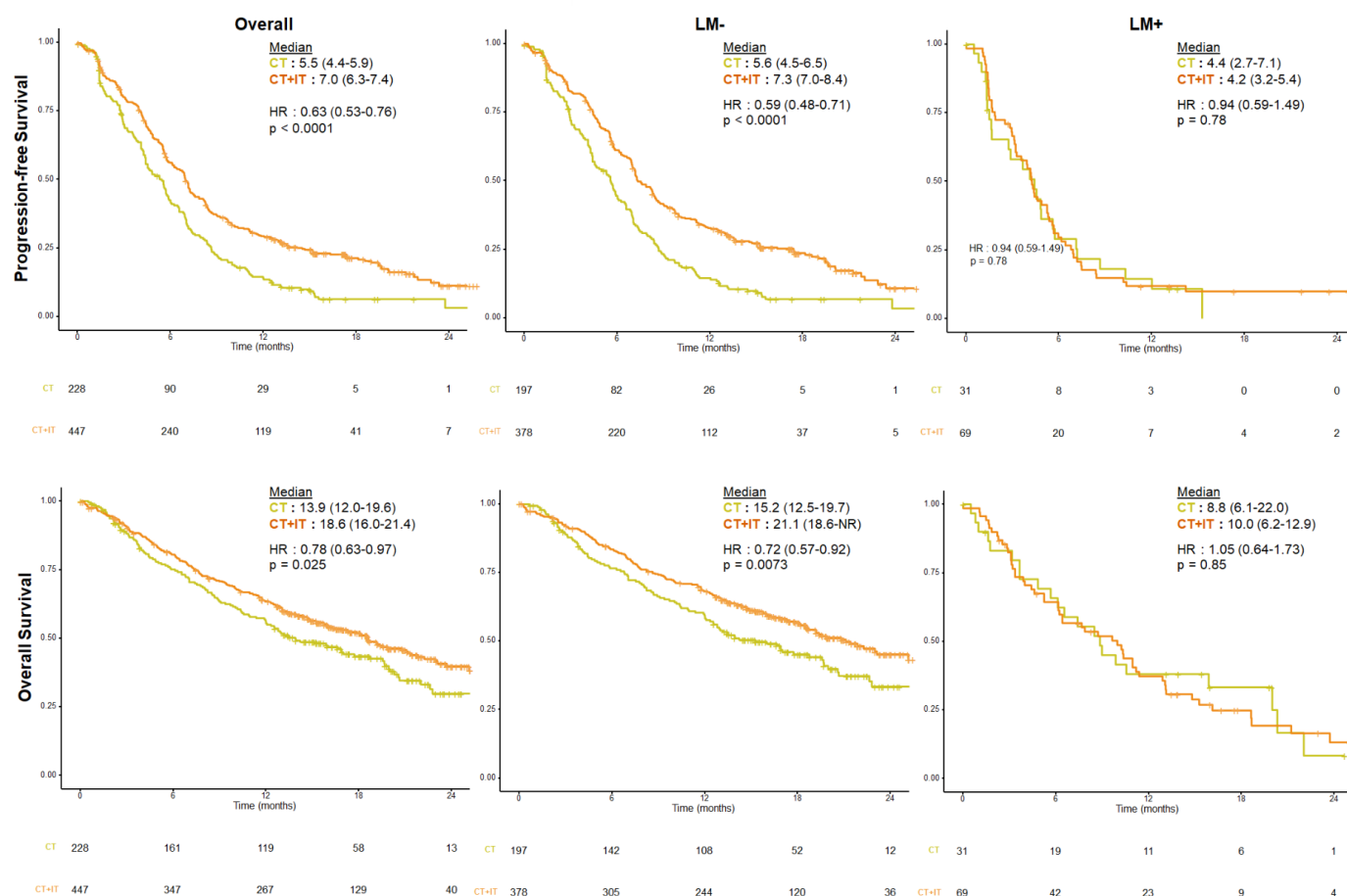


Figure 1 LMs are associated with no benefit from CT+IT over CT (IMpower130). CT, chemotherapy; IT, immunotherapy; LM, liver metastasis.

metastatic lung cancers¹⁷ sequenced using Smart-seq2 protocol from 3CA curated cancer cell atlas (<https://www.weizmann.ac.il/sites/3CA/>). We used only samples with at least 300 cells, diagnosed as LUAD and biopsied from liver/pleura/lymph node metastasis or primary tumors. The dataset was processed and analyzed with Seurat V.5.0.2 package. Individual samples were integrated with Harmony algorithm and then clustered (FindClusters(resolution=1)) using 50 Principal Component Analysis (PCA) components and finally visualized with Uniform Manifold Approximation and Projection (UMAP). Clusters of the cells were manually annotated using original annotation information from 3CA curated cancer cell atlas and with the assistance of the ACT server using the top 30 marker genes expressed by each cluster. Cell-cell communication (CCC) analysis was performed using CellChat software specifically for VEGFA axis based on the integrated and annotated Seurat object.

RESULTS

Liver metastases predict lack of survival benefit from adding immunotherapy to first-line chemotherapy (IMpower130 trial)

This study included 1,713 patients with previously untreated EGFR-wild-type or ALK-wild-type ns-NSCLC, enrolled in the IMpower130 (n=675) and IMpower150

(n=1038) clinical trials, in which the presence of LMs was both a stratification factor and part of a preplanned subgroup analysis. Baseline patient characteristics are described in table 1.

Baseline characteristics were largely comparable between IMpower130 and IMpower150, with the exception of brain metastases prevalence (9.9% vs 0.5%), tobacco use history, and number of metastatic sites (online supplemental table 1). Overall, 236 patients (13.8%) had LM+: 100 (14.8%) in IMpower130 and 136 (13.1%) in IMpower150. LM+ patients had a higher number of metastatic sites, lower plasma albumin levels, and a poorer Lung Immune Prognostic Index¹⁸ (online supplemental table 2). There were no major clinical differences between treatment groups, except that patients receiving CT alone had more metastatic sites, particularly in the central nervous system (online supplemental table 3). In the subset of patients for which whole exome sequencing was performed (n=476), the presence of LMs was not associated with *KEAP1* (LM-: 22.3% vs LM+: 28.0%, p=0.47) nor *STK11* mutations (LM-: 25.6% vs LM+: 26.0%, p=1.00). After a median follow-up of 16.6 months, the median OS was 17.1 months, and the median PFS was 6.9 months. Patients treated with CT alone had poorer outcomes compared with those receiving combination

therapies. The best outcomes were observed with CT plus IT and antiangiogenic (AA) therapy (CT+IT+AA), with a median PFS of 8.3 months and a median OS of 19.8 months (online supplemental table 3).

In IMpower130, 100 patients (14.8%) had LMs, of whom 31 and 69 received CT and CT+IT, respectively (table 1). compared with LM- patients, LM+ patients treated with CT had similar median PFS (4.4 vs 5.6 months, $p=0.21$) but significantly shorter OS (8.8 vs 15.2 months, $p=0.025$). This difference was more pronounced with CT+IT: LM+ patients had significantly shorter PFS (4.2 vs 7.3 months, $p<0.001$) and OS (10.0 vs 21.1 months, $p<0.001$). After adjustment for clinical covariates, LMs remained independently associated with poorer outcomes with CT+IT, but not with CT alone (online supplemental table 4).

Strikingly, LM+ patients derived no survival benefit from CT+IT compared with CT alone, with overlapping PFS (4.2 vs 4.4 months; $p=0.78$) and OS (10.0 vs 8.8 months; $p=0.85$). In contrast, LM- patients experienced significantly improved PFS and OS with CT+IT (figure 1). Overall, these findings suggest a differential impact of LMs on treatment efficacy with LMs associated with no benefit from IT.

Bevacizumab specifically synergizes with chemioimmunotherapy in patients with liver metastases (IMpower150 and pooled analysis)

In IMpower150, 136 patients (13.1%) had LMs, of whom 47 (34.6%), 42 (30.9%), and 47 (34.6%) received CT+AA, CT+IT, and CT+IT+AA, respectively (table 1). No benefit of CT+IT over CT+AA was observed in LM+ patients, confirming findings from IMpower130 (HR for PFS: 0.79, $p=0.31$; HR for OS: 0.91, $p=0.71$). Interestingly, and as previously suggested,¹⁹ LM had no detrimental impact on PFS or OS in patients treated with CT+IT+AA (HR for PFS: 0.91, $p=0.65$; HR for OS: 0.76, $p=0.29$), in contrast to those treated with CT+AA or CT+IT (online supplemental tables 5,6). These findings prompted us to investigate a potential synergy between AA and CT+IT specifically in LM+ patients. In IMpower150, the LM+ subgroup showed a survival benefit from CT+IT+AA over CT+IT (HR for PFS: 0.58, $p=0.03$; HR for OS: 0.50, $p=0.02$), an effect not observed in LM- patients (online supplemental figure 2).

We then analyzed the pooled cohort from both trials. In LM- patients, adding AA to CT+IT did not improve OS (19.9 vs 19.8 months, $p=0.94$; figure 2A). In contrast, among LM+ patients treated with CT+IT+AA, median PFS was 7.4 months—comparable to that of LM- patients treated with CT+IT (7.1 months, $p=0.84$). Similarly, median OS in LM+ patients receiving CT+IT+AA was 16.8 months, also comparable to that of LM- patients treated with CT+IT (19.8 months, $p=0.40$). CT+IT+AA was the only regimen to significantly improve both PFS and OS over CT alone in LM+ patients (HR for PFS: 0.49, $p=0.006$; HR for OS: 0.52, $p=0.03$; figure 2B). Notably, patients with LM were the only subgroup to derive an OS benefit from CT+IT+AA (figure 2C), with a trend for PFS ($p=0.10$). This interaction was not observed between

CT+AA or CT and CT+IT ($p=0.42$) (online supplemental figures 2,3), suggesting that AA may be particularly beneficial when added to CT+IT in patients with LMs. To rule out that baseline differences between trials could account for these findings, a multivariable analysis adjusting for the number of metastatic sites, age, smoking status, and brain metastasis status confirmed that the benefit of bevacizumab remained confined to LM+ patients (PFS: HR 0.59, 95% CI 0.38 to 0.91, $p=0.018$; OS: HR 0.50, 95% CI 0.29 to 0.87, $p=0.014$), with no benefit in LM- patients (PFS: HR 0.84, 95% CI 0.71 to 1.00, $p=0.050$; OS: HR 1.12, 95% CI 0.90 to 1.41, $p=0.301$). Comparable outcomes between the IMpower130 and IMpower150 control arms further argued against a differential effect driven by CT backbone alone (PFS log-rank $p=0.14$; OS log-rank $p=0.53$; online supplemental figure 4).

Altogether, these results suggest that bevacizumab may specifically help restore the efficacy of the addition of IT to CT in patients with LMs.

Liver metastases display a distinct TME with myeloid enrichment and lymphoid exclusion

In order to investigate potential mechanisms of the synergy between AA treatment and IT in the context of LMs we retrieved and performed an exploratory analysis of bulk RNA-seq from IMpower150 ($n=922$, including $n=36$ LMs). The analysis was validated by an independent cohort of bulk RNA-seq of advanced metastatic cancers META-PRISM¹⁵ (NSCLC cohort only, $n=165$, including $n=19$ LMs) and scRNA-seq data ($n=20$, including $n=4$ LMs) from a publicly available dataset¹⁶ of metastatic LUADs. A summary of all molecular datasets used in this study and the number of liver samples is provided in online supplemental table 7. Unfortunately, no paired primary-LM samples were available for comparison. Bulk RNA-seq of advanced metastatic lung cancers from IMpower150 and META-PRISM revealed a distinct grouping of 29/36 (81%) and 10/19 (53%) LM samples, respectively, based on gene expression profiles, while samples from other locations did not form specific groups, suggesting a particular transcriptional profile of LM samples (figure 3A, online supplemental figure 5A). Then we assessed the level of gene expression for the main gene targets of IT and AA therapies (*VEGFA-A/VEGFA*, *VEGFR-1/FLT1*, *VEGFR-2/KDR*, *PD-L1/CD274*) between LM and other metastatic sites. LMs demonstrated significantly higher expression of the *VEGFA* gene ($p=0.031$, Mann-Whitney U test, two-sided) in the META-PRISM cohort and the similar trend, although without statistical significance observed for IMpower150 ($p=0.092$, Mann-Whitney U test, two-sided; figure 3B, online supplemental figure 5B). The expression of *CD274* was not statistically different between the groups for both datasets (figure 3B, online supplemental figure 5B). Expression of *PDCD1*, encoding PD-1, was significantly lower in liver, than in other localizations ($p=1.1\text{e-}05$ and $p=2.7\text{e-}06$ for IMpower150 and META-PRISM respectively, Mann-Whitney U test, two-sided; online supplemental figure

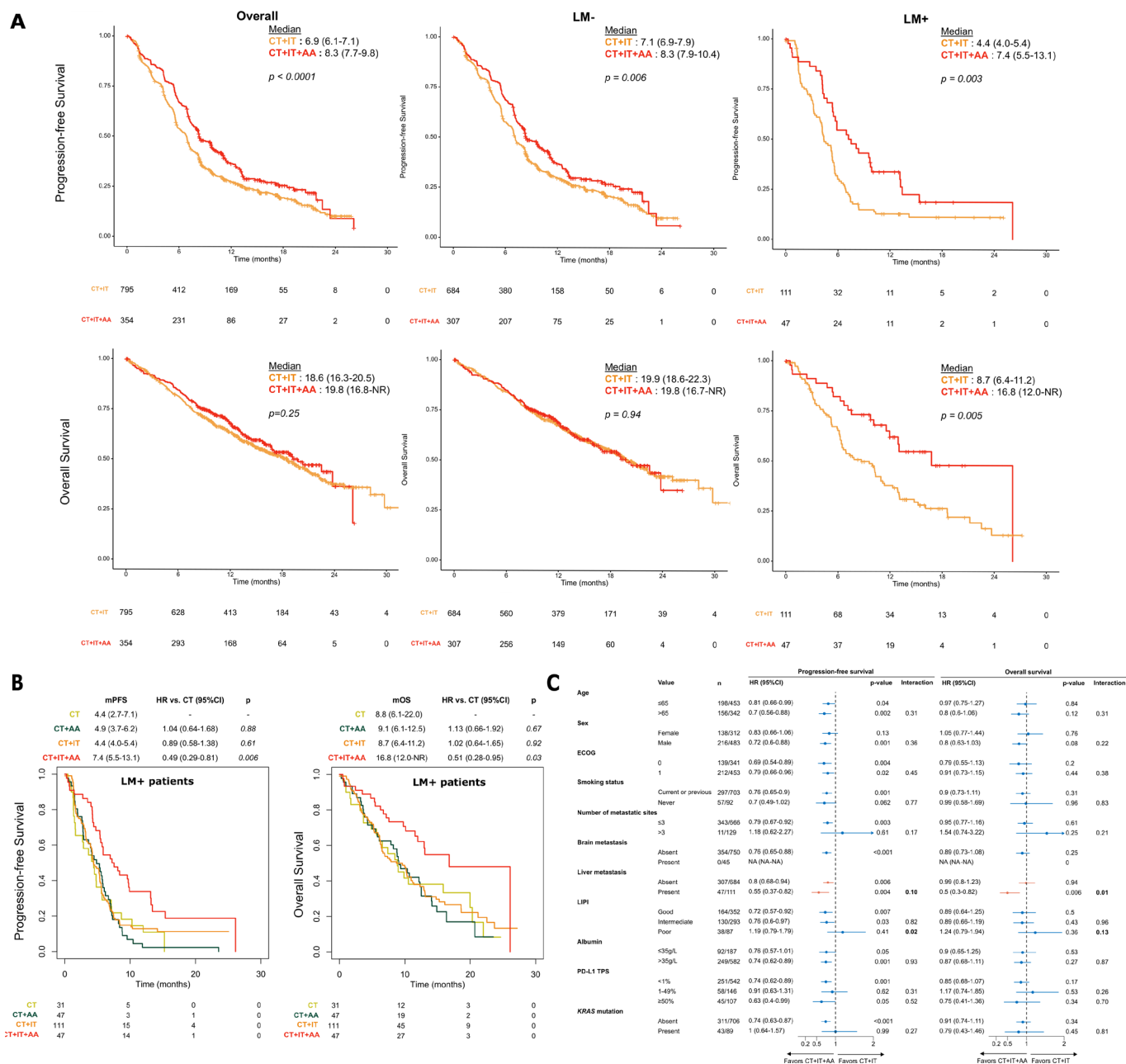
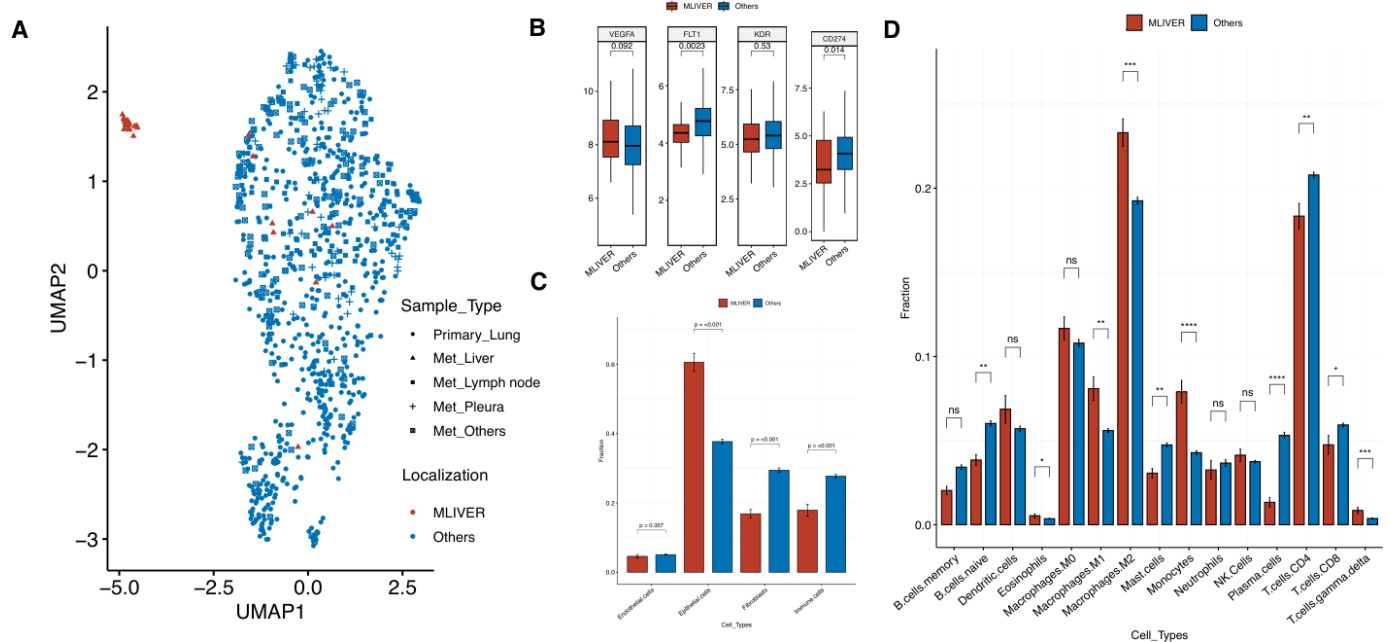


Figure 2 Bevacizumab specifically synergizes with chemoimmunotherapy in patients with liver metastases. (A) Kaplan-Meier curves of progression-free survival and overall survival in patients treated in IMpower150 with chemoimmunotherapy (CT+IT) with or without bevacizumab (CT+IT+AA), in the overall population and depending on the presence (LM+) or the absence (LM-) of liver metastases. (B) Pooled analysis of progression-free and overall survival depending on the first-line treatment regimen for LM+ patients treated in IMpower130 and IMpower150. (C) Pooled subgroup analysis of IMpower130 and IMpower150 comparing CT+IT with or without bevacizumab in different subgroups. AA, antiangiogenic; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IT, immunotherapy; LIPI, Lung Immune Prognostic Index; LM, liver metastasis; mOS, median overall survival; mPFS, median progression-free survival; PD-L1, programmed death-ligand 1; TPS, Tumor Proportion Score.

6A,B). Similarly, the expression of different lymphocyte markers was significantly downregulated in LM samples in both cohorts (online supplemental figure 6A,B). To better understand the interplay between gene expression and TME composition of LMs in aNSCLC samples we performed deconvolution of bulk RNA-seq data with CIBERSORTx. The analysis of bulk RNA-seq profiles revealed that the fractions of epithelial cancer cells were significantly enriched in LM in comparison with other

locations for both IMpower150 and META-PRISM cohorts while the immune and stromal cell fractions were significantly depleted (figure 3C, online supplemental figure 7A). Furthermore, we analyzed separately the immune compartment of LM and revealed that it was significantly enriched in myeloid cell types (Macrophages M1/M2 and Monocytes for IMpower150; Macrophages M0/M2 for META-PRISM) in comparison with other locations (figure 3D, online supplemental figure 7B). Interestingly,



the association between LMs and increased relative abundance of macrophages was independent from other clinical and biological alterations (*KRAS*, *STK11* and *KEAP1* mutations in particular—online supplemental table 8). Altogether, these results indicate that LMs exhibit a lymphocyte-depleted and myeloid-enriched immune microenvironment distinct from other metastatic sites.

Macrophages orchestrate specific VEGF-A autocrine and paracrine signaling in liver metastases

To better understand which specific cells can be the source of high *VEGFA* expression in LM, we reanalyzed available scRNA-seq dataset of LUAD with metastatic samples from the liver,¹⁶ selecting n=20 samples with at least 300 cells each. In total 15,156 cells were analyzed for metastatic sites in the liver (n=4), pleura (n=4) and lymph nodes (n=4) in addition to primary LUAD tumors (n=8). Individual samples were successfully integrated, clustered and annotated (figure 4A). Similarly to bulk RNA-seq data, LUAD scRNA-seq samples from LM demonstrated an elevated fraction of macrophages (online supplemental figure 8A). *VEGFA* gene was abundantly expressed in different types of myeloid cells, such as macrophages, mast cells and monocyte-derived dendritic cells (mo-DCs), but also

in malignant cells and fibroblasts (figure 4B) in primary and metastatic LUAD samples (online supplemental figure 8C). Both VEGF-A receptors (VEGFR-1/*FLT1* and VEGFR-2/*KDR*) were predominantly expressed in endothelial cells, with higher expression observed in those from LMs compared with other sites (online supplemental figure 8C). Interestingly, *FLT1* gene was also expressed by a significant fraction (40%) of macrophages (figure 4C). At the same time in 25% of macrophages coexpression of *VEGFA* and *FLT1* was observed implying a possible autocrine loop between VEGF-A and VEGFR-1 in this cell type (online supplemental figure 8D). To further investigate CCCs involving the *VEGFA* gene, we used CellChat software to infer significant CCC between various cell types in LMs and primary samples from scRNA-seq data. The analysis confirmed a significant *VEGFA*-*VEGFR1* autocrine loop in macrophages within both primary tumors and LMs (figure 4D–E). The most pronounced interactions occurred between cells secreting VEGFA—including mast cells, macrophages, malignant cells, and fibroblasts—and endothelial cells expressing the corresponding receptors VEGFR1, VEGFR2, and VEGFR1R2 (figure 4D–E). Notably, in primary tumors, a greater

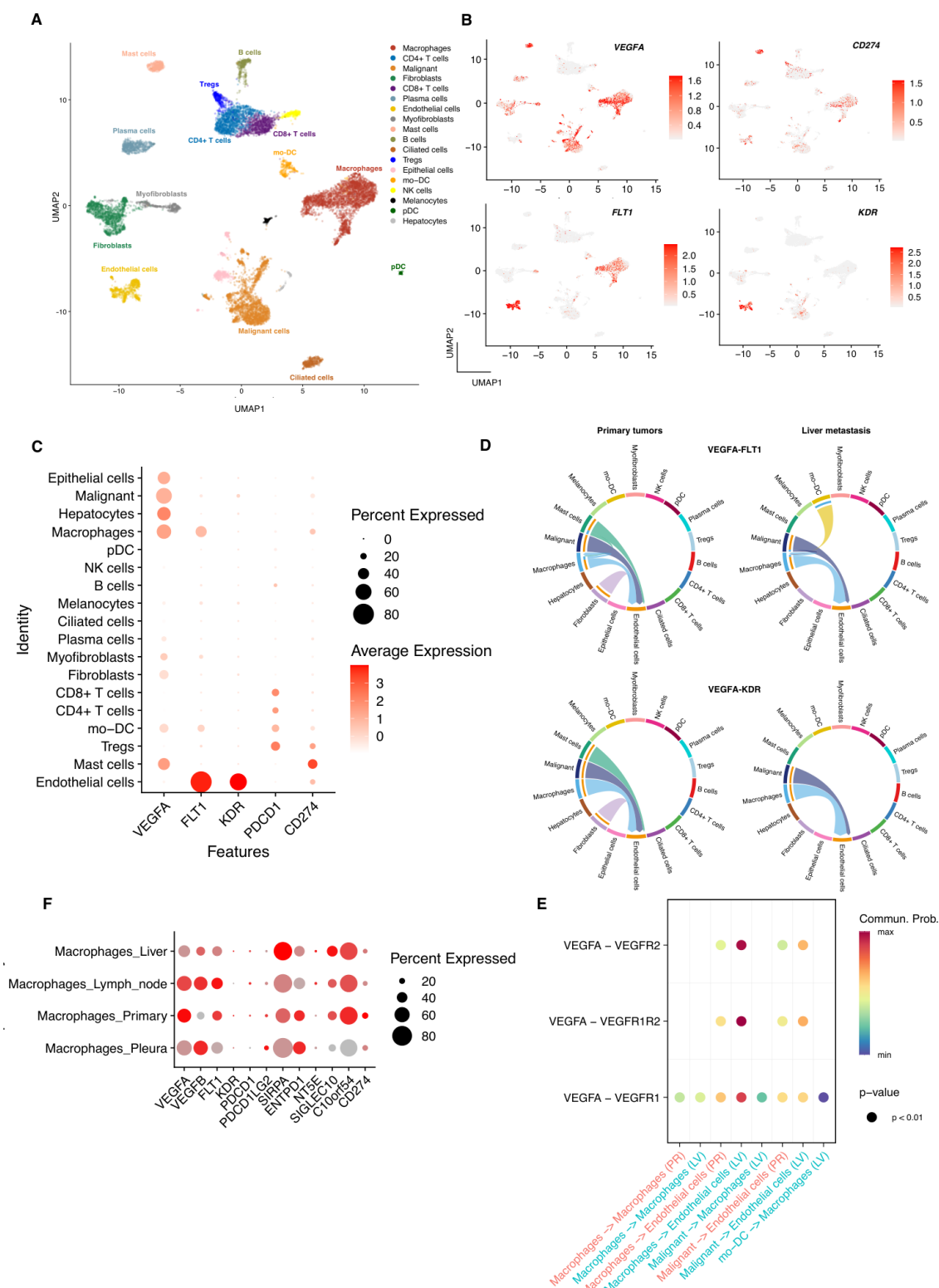


Figure 4 Macrophages orchestrate specific VEGF-A autocrine and paracrine signaling in liver metastases. (A) UMAP visualization of the annotated clusters of cells from scRNA-seq of metastatic and primary LUAD samples. (B) Expression of VEGFA, CD274, FLT1 and KDR genes in different clusters of scRNA-seq dataset. (C) Dotplot visualization of the average expression and the fractions of expressing cells for VEGFA, PDCD1, CD274, FLT1 and KDR genes in LUAD scRNA-seq dataset. (D) Significant cell-cell communications among primary and liver metastases samples inferred with CellChat software for VEGFA-FLT1 and VEGFA-KDR axis. (E) Significant ($p < 0.01$) communication probabilities between different cell types among primary tumors and liver metastases for VEGFA-involving pathways. (F) scRNA-seq-based gene expression of angiogenic and immune-inhibitory molecules in macrophages from different localizations of LUAD. LUAD, lung adenocarcinoma; Mo-DC, monocyte-derived dendritic cell; NK, natural killer; pDC, plasmacytoid dendritic cells; scRNA-seq, single-cell RNA sequencing; Tregs, regulatory T cells; UMAP, Uniform Manifold Approximation and Projection; VEGF, vascular endothelial growth factor.

diversity of cell types (mast cells, malignant cells, macrophages, and fibroblasts) communicated with endothelial cells expressing FLT1 and KDR receptors (figure 4D–E). In contrast, in LMs, there were more significant VEGFA-based interactions especially between macrophages and endothelial cells (figure 4D–E). We then investigated the cellular origin of expression of two main anti-PD(L)-1 targets: PD1/*PDCD1* and PD-L1/*CD274*. PD1/*PDCD1* was mostly expressed by CD8+T cells, CD4+T cells, Tregs and mo-DC cells (figure 4C; online supplemental figure 8B,C), whereas PD-L1/*CD274* was preferentially expressed by mast cells, Tregs and macrophages. We additionally assessed the gene expression of another set of immune checkpoint molecules in macrophages (figure 4F) and found that inhibitory molecules *SIRPA* (*SIRPα*), *ENTPD1* (*CD39*), *SIGLEC10* (*Siglec-10*) and *c10orf54* (*VISTA*) were strongly expressed by macrophages confirming their possible immune-suppressive role in LUAD TME (online supplemental figure 8D).

Overall, these findings indicate that macrophages in LMs may contribute to an immunosuppressive microenvironment and sustain a VEGF-A/VEGFR1-2 autocrine and paracrine signaling, potentially reinforcing immune evasion.

DISCUSSION

LMs are a major issue in patients treated with ICBs, where they have extensively been associated with poorer survival outcomes in various cancer types, including melanoma, colorectal cancer or NSCLC.^{11,20} We analyzed 1,713 treatment-naïve patients with ns-aNSCLC from the IMpower130 and IMpower150 phase III trials, where LMs were a stratification factor. We prospectively demonstrate that patients with LM appeared to derive no PFS or OS benefit from adding atezolizumab to CT, unlike those without LM. The benefit of adding bevacizumab to CT and atezolizumab was specific to LM+ patients, possibly due to a VEGF-A^{high}, myeloid-rich TME with poor lymphocyte infiltration and enhanced VEGF-A/VEGFR-1 crosstalk.

Our study is the first to assess the synergistic activity of AA agents and immune checkpoint inhibitors in patients with ns-aNSCLC with LMs, by directly comparing CT+IT+AA versus CT+IT. While a subgroup analysis of IMpower150 suggested no detrimental effect of LM with CT+IT+AA,¹⁹ it did not compare these two regimens. Here, we observe that CT+IT+AA was the only regimen associated with improvements in both PFS and OS over CT in LM+ patients. The relatively low prevalence of LMs (13.8%) and the asymmetric contribution of the two trials to the pooled analysis are acknowledged limitations; however, the prospective stratification by LM status in both trials and the consistent LM+ prevalence across treatment arms (13–15%) provide reassurance that these imbalances reflect trial design rather than differential selection bias.

Intriguingly, this synergy was not observed in the recently published LEAP-007 study evaluating pembrolizumab with or without lenvatinib (pan-VEGFR inhibitor) as a first-line treatment for *EGFR/ALK/ROS1*-unaltered NSCLC with a PD-L1 Tumor Proportion Score $\geq 1\%$.¹⁹ Key differences exist between the LEAP-007 cohort and our study: inclusion of both squamous and non-squamous histologies, PD-L1-based patient selection, and no stratification by LMs. In the Harmoni-6 trial, a numerically higher PFS benefit of ivonescimab (an anti-PD-1 and anti-VEGFA bispecific antibody) plus CT over tislelizumab plus CT was observed in LM+ patients (HR 0.53, 95% CI 0.26 to 1.08) as compared with LM- patients (HR 0.64, 95% CI 0.48 to 0.85), though the wide CI precludes firm conclusions in this subgroup²¹ and this trial investigated squamous cell carcinomas. More recently, a strong and similar effect was recently observed in the CAMPASS trial, in which benmelstobart (anti-PD-L1) combined with anlotinib (a multikinase inhibitor targeting VEGFR1/2/3) outperformed first-line pembrolizumab in PD-L1-positive NSCLC, with a more pronounced PFS benefit in LM+ patients (HR 0.29, 95% CI 0.11 to 0.71) than in LM- patients (HR 0.74, 95% CI 0.57 to 0.97; *p* for interaction=0.001).²² Eventually, a similar trend was observed in a phase II trial in microsatellite stable (MSS) colorectal cancer, where adding bevacizumab to anti-PD-1 and histone deacetylase (HDAC) inhibition appeared to reverse the negative prognostic impact of LM²³ raising the hypothesis of a potential tumor-agnostic effect that remains to be confirmed in dedicated prospective studies. These cross-trial observations should be interpreted with caution given the heterogeneity in trial designs, patient populations, and treatment regimens, and should be considered hypothesis-generating rather than conclusive.

Our translational results support the poor prognosis associated with LMs, but also aim to explore the observed clinical synergy between bevacizumab and atezolizumab when combined with CT. Bulk RNA sequencing data from IMpower150 and the META-PRISM cohort suggest that LMs have higher VEGF-A expression compared with other tumor sites. These data also indicate increased myeloid cell infiltration in LM, consistent with prior evidence that specific neutrophil subsets are enriched in LMs²⁴ and promote VEGF-A-dependent angiogenesis in hypoxic niches.²⁵ Using publicly available scRNA-seq data, we further suggest that endothelial cells in LM express higher levels of *Flt1* compared with those in other metastatic sites, enhancing VEGF-A/VEGFR1-2 crosstalk between macrophages and endothelial cells. Given VEGF-A's well-established role in impairing T cell trafficking via endothelial modulation,⁷ this enhanced VEGF-A/VEGFR1-2 interaction may contribute to the reduced CD8+ T cell infiltration observed in LMs. Bevacizumab may synergize with CT and atezolizumab by disrupting this crosstalk and promoting T cell infiltration into the tumor.

Eventually, our data imply that VEGF-A-secreting tumor-associated macrophages (TAMs) also express

VEGFR-1, suggesting an autocrine VEGF-A/VEGFR-1 loop that could promote their immunosuppressive and proangiogenic functions. This hypothesis is supported by converging evidence from multiple experimental models. In vitro, autocrine VEGF-A signaling in protumorous macrophages upregulates PD-L1 expression, and such macrophages suppress CD4⁺/CD8⁺ T cells in vivo.²⁶ The proangiogenic role of VEGFR1+TAMs has been further demonstrated across tumor models: FLT1 knockdown specifically inhibited macrophage infiltration in renal cell carcinoma,²⁷ while FLT1 blockade synergized with immune checkpoint inhibitors in melanoma by reducing protumorous macrophage infiltration and restoring CD8⁺ T cell density.²⁸ VEGF-A/VEGFR-1 signaling in metastasis-associated macrophages also drives expression of prometastatic factors MMP9 and CSF1, fueling angiogenesis and metastatic spread.²⁹ Beyond oncology, VEGFR1⁺ macrophages sustain neoangiogenesis in endometriosis,³⁰ and VEGF-A promotes macrophage recruitment and M2 polarization in other physiological contexts,³¹ underscoring the broader relevance of this signaling axis. Whether this autocrine loop specifically contributes to the immunosuppressive TME of LMs and can be disrupted by bevacizumab remains to be formally demonstrated.

Altogether, these hypothesis-generating findings suggest that, in patients with LMs from ns-aNSCLC, the addition of bevacizumab to chemoimmunotherapy warrants further evaluation as a potentially preferred first-line option. Mechanistically, this combination may contribute to reversing the immune desert of LMs by disrupting VEGF-A/VEGFR-1-2 signaling, both autocrine in TAMs and paracrine between TAMs and endothelial cells; targeting this macrophage-centered axis could plausibly restore vascular function and enable T cell infiltration, although these mechanisms remain to be formally validated. Looking ahead, our findings support two key directions for clinical translation. First, LMs should be prospectively incorporated as a stratification factor in future randomized phase III trials to more accurately evaluate treatment benefit in this high-risk subgroup. Second, organ-specific tumor-immune interactions warrant investigation in smaller translational studies, ideally including paired and longitudinal sampling of primary and metastatic lesions and especially LMs, to validate the biological mechanisms and inform tailored therapeutic strategies.

Author affiliations

¹Laboratoire d'Immunomonitoring, INSERM U1363, Gustave Roussy, Villejuif, France

²Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris, France

³Drug Development Department, Gustave Roussy, Villejuif, Paris

⁴Translational Cancer Genomics team, INSERM U981, Gustave Roussy, Villejuif, Île-de-France, France

⁵Computational Sciences Center of Excellence, Genentech, South San Francisco, California, USA

⁶INSERM UMR 1186, Integrative Tumour Immunology and Immunotherapy, Gustave Roussy, Villejuif, France

⁷Genentech, South San Francisco, California, USA

⁸Rancho BioSciences LLC, San Diego, California, USA

⁹Roche Products, Welwyn Garden City, UK

¹⁰Medical Oncology Department, Hospital Clinic de Barcelona, Barcelona, Spain

¹¹Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain

¹²INSERM U1363, Laboratory of Molecular Radiotherapy and Therapeutic Innovation, Gustave Roussy, Villejuif, France

¹³Laboratoire de Recherche Translationnelle en Immunothérapies (LRTI), INSERM U1015, Gustave Roussy, Villejuif, Île-de-France, France

¹⁴Medical Oncology Department, Gustave Roussy, Villejuif, Île-de-France, France

Acknowledgements This publication is based on research using data from data contributors (Roche) that has been made available through Vivli. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Contributors MRD: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Roles/Writing—original draft; and Writing—review and editing. Guarantor. AY: Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Visualization; Roles/Writing—original draft; and Writing—review and editing. SN: Investigation; Methodology; Resources; Software; Supervision; Validation; Writing—review and editing. MKS: Resources; Supervision; Writing—review and editing. BN: Resources; Supervision; Writing—review and editing. VG: Formal analysis; Investigation; Resources; Software; Visualization; Writing—review and editing. VMN: Resources; Supervision; Writing—review and editing. LM: Conceptualization; Project administration; Resources; Supervision; Validation; Writing—review and editing. J-LP: Supervision; Validation; Writing—review and editing. SM: Investigation; Writing—review and editing. CM: Supervision; Validation; Writing—review and editing. BB: Conceptualization; Resources; Supervision; Validation; Writing—review and editing. YL: Investigation; Methodology; Resources; Supervision; Validation; Writing—review and editing. AM: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review and editing. NC: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review and editing. EA: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Roles/Writing—original draft; Writing—review and editing and Overall Content Guarantor. AI was used to improve the quality of medical writing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MRD, AY, SN, JLP, SM, NC: No conflicts of interest to disclose. MKS, BN, VG, VM: Employees of Roche/Genentech. LM: Honoraria for lectures and educational activities from Bristol-Myers Squibb, AstraZeneca, Roche, Takeda, Janssen, Pfizer, MSD, and Radonova; Consulting and advisory roles for Roche, Takeda, Janssen, and MSD; Research grants from Inivata, AstraZeneca, and Gilead; Travel, accommodations, and expenses covered by Bristol-Myers Squibb, Roche, Takeda, AstraZeneca, and Janssen. BB: Research funding (to institution) from AstraZeneca, Pfizer, Eli Lilly, Onxeo, Bristol Myers Squibb, Inivata, AbbVie, Amgen, Blueprint Medicines, Celgene, GlaxoSmithKline, Sanofi, Takeda, Cristal Therapeutics, Daiichi Sankyo, Janssen, OSE Immunotherapeutics, BeiGene, Boehringer Ingelheim, Genentech/Roche, Tolerol Pharmaceuticals, 4D Pharma, Aptitude Health, and Cergentis, outside the submitted work. CM: Reports grants and personal fees from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Eli Lilly, MedImmune, MSD, Novartis, Pfizer, Roche, Sanofi, and Orion; Principal or subinvestigator of clinical trials sponsored by numerous companies including AbbVie, AstraZeneca, Bayer, BeiGene, BMS, Boehringer Ingelheim, Celgene, Daiichi Sankyo, GSK, Incyte, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda, and others. YL: Consulting or advisory roles for Janssen, Astellas Pharma, Roche, AstraZeneca, MSD Oncology, Seagen, Bristol Myers Squibb, Taiho Pharmaceutical, Loxo/Lilly, Pfizer/EMD Serono, Merck KGaA, Gilead Sciences; Research funding (to institution) from Janssen Oncology, MSD Oncology, AstraZeneca, Exelixis, Incyte, Pfizer, Sanofi, Seagen, Astellas Pharma, Gilead Sciences, Merck KGaA, Taiho Pharmaceutical, BMS, Roche, and Tyra Biosciences; Travel, accommodations, and expenses covered by Astellas Pharma, Janssen Oncology, Roche, MSD Oncology, AstraZeneca, and Seagen. AM: Stock and other ownership interests in Pegascy; Honoraria from Bristol-Myers Squibb, AstraZeneca, MedImmune, Oncovir, and Merieux; Consulting or advisory roles for multiple companies including Lytx Biopharma, Eisai, Pierre Fabre, Merck Serono, Novartis, Amgen, Pfizer, AstraZeneca, Sanofi, Roche, Boehringer Ingelheim, MSD, and others; Speakers' bureau for MSD, Bristol-Myers Squibb, AstraZeneca, and Roche; Research funding (to institution) from Mersu, Bristol-Myers Squibb, Boehringer Ingelheim, Transgene, and MSD; Patent on monoclonal antibodies against CD81 (Stanford University); Travel, accommodations, and expenses covered

by Bristol-Myers Squibb, MSD, Roche, and AstraZeneca; Other relationship with Pegascy. EA: Honoraria for lectures and educational activities from Sanofi-Genzyme; Consulting and advisory roles for Amgen and Sanofi.

Patient consent for publication Not applicable.

Ethics approval The IMpower130 and IMpower150 trials were approved by local institutional review boards and ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. The present work is a preplanned analysis of de-identified data accessed through the Vivli platform following approval of a research proposal. No additional consent was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <https://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Matthieu Rouleaux-Dugage <https://orcid.org/0000-0003-3192-2342>

Barzin Nabet <https://orcid.org/0000-0002-4824-3533>

Stéphanie Corgnac <https://orcid.org/0000-0002-3014-9178>

Laura Mezquita <https://orcid.org/0000-0003-0936-7338>

Aurelien Marabelle <https://orcid.org/0000-0002-5816-3019>

REFERENCES

- Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al*. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:2078–92.
- Socinski MA, Jotte RM, Cappuzzo F, *et al*. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018;378:2288–301.
- Paz-Ares L, Ciuleanu T-E, Cobo M, *et al*. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:198–211.
- Sezer A, Kilickap S, Gümüş M, *et al*. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet* 2021;397:592–604.
- Herbst RS, Giaccone G, de Marinis F, *et al*. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med* 2020;383:1328–39.
- Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;375:1823–33.
- Fukumura D, Kloepper J, Amoozgar Z, *et al*. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018;15:325–40.
- Kuo H-Y, Khan KA, Kerbel RS. Antiangiogenic-immune-checkpoint inhibitor combinations: lessons from phase III clinical trials. *Nat Rev Clin Oncol* 2024;21:468–82.
- West H, McCleod M, Hussein M, *et al*. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924–37.
- Tumeh PC, Hellmann MD, Hamid O, *et al*. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. *Cancer Immunol Res* 2017;5:417–24.
- Yu J, Green MD, Li S, *et al*. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med* 2021;27:152–64.
- Lee JC, Mehdizadeh S, Smith J, *et al*. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. *Sci Immunol* 2020;5:eaba0759.
- Kumagai S, Koyama S, Itahashi K, *et al*. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell* 2022;40:201–18.
- Yang M, Zhang C. The role of liver sinusoidal endothelial cells in cancer liver metastasis. *Am J Cancer Res* 2021;11:1845–60.
- Pradat Y, Viot J, Yurchenko AA, *et al*. Integrative Pan-Cancer Genomic and Transcriptomic Analyses of Refractory Metastatic Cancer. *Cancer Discov* 2023;13:1116–43.
- Wang Y-H, Hou H-A, Lin C-C, *et al*. A CIBERSORTx-based immune cell scoring system could independently predict the prognosis of patients with myelodysplastic syndromes. *Blood Adv* 2021;5:4535–48.
- Maynard A, McCoach CE, Rotow JK, *et al*. Therapy-Induced Evolution of Human Lung Cancer Revealed by Single-Cell RNA Sequencing. *Cell* 2020;182:1232–51.
- Mezquita L, Auclin E, Ferrara R, *et al*. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. *JAMA Oncol* 2018;4:351–7.
- Nogami N, Barlesi F, Socinski MA, *et al*. IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. *J Thorac Oncol* 2022;17:309–23.
- Tian B-W, Han C-L, Wang H-C, *et al*. Effect of liver metastasis on the efficacy of immune checkpoint inhibitors in cancer patients: a systemic review and meta-analysis. *Clin Exp Metastasis* 2023;40:255–87.
- Chen Z, Yang F, Jiang Z, *et al*. Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (HARMONI-6): a randomised, double-blind, phase 3 trial. *The Lancet* 2025;406:2078–88.
- Zhong H, Wang J, Yang R, *et al*. Benmelstobart plus anlotinib versus pembrolizumab as first-line treatment for PD-L1-positive, advanced non-small-cell lung cancer (CAMPASS): a blinded, randomised, controlled, phase 3 trial. *Lancet Oncol* 2026;27:419–31.
- Wang F, Jin Y, Wang M, *et al*. Combined anti-PD-1, HDAC inhibitor and anti-VEGF for MSS/pMMR colorectal cancer: a randomized phase 2 trial. *Nat Med* 2024;30:1035–43.
- Salcher S, Sturm G, Horvath L, *et al*. High-resolution single-cell atlas reveals diversity and plasticity of tissue-resident neutrophils in non-small cell lung cancer. *Cancer Cell* 2022;40:1503–20.
- Ng MSF, Kwok I, Tan L, *et al*. Deterministic reprogramming of neutrophils within tumors. *Science* 2024;383:ead6493.
- Lai Y-S, Wahyuningtyas R, Aui S-P, *et al*. Autocrine VEGF signalling on M2 macrophages regulates PD-L1 expression for immunomodulation of T cells. *J Cell Mol Med* 2019;23:1257–67.
- Li C, Liu B, Dai Z, *et al*. Knockdown of VEGF receptor-1 (VEGFR-1) impairs macrophage infiltration, angiogenesis and growth of clear cell renal cell carcinoma (CRCC). *Cancer Biology & Therapy* 2011;12:872–80.
- Lacal PM, Atzori MG, Ruffini F, *et al*. Targeting the vascular endothelial growth factor receptor-1 by the monoclonal antibody D16F7 to increase the activity of immune checkpoint inhibitors against cutaneous melanoma. *Pharmacol Res* 2020;159:104957.
- Celus W, Di Conza G, Oliveira AI, *et al*. Loss of Caveolin-1 in Metastasis-Associated Macrophages Drives Lung Metastatic Growth through Increased Angiogenesis. *Cell Rep* 2017;21:2842–54.
- Sekiguchi K, Ito Y, Hattori K, *et al*. VEGF Receptor 1-Expressing Macrophages Recruited from Bone Marrow Enhances Angiogenesis in Endometrial Tissues. *Sci Rep* 2019;9:7037.
- Wheeler KC, Jena MK, Pradhan BS, *et al*. VEGF may contribute to macrophage recruitment and M2 polarization in the decidua. *PLoS One* 2018;13:e0191040.