Ideal treatment regimen for patients with ≥ 1 brain metastasis from primary non-small cell lung cancer – a systematic review and network meta-analysis

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INTRODUCTION

- Approximately 10% of patients with non-small cell lung cancer (NSCLC) present with brain metastases (BM) at the time of diagnosis
- The ideal management schema that incorporates all evidence-based treatment strategies is not clear
- The aim of this systematic review was to critically evaluate and compare different management paradigms for BM from NSCLC

METHODS

- MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, and CENTRAL were searched for randomized controlled trials (RCTs) based on ≥10 patients
- References of key studies were searched
- The primary outcomes were intracranial progression-free survival (CNS PFS) and overall progression-free survival (PFS); secondary outcomes included overall survival (OS)

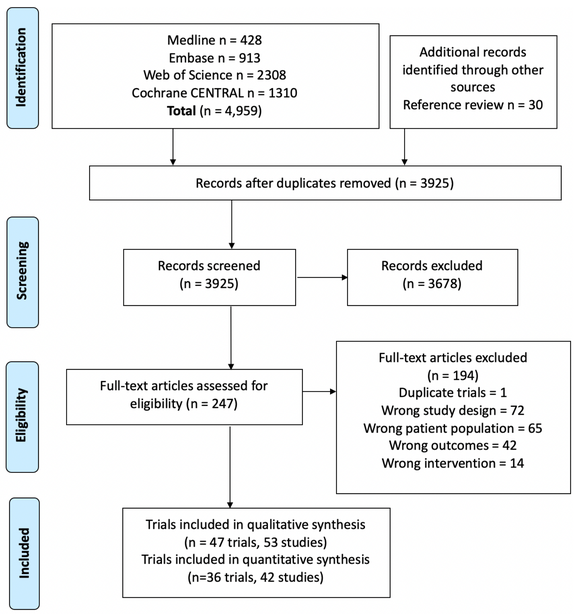


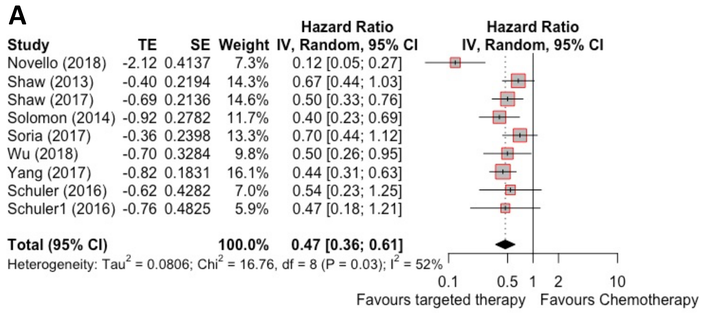
Figure 1 – PRISMA diagram outlining search results and stages of screening, with reasons for full-text study exclusion

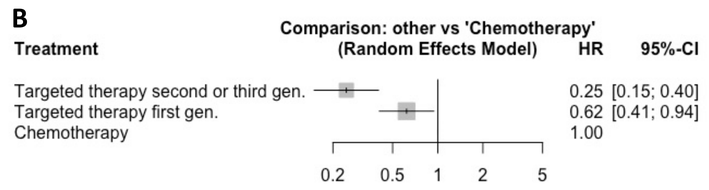
RESULTS

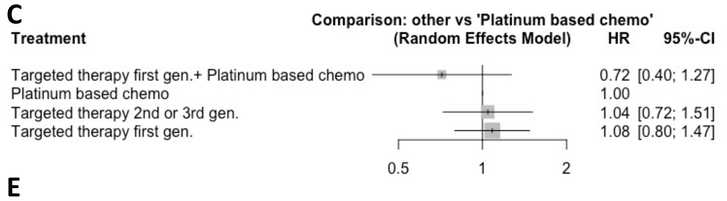
Summary of included trials

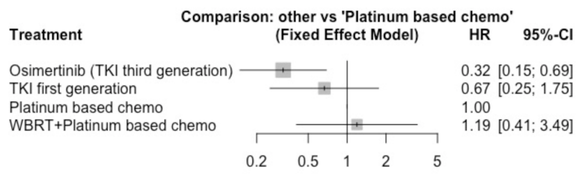
- **36** trials representing **4349** patients were included in quantitative analysis; median sample size **88**, range **28-554**
- Eligibility criteria:
  - Most trials were open-label, parallel, superiority trials and all included patients aged ≥18 with NSCLC and ≥1 BM proven on CT/MRI
  - 9/36 trials restricted to EGFR-mutant patients only, 10/36 to ALK-rearranged only, and 4/36 to wild-type only
  - 35/36 trials excluded patients with non-favorable performance status, 24/36 excluded patients with symptomatic or untreated BMs
- We combined similar interventions (TKIs, traditional chemotherapy regimens, etc.) into single nodes for analysis where necessary

Efficacy









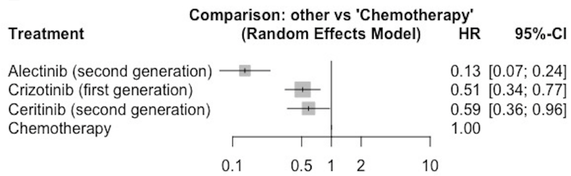
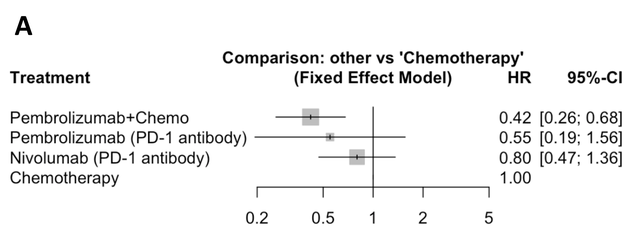


Figure 2 – Comparative efficacy of targeted therapies compared to conventional therapy in EGFR-mutant or ALK-rearranged NSCLC patients. **A)** Traditional meta-analysis showing overall PFS of targeted therapies versus traditional chemotherapy. All studies shown compared a TKI against conventional platinum-based chemotherapy. **B)** Network meta-analysis of CNS PFS of targeted therapies (ALKi or EGFRi) versus chemotherapy. **C)** Network meta-analysis of OS of targeted therapies (ALKi or EGFRi) versus chemotherapy. **D)** CNS PFS of EGFR+ patients treated with an EGFRi versus conventional therapy. **E)** Overall PFS of ALK-rearranged patients treated with ALKi versus conventional therapy



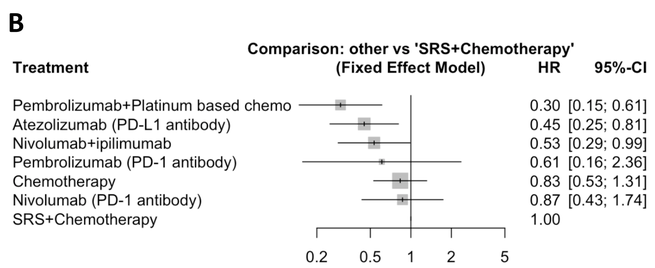


Figure 3 – Comparative efficacy of various treatments in wild-type or all-comer NSCLC patients. **A)** Network meta-analysis of PFS in wild-type and all-comer patients. **B)** Network meta-analysis of OS in wild-type and all-comer patients.

Table 1 – Risk of Bias assessment of studies included in quantitative analysis (completed using Cochrane RoB 2.0 tool)

Category	*# of studies*		
	Low	High	Unclear
Random Sequence Generation	5/36	0/36	12/36
Allocation Concealment	2/36	1/36	14/36
Blinding (Personnel and Participants)	3/36	8/36	6/36
Blinding (Assessor)	5/36	6/36	6/36
Incomplete Outcome Data	14/36	0/36	3/36
Selective Outcome Reporting	34/36	0/36	2/36
Overall RoB	14/36	2/36	20/36

CONCLUSIONS

- Many studies included patients who may have received previous treatment for BMs, presenting a possible confounder – however, these patients represent "real-world" case scenarios for BM management
- Ideal evidence-based management of NSCLC BMs is not clear-cut in the current literature
- For patients with targetable mutations, targeted therapies are significantly more effective than general chemotherapy
- Immunotherapies show promise for patients without targetable mutations
- Most trials exclude patients with unfavorable performance status, which may limit generalizability