Organ-specific immune checkpoint inhibitor treatment in lung cancer: a systematic review and meta-analysis

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ABSTRACT

Objectives Based on the acknowledged organ-specific immune microenvironment, little is known regarding the efficacy of immunotherapy in patients with lung cancer according to metastatic sites. This meta-analysis aimed to explore the efficacy of immune checkpoint inhibitors (ICIs) vs chemotherapy in patients with lung cancer with liver metastases (LM) or brain metastases (BM).

Design Meta-analysis and systematic review.

Data sources We systematically searched in electronic databases (PubMed, EMBASE, Cochrane Library and Web of Science), up to 31 January 2022. We also reviewed the abstracts from major international conferences. Eligibility criteria were randomised controlled phase II or III trials reporting the overall survival (OS) or progression-free survival (PFS) of LM or BM subsets.

Data extraction and synthesis Hazard ratios (HRs) with 95% CIs for OS and PFS were extracted and aggregated using a random-effects model.

Results Twenty-four randomised controlled trials with available outcomes for patients with BMs or LMs were identified. A total of 1124 patients with BM and 2077 patients with LM were included in the analysis. The pooled OS HR of patients with LMs was 0.83 (95% CI 0.72 to 0.95), and that of patients without LM 0.73 (95% CI 0.69 to 0.79). LM was associated with less benefits from ICIs. In patients with BM treated with ICIs, the pooled OS HR compared with the control arms was 0.71 (95% CI 0.53 to 0.94). Subgroup analyses by histology suggested that only patients with non-small cell lung cancer (NSCLC) with BM could gain benefit from ICIs (HR 0.53, 95% CI 0.41 to 0.68). BM negatively influenced efficacy of immunotherapy in patients with small cell lung cancer.

Conclusions Our results showed immunotherapy demonstrated efficacy in patients with lung cancer with LM and BM, survival benefits dominantly favoured patients with NSCLC. Patients with lung cancer with LM obtained less benefits from ICIs than those without. Therefore, organ-specific immunotherapeutic approaches should be considered.

PROSERO registration number CRD42020212797.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis focuses on efficacy of immune checkpoint inhibitors (ICIs) in patients with lung cancer with different metastatic sites, including the largest number of prospective randomised trials.

⇒ Interaction test is employed to demonstrate metastatic site as a predictor in patient-administered ICIs.

⇒ Both small cell lung cancer and non-small cell lung cancer patients are enrolled.

⇒ Some trials are ongoing, with immature overall survival data right now.

INTRODUCTION

Lung cancer is a major public health problem worldwide, nearly one-quarter of cancer deaths are due to lung cancer in the USA1; while, it is estimated to cause 815,693 new cases of lung cancer, and 714,699 deaths in China in 2020.2 Approximately, one-third to two-thirds of patients are diagnosed with advanced disease.3 4 A population-based study of metastatic sites including 9830 advanced lung cancer patients showed that liver metastasis (LM) and brain metastasis (BM) represented the most frequent metastatic sites at diagnosis (20% and 39%, respectively).5 Another report from the Surveillance, Epidemiology and End Results database collected patients’ records from 2010 to 2014, including 54,697 metastatic patients with lung cancer, 5677 (10.4%) and 10945 (20.0%) patients with isolated LM and BM, respectively. Five-year cancer-specific survival (CSS) rates and median CSS in patients with BM and LM are 5.9% and 2.2%, 8.2 months and 5.5 months, respectively.6 In the era of chemotherapy, prognosis of patients with lung cancer with BM or LM is dismal.

Tumour cells can induce immune tolerance via engagement of inhibitory immune checkpoints, such as programmed cell death protein-1 (PD-1) or its ligand (PD-L1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), leading to the escape from tumor-specific T-cell responses. Immune checkpoint inhibitors (ICIs), which block coinhibitory molecules, have been developed to stimulate cancer-specific immune response, in another
word, to unleash T-cell responses to eliminate tumour cells. ICIs represent a major breakthrough in the field of oncology. The first prospective clinical trial of ICI in non-small cell lung cancer (NSCLC) demonstrated a 5-year overall survival (OS) rate of 23.2% for treatment-naive patients and 29.6% for patients with PD-L1 of at least 50%. For extensive stage small cell lung cancer (ES-SCLC), first-line PD-L1 inhibitors combined with etoposide and carboplatin first improved OS compared with chemotherapy alone over three decades. The success of the IMpower 133 trial showed the first reddening of the dawn for the treatment of ES-SCLC. The NCCN guidelines recommended regimens with ICIs for negative for actionable molecular markers as a priority for both NSCLC and SCLC. However, currently guidelines suggest with ICIs as the first-line treatment for lung cancer irrespective of the metastatic sites. The pooled analysis of CheckMate 017 and 057 showed that ICI could improve the survival of previously treated patients with NSCLC with LM as well as non-LM comparator. In OAK study, atezolizumab failed to improve OS for patients with NSCLC with supratentorial metastases. The Keynote189 study demonstrated that chemotherapy combined with pembrolizumab significantly improved progression-free survival (PFS) and OS for non-squamous patients with NSCLC with LM or stable BM or versus pemetrexed and platinum as first-line treatment. Conflicting evidence varies from trial to trial, power is constrained by differences in study design and the small proportion of enrollment in each trial. There is an urgent need for an in-depth understanding of organ-specific treatments. Thus, the present study gathering latest evidence aimed to explore the efficacy of ICIs versus chemotherapy for patients with lung cancer with BM or LM and the impact of metastatic sites on the efficacy of ICIs.

METHODS
This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO). We followed the guideline of Preferred Items for Systematic Reviews and Meta-analysis guidelines. Two investigators (S-Y and S-Y) independently reviewed the list of retrieved articles to choose potentially relevant articles, extracted data and assessed the included trials’ risk of bias. Disagreements were solved by consensus or by a third party (Y W).

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data sources and searches
A comprehensive literature search was conducted using PubMed, EMBASE, Cochrane Library, Web of Science to identify all relevant articles from the inception of each database up to January 31, 2022. In addition, we reviewed the abstracts from all the major conference proceedings, including the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Conference on Lung Cancer (WCLC) from 2016 to 2021. The search was extended by review of references of articles. Our search strategy included the following terms: “lung cancer”, “non-small cell lung cancer”, “small cell lung cancer”, “PD-1”, “PD-L1”, “CTLA-4”, “brain”, “cerebral”, “liver”, “hepatic”. The complete strategy is presented in online supplemental table 1.

Selection of studies
The inclusion criteria as follows: (1) patients with histo-logically confirmed NSCLC or SCLC; (2) phase II and III randomised controlled trials (RCTs) investigating the regimens containing ICIs vs chemotherapy; (3) subgroup analysis for PFS or OS using a HR of patients with baseline brain metastasis (BM) or liver metastasis (LM). Post-hoc analyses of RCT were considered eligible.

Data extraction
S-Y and S-Y independently extracted data using standardised data extraction sheets: trial name if applicable; National Clinical Trial (NCT) number, phase, corresponding author, year; study randomisation, blinding, age, sex, number of participants, patients with BM, patients with LM, HR for OS and PFS, and HR for OS and PFS based on subgroups of interest. When multiple publications for the same study, we selected the latest or most complete publication publication dealing with the primary endpoints in the review as a study identifier.

Measures of treatment effect
The primary outcomes were OS and PFS of patients with LM or BM, and the secondary outcome was heterogeneity in the efficacy of ICIs according to metastatic sites. The exploratory outcome was safety. For time to event outcomes OS and PFS, we performed a meta-analysis using HRs to measure treatment effects, since they summarised the treatment effect for the entire study duration rather than reflecting one point on the Kaplan-Meier curve. If the data were insufficient, the results were described narratively. OS was defined as the time from randomisation to death from any cause. PFS was defined as the time from randomisation to cancer progression or death from any cause, whichever occurred first. Heterogeneity was measured in terms of the ratio of the HR for death in the intervention arm compared with those in the control arm reported in LM or BM to the same HR reported in non-LM or non-BM). A pooled HRs ratio estimate lower than one indicated a greater treatment effect in patients with BM or LM, and a value higher than one indicated a greater effect in comparators.

Risk of bias
We used the Cochrane risk of bias assessment to explore sources of bias in the included randomised
analyses of multicentre, prospective, randomised clinical trials. Sixteen RCTs investigated PD-1 inhibitors, eight studies investigated PD-L1 inhibitors, two investigated ICIs combined with vascular endothelial growth factor (VEGF) inhibitors, one investigated CTLA-4 inhibitors and two investigated PD-1 inhibitors plus CTLA-4 inhibitor. Sixteen involving trials were open label, and eight studies were double blind. The characteristics of each trial are shown in table 1.

**Qualities assessment**

Follow-up ranged from 8.6 months to 59.9 months. The results of the quality assessment are shown in figure 2. The investigators judged 16 open-label trials to be "high risk" in blinding of participants and personnel. However, the blinding of outcome assessment was considered low risk if the data were overlooked by an independent data and safety monitoring committee. Three of the four trials with investigator assessed PFS as the primary outcome were considered low risk since they demonstrated the high concordance of investigator-assessed PFS with assessment of blinded independent central review, except that the IMpower 132 trial failed to provide the information. CheckMate331, employing investigator-assessed PFS as an outcome, was considered "unclear risk" (only wild-type populations from the IMpower130 and IMpower150 cohorts were included in this study to minimise the heterogeneity). One post hoc analysis and one pooled analysis were awarded eight stars.

**Survival of LM**

Thirteen reports provided data on PFS of 1215 patients with LM, 13 studies of 1888 participants had OS outcomes. The pooled HRs of the individual studies based on the random-effect models are shown in figure 3A and B. ICIs could significantly improve PFS (HR 0.70, 95% CI 0.59 to 0.82; I²=37.03%, p=0.09). There was evidence of a difference in OS-favouring ICIs (HR 0.83, 95% CI 0.72 to 0.95, p=0.01; I²=46.08%). For patients with non-LM, ICIs statistically significantly improved PFS (HR 0.59, 95% CI 0.54 to 0.64; I²=32%, p=0.13, figure 3C). Furthermore, ICIs could decrease 27% risk of death for patients without LM (p<0.01), without showing heterogeneity (I²=0.0%, figure 3D).

**Survival of BM**

A meta-analysis of 10 RCTs including 635 patients with BM demonstrated that regimens containing ICIs improved PFS (HR 0.53, 95% CI 0.40 to 0.69, p<0.01; I²=43.76%, p=0.07) versus chemotherapy alone. In a meta-analysis based on the results of 963 patients from 13 clinical trials, OS was significantly improved for administered ICIs (HR 0.71, 95% CI 0.53 to 0.94, p=0.02), with substantial heterogeneity (I²=65.05%, p=0.01) (figure 4A,B). In patients without BM, the HR for OS and PFS of the individual studies and the combined results based on the random-effects model are shown in figure 4C,D. ICIs accounted for OS and PFS benefit compared to chemotherapy.
for a 41% decreased risk of disease progression (95% CI 0.52 to 0.68, p<0.01; I²=61.02%) and a 26% decreased risk of death (95% CI 0.67 to 0.81, p<0.01; I²=58.49%), with heterogeneity among single study.

**INTERACTIONS OF OS-HRS**

Thirteen studies reported that the HRs in patients with BM and non-BM. The pooled ratio of OS-HRs reported in patients with BM versus those reported in the non-BM in each trial was 0.96 (95% CI 0.97 to 1.19, I²=37%). However, the pooled ratio of the OS-HR interaction was 0.77 (95% CI 0.60 to 0.98) for NSCLC and 1.27 (95% CI 0.97 to 1.68) for SCLC, indicating that for patients with SCLC and with BM did not respond to ICIs.

Eleven studies reported HR in patients with LM and non-LM. The pooled ratio of OS-HRs reported in LMs versus non-LMs in each trial was 1.17 (95% CI 1.01 to 1.37), with no evidence of heterogeneity, indicating a statistically significant larger benefit in patients with non-LM (online supplemental figure 1).

**Subgroup analysis**

The sensitivity analysis is shown in online supplemental figure 2. We only considered subgroups that included no less than two studies. Owing to the evidence of differences in individual studies exist, subgroup analyses according to histology were conducted. Neither did ICIs improve PFS (pooled HR 1.03, 95% CI 0.66 to 1.61) nor OS (pooled HR 1.08, 95% CI 0.80 to 1.46) in patients with SCLC with BM; however, ICIs could decrease the risk of disease progression by 56% and the risk of death by 47% in NSCLC (p<0.01, online supplemental figure 3). PD-1 inhibitor plus CTLA-4 inhibitor would decrease the risk of death by 49% for patients with NSCLC with BM (p<0.01). In the subset of LM, significant decreases in the risk of progression (HR 0.65, 95% CI 0.53 to 0.79) and risk of death (HR 0.79, 95% CI 0.66 to 0.94) were observed.
Table 1  Characteristics of studies

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Patients /number</th>
<th>Intervention arm</th>
<th>Control arm</th>
<th>PFS</th>
<th>Baseline BM</th>
<th>Baseline LM</th>
</tr>
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<tbody>
<tr>
<td>CA184-156</td>
<td>2016</td>
<td>Germany</td>
<td>Double-blind, ES-SCLC/ 954</td>
<td>Etoposide+platinum + ipilimumab</td>
<td>Etoposide+platinum</td>
<td>Treatment arm: 4.6 m; control arm: 4.4 m</td>
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<tr>
<td>Keynote 024</td>
<td>2016</td>
<td>Germany</td>
<td>Open-label, PD-L1 ≥ 50% NSCLC/305</td>
<td>Pembrolizumab</td>
<td>Platinum-based chemotherapy</td>
<td>Treatment arm: 7.7 m; control arm: 5.5 m</td>
<td>28</td>
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<tr>
<td>IMpower 133</td>
<td>2018</td>
<td>USA</td>
<td>Double-blind, ES-SCLC/403</td>
<td>Carboplatin+etoposide + atezolizumab</td>
<td>Carboplatin and etoposide</td>
<td>Treatment arm: 5.2 m; control arm: 4.3 m</td>
<td>35</td>
<td>149</td>
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<td>IMpower 150</td>
<td>2019</td>
<td>USA</td>
<td>Open-label, NSCLC/1202</td>
<td>Atezolizumab+bevacizumab + carboplatin+paclitaxel</td>
<td>Bevacizumab+carboplatin + paclitaxel</td>
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<td>109</td>
<td></td>
<td></td>
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<td>CheckMate 017 &amp; 057</td>
<td>2019</td>
<td>USA</td>
<td>Open-label, Treated NSCLC/854</td>
<td>Nivolumab</td>
<td>Docetaxel</td>
<td>Treatment arm: 2.56 m; control arm: 3.52 m</td>
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<td>IMpower 130</td>
<td>2019</td>
<td>Italy</td>
<td>Open-label, Wild-type non-squamous NSCLC/679</td>
<td>Atezolizumab+carboplatin + nab-paclitaxel</td>
<td>Carboplatin+nab-paclitaxel</td>
<td>Treatment arm: 7.0 m; control arm: 5.5 m</td>
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<tr>
<td>OAK</td>
<td>2019</td>
<td>USA</td>
<td>Open-label, Treated NSCLC/850</td>
<td>Atezolizumab</td>
<td>Docetaxel</td>
<td>Treatment arm: 2.8 m; control arm: 4.0 m</td>
<td>123</td>
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<tr>
<td>Keynote 189</td>
<td>2020</td>
<td>USA</td>
<td>Double-blind, Non-squamous NSCLC/616</td>
<td>Pembrolizumab+pemetrexed+ cisplatin/carboplatin</td>
<td>Pemetrexed+cisplatin/ carboplatin</td>
<td>Treatment arm: 9.0 m; control arm: 4.9 m</td>
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<td>115</td>
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<td>CameL</td>
<td>2020</td>
<td>China</td>
<td>Non-squamous NSCLC/412</td>
<td>Camrelizumab+carboplatin + pemetrexed</td>
<td>Carboplatin and pemetrexed</td>
<td>Treatment arm: 11.3 m; control arm: 8.3 m</td>
<td>17</td>
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<tr>
<td>Keynote 604</td>
<td>2020</td>
<td>USA</td>
<td>Double-blind, ES-SCLC/663</td>
<td>Pembrolizumab +etoposide and platinum (cisplatin or carboplatin)</td>
<td>etoposide and platinum (cisplatin or carboplatin)</td>
<td>Treatment arm: 4.5 m; control arm: 4.3 m</td>
<td>54</td>
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<td>IMpower 132</td>
<td>2020</td>
<td>Japan</td>
<td>Open-label, Non-squamous NSCLC/ 578</td>
<td>Atezolizumab+pemetrexed + carboplatin</td>
<td>Pemetrexed+carboplatin</td>
<td>Treatment arm: 7.6 m; control arm: 5.2 m</td>
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</tr>
<tr>
<td>IMpower 131</td>
<td>2020</td>
<td>USA</td>
<td>Open-label, Squamous NSCLC /1021</td>
<td>Atezolizumab+carboplatin + nab-paclitaxel</td>
<td>Carboplatin +nab-paclitaxel</td>
<td>Atezolizumab+CnP:6.3 m; CnP: 5.7 m</td>
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<tr>
<td>ORITENT-11</td>
<td>2020</td>
<td>China</td>
<td>Double-blind, Non-squamous NSCLC/ 397</td>
<td>Pemetrexed+platinum + sintilimab</td>
<td>Pemetrexed+cisplatin/ carboplatin</td>
<td>Treatment arm: 9.2 m; control arm: 5.0 m</td>
<td>58</td>
<td>NA</td>
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<td>CASPIAN</td>
<td>2021</td>
<td>Spain</td>
<td>Open-label, ES-SCLC/805</td>
<td>etoposide and platinum (cisplatin or carboplatin)+durvalumab</td>
<td>etoposide and platinum (cisplatin or carboplatin)</td>
<td>Treatment arm: 5.1 m; control arm: 5.4 m</td>
<td>55</td>
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<td>Checkmate 9LA</td>
<td>2021</td>
<td>Spain</td>
<td>Open-label, NSCLC/ 719</td>
<td>Nivolumab+ipilimumab+ platinum doublet</td>
<td>Histology-based, platinum doublet</td>
<td>Treatment arm: 6.7 m; control arm: 5.0 m</td>
<td>122</td>
<td>154</td>
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<td>CheckMate 227</td>
<td>2021</td>
<td>Spain</td>
<td>Open-label, NSCLC/ 1739</td>
<td>Nivolumab+ipilimumab</td>
<td>Chemotherapy</td>
<td>Treatment arm: 5.1 m; control: 5.6 m</td>
<td>81</td>
<td>156</td>
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<tr>
<td>RATIONALE 307</td>
<td>2021</td>
<td>China</td>
<td>Open-label, sqNSCLC/355</td>
<td>Tislelizumab+paclitaxel and carboplatin</td>
<td>Paclitaxel and carboplatin</td>
<td>Treatment arm: 7.6 m; control: 5.5 m</td>
<td>29</td>
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<td>RATIONALE 304</td>
<td>2021</td>
<td>China</td>
<td>Open-label, nsq-NSCLC/ 332</td>
<td>Tislelizumab+platinum and pemetrexed</td>
<td>Platinum (carboplatin or cisplatin) and pemetrexed</td>
<td>Treatment arm: 9.7 m; control: 7.6 m</td>
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<td>EMPOWER -Lung 1</td>
<td>2021</td>
<td>Turkey</td>
<td>Open-label, PD-L1≥50%, NSCLC/ 563</td>
<td>Cemiplimab</td>
<td>Platinum-doublet chemotherapy</td>
<td>Treatment arm: 8.2 m; control: 5.7 m</td>
<td>68</td>
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Continued
and moderate heterogeneity occurred when pooling PFS-HR and OS-HR from studies of NSCLC ($I^2=36.05\%$; $I^2=43.27\%$; online supplemental figure 4). No survival benefit was observed in patients with SCLC with LM ($I^2=51.34\%$), however, a meta-analysis of three RCTs including 548 patients with LM yielded a statistically significant improvement in OS for patients who received first-line ICIs as compared with chemotherapy (pooled HR 0.81, 95% CI 0.68 to 0.98; $p=0.03$), with no heterogeneity ($I^2=0\%$). Two RCTs reported PFS for patients with SCLC with LM, and there was no difference between ICIs and chemotherapy (pooled HR 0.86, 95% CI 0.68 to 1.07, $p=0.168$). ICIs combined with anti-angiogenesis could improve PFS in patients with NSCLC with LM (HR 0.44, 95% CI 0.30 to 0.64), PD-1 combined with CTLA-4 was not associated with longer OS (HR 0.79, $p=0.13$).

**Safety analysis**

Only the OAK studies reported a safety analysis of patients with BM treated with atezolizumab versus docetaxel. The highest incidence of treatment-related neurologic adverse event (AE) was headache for patients treated with atezolizumab. All neurologic AEs were numerically higher in atezolizumab arm (45.0% vs 34.5%), although treatment-related neurologic AE was higher incidence in docetaxel arm (27.3% vs 18.3%). Grade 3 treatment-related neurologic AEs were higher in the atezolizumab arm, and the incidence was low in each arm. The CheckMate 017 and 057 separately analysed treatment-related adverse events in patients with LM and found that rates in treatment-related AEs for patients with LM were generally similar to those in the nivolumab group, except for slight increase in live enzyme elevations and renal events.

**Publication bias**

The funnel plot of publication bias of PFS-HR and OS-HR by metastatic sites is shown in online supplemental figure 5. The funnel plots revealed no significant asymmetry. Results of Egger's and Begg's tests are shown in online supplemental table 2.

**DISCUSSION**

To the best of our knowledge, this meta-analysis gathered the largest number of RCTs to investigate organ-specific immunotherapy. Our results were well designed and comprehensively synthesised to provide evidence for patients with lung cancer with traditionally unfavourable prognostic factors of LM or BM. For patients with lung cancer with or without LM or BM, ICIs could significantly prolong the PFS and OS. In addition, the interaction test revealed that LM negatively affected ICI efficacy.

A previous study conducted by Yang et al suggested that patients with NSCLC obtained benefits from ICIs, regardless of LM or BM. Qin et al performed a meta-analysis in terms of ICIs in patients with lung cancer with LM and found that patients with NSCLC with or without LM obtained comparable benefits. However, our results...
demonstrated that the magnitude of benefit in patients with LM was significantly lower than that in those without LM. Recently, a retrospective analysis of 232 patients administered with ICIs confirmed that the hypothesis patients with LM had worst prognosis despite treated with ICIs, comparing with patients with non-LM (median PFS: 2.3 vs 5.0 months, p<0.001; median OS: 9.8 vs 23.5 months, p=0.031). Accumulated results show that tumours that metastasised to the liver are more likely to resist therapy, and liver-associated with induction of immune tolerance could be an explanation for this phenomenon. Liver-induced peripheral tolerance was initially described in the setting of orthotopic liver transplantation. Unlike kidney or heart allografts, liver allografts are often well accepted, irrespective from histocompatibility. In addition, in vitro, liver allografts confer on the recipient tolerance to other transplanted organs from the same donor, suggesting that the transplanted liver can be induced systemic immune tolerance. The unique tolerogenic immune orientation of the liver may drive less sensitive to ICIs in patients with LM.

Liver-induced immune tolerance may result from the structure and composition of the liver. Liver is a highly vascularised organ with myeloid-derived suppressor cells (MDSCs) and hepatic stellate cells (HSC) that constitute its architecture. Liver sinusoidal endothelial cells, Kupffer cells, dendritic cells and HSC predominantly promote a network of active immunosuppressive pathways, diminishing the activation of CD8+ and CD4+ effector T cells. The presence of LM was associated with reduced CD8+ T cell infiltration at the invasive margin. Moreover, LM recruits and polarises monocyte-derived macrophages to favour the M2 phenotype, thereby altering the immune microenvironment. One comprehensive preclinical investigation on the mechanism of constraining immunotherapy showed that LM also siphoned activated CD8+ T cells from circulation. Unbiased single-cell sequencing identified hepatic monocyte-derived CD11b+ F4/80+ macrophages as critical mediators that induced antigen-specific CD8+ T cell apoptosis via the Fas/FasL pathway in the LM microenvironment. Regulatory T cell (Treg) activation may lead to the distal immunosuppression. At a fundamental level, the dominant forces that promote tumour growth include the intrinsic properties of tumour cell and the organ in which the tumour resides. The immune context of LM may have a strong influence on the reactive immune response to anticancer therapy.

Our results showed that LM decreased the sensitivity to ICIs in lung cancer. Carefully investigated, the sensitivity can vary according to the drugs: PD-1/L1 plus bevacizumab plus chemotherapy could decrease the risk of disease progression by 56% in patients with NSCLC with LM. The clinical benefit of targeting both VEGF and PD-L1 signalling in unrectatable liver cancer was confirmed in the IMbrave150 clinical trial. VEGF can dampen the antitumor immune response by inhibiting T
### Figure 3
Forest plot of HR in lung cancer patients with liver metastases. (A) HR for progression-free survival of all patients with liver metastases; (B) HR for overall survival of all patients with liver metastases; (C) HR for progression-free survival of all patients without liver metastases; (D) HR for overall survival of all patients without liver metastases.

### Figure 4
Forest plot of HR in lung cancer patients with brain metastases. (A) HR for progression-free survival of all patients with brain metastases; (B) HR for overall survival of all patients with brain metastases; (C) HR for progression-free survival of all patients without brain metastases; (D) HR for overall survival of all patients without brain metastases.
cell function and dendritic cell differentiation and activation and activation of Treg and MDSCs. Therefore, anti-VEGF acts synergistically with ICIs. Furthermore, anti-VEGF can normalise tumour vascular, thus enhancing the immunotherapeutic effect by promoting tissue perfusion and immune cell infiltration. Radiotherapy is another method to alleviate the immunosuppressive microenvironment in liver. Hypofractionated radiation generates immunomodulatory effects such as in situ vaccination, activation of dendritic cells and upregulation of cytokines and chemokines. A recent study showed that low-dose radiotherapy of murine tumours promotes T-cell infiltration (CD8+, CD4+ and CD11b+ cells) in immune desert tumours and affects the response to ICIs in an interferon-dependent manner, as confirmed in human tumours in vitro. In a mouse model, hepatic radiotherapy could blunt immunosuppressive myeloid elements and stimulate T cell immunity in the liver, thus restore the response to immunotherapy. Clinical trials of the combination of ICIs and other elements, such as antiangiogenesis or radiotherapy, are ongoing.

Another hypothesis of our study was that BM may not be an unfavourable factor in ICI era. The brain is a privileged organ under the protection of brain-blood barrier (BBB). The BBB is comprised of endothelial cells, pericytes, basement membrane proteins and astrocytes. Conventional drug concentrations in the brain are low, due to the limited penetration of drugs through BBB and rapid efflux from the brain to the blood.

Another reason for the low intracranial response was that the BMs differ from the primary. Tumour cells that metastasise to the brain are often distinct from their primary, processing capacity for penetrating the BBB. Primary tumours and BMs usually have a common genomic signature, additional alterations are frequently identified in BMs. Comparison of matched samples from (primary tumour and brain lesions) small cohorts revealed that BMs were more likely to be immunologically 'cold', with lower PD-L1 expression and lymphocyte infiltration. A specimen analysis of 86 formalin-fixed, paraffin-embedded samples from lung primary and intracranial metastases of 43 patients using RNA sequencing confirmed that the brain metastatic lesions had low tumour-infiltrating lymphocytes, fewer effector memory CD8+ T cells and more macrophages and neutrophils. The scores of some immune-related signatures (eg, MHC non-class signature, IFNγ signature and T-cell-inflamed gene-expression profile signature) were reduced in metastases. Comparing to primary, BM seems to be less immunogenic.

It is important to determine whether ICIs could be effective in patients with NSCLC with BM. Recently, there has been evidence of immune surveillance of the normal human CNS by CD3+/CD8+ lymphocytes. Sample analyses support the evidence that BMs of NSCLC are surrounded and infiltrated by CD8+ T cells and activated astrocytes and microglia. Emerging real-world evidence has demonstrated the efficacy of ICIs in patients with BM. This retrospective analysis included 255 patients with NSCLC with BM-administered ICIs, of whom including 100 patients with active BM. The intracranial ORR for patients with active BMs was 27.3%, and the intracranial disease control rate was 60.3%. Patients with active BM had significantly more brain disease progression than did those with stable BM (54.2% vs 30%, p<0.001). A representative phase II study conducted by Goldberg et al enrolled patients with small asymptomatic BM and found that the intracranial response rate to pembrolizumab was 33% in NSCLC and paralleled systemic response. Further studies may employ Response Assessment in Neuro-Oncology Brain Metastases criteria to assess intracranial efficacy independently.

Our investigation showed that patients with SCLC with BM could not benefit from ICIs; even PD-L1 inhibitor plus CTLA-4 inhibitor in combination with chemotherapy did not perform well in patients with BM in the CASPIAN trial. Radiation is the mainstay treatment for BM. Radiation can prime immunity by releasing of tumour antigens and proinflammatory signals, enhancing antigen presentation and altering the tumour environment to facilitate T cell infiltration. A combination of these methods in patients with BM is warranted. An abstract from the 2021 ASCO meeting indicated that upfront brain stereotactic radiosurgery (SRS) combined with nivolumab was well tolerated with a 4-month free-of-neurocognitive-decline survival estimating 89%. With accumulating data, the safety of checkpoint inhibitor monotherapy plus SRS is confirmed. A more effective combination may overcome the resistance to ICI.

The strength of our analysis was the reliability of the data derived from RCTs with little bias. We conducted a latest meta-analysis to assess the organ-specific benefits, and independently evaluated the impact of BM or LM on the efficacy of ICIs. A limitation of our meta-analysis was that it is based on published clinical trials rather than on individual patients’ data. Further individual patient-level studies or real-world studies may enhance the results and deeply investigate the optimal tailored treatment for patients with LM and SCLC patients with BM.

Our results showed that immunotherapy demonstrated consistent efficacious in patients with lung cancer with LM and BM, and subgroup analysis showed that survival benefits dominantly favoured patients with NSCLC. Patients with lung cancer with LM negatively affect the efficacy of ICIs. Tailored treatments should include organ-specific therapeutic approaches.

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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 None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

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