

Comparative Efficacy of ALK-inhibitors in ALK Inhibitor-Naive ALK+ Lung Cancer Brain Metastases: A Network Meta-Analysis

VA



Haddad P¹, Gallagher K¹, Hammoud D¹

¹ LSUHSC-S/Overton Brooks VAMC, Shreveport Louisiana, United States



Background

Lung cancer has been the leading cause of cancer death for both men and women worldwide. Non-small-cell lung cancer (NSCLC) displays an array of molecular abnormalities most commonly involving ALK and EGFR pathways. NSCLC with ALK rearrangements comprises around 5% of cases. Over the years, several ALK inhibitors (ALKI) have been approved with notable activity in brain metastases. However, there have been limited comparative studies exploring their relative efficacies. This analysis was conducted to compare the relative efficacy of ALKIs against ALKI-naïve ALK+ lung cancer brain metastases.

Methods

A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language; diagnosis of ALKI-naïve ALK+ lung cancer trials with brain metastases; treatment with Crizotinib (CRZ), Alectinib (ALC), Brigatinib (BRG), and Ceritinib (CER); and comparative studies reporting brain metastases specific responses/events. A Bayesian and a frequentists network meta-analysis were conducted using netmeta package and the random-effects model.

Results

Eight studies comprising a total of 665 participants with ALKI-naïve ALK+ lung cancer brain metastases were included (Fig.1). When compared pairwise to CRZ, ALC (RR=0.49;95%CI:0.36-0.66), BRG (RR=0.39;95%CI:0.24-0.64), and CER (RR=0.36;95%CI:0.19-0.68) demonstrated significantly superior response rates in patients with untreated or previously treated lung cancer brain metastases (Fig.2). When the efficacy of each ALKI was compared to each other, BRG and CER were ranked the highest followed by ALC and CRZ in decreasing order (Fig.3&4).

Conclusions

This network meta-analysis is the first to compare and rank approved ALKIs used in treating metastatic ALK+ lung cancer. It indicates that BRG, CER, and ALC are better therapeutic options for patients with ALK-naïve ALK+ lung cancer brain metastases when compared to CRZ.

Results Figures

Figure 1- Network plot of all studies

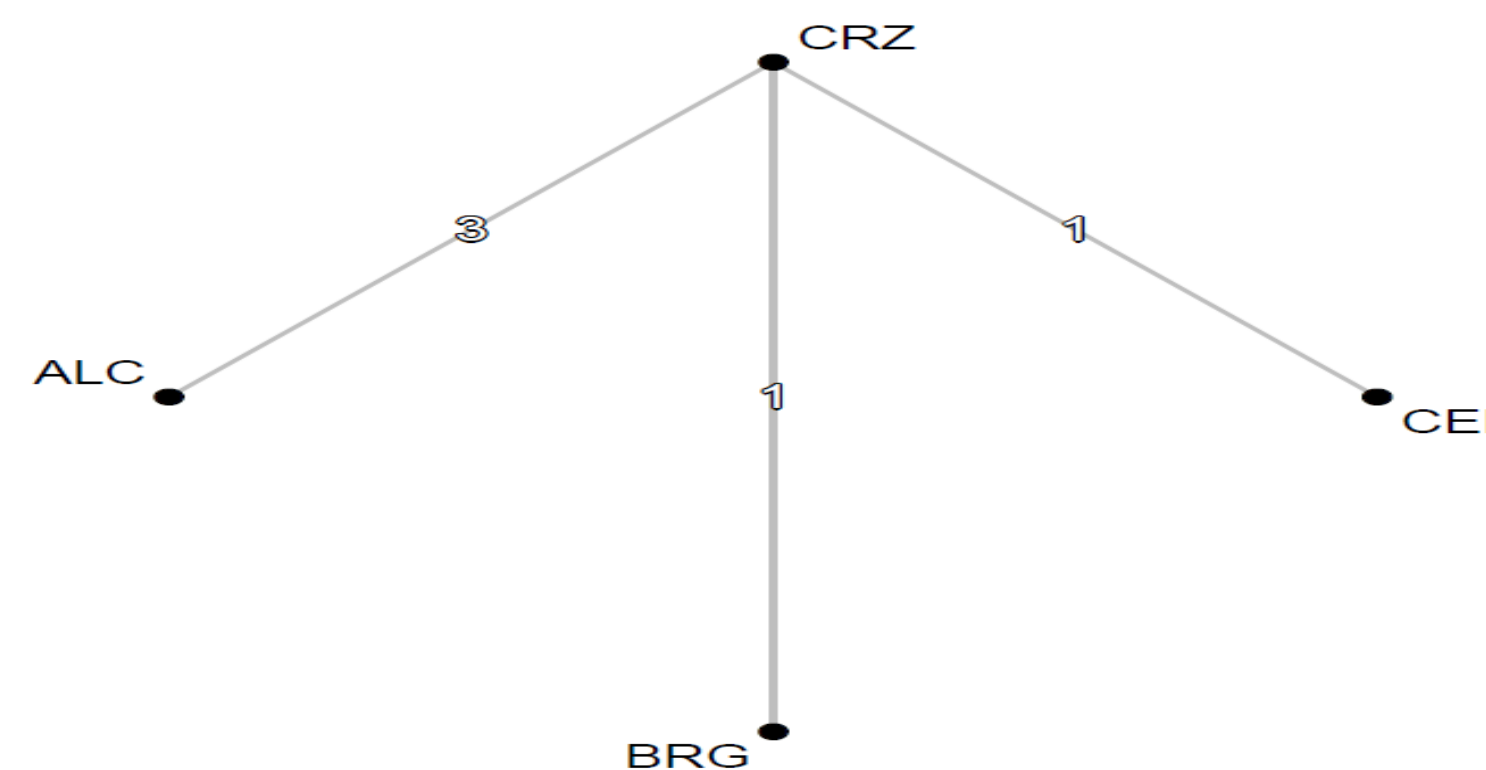


Figure 2- Pairwise comparison of RR of no response

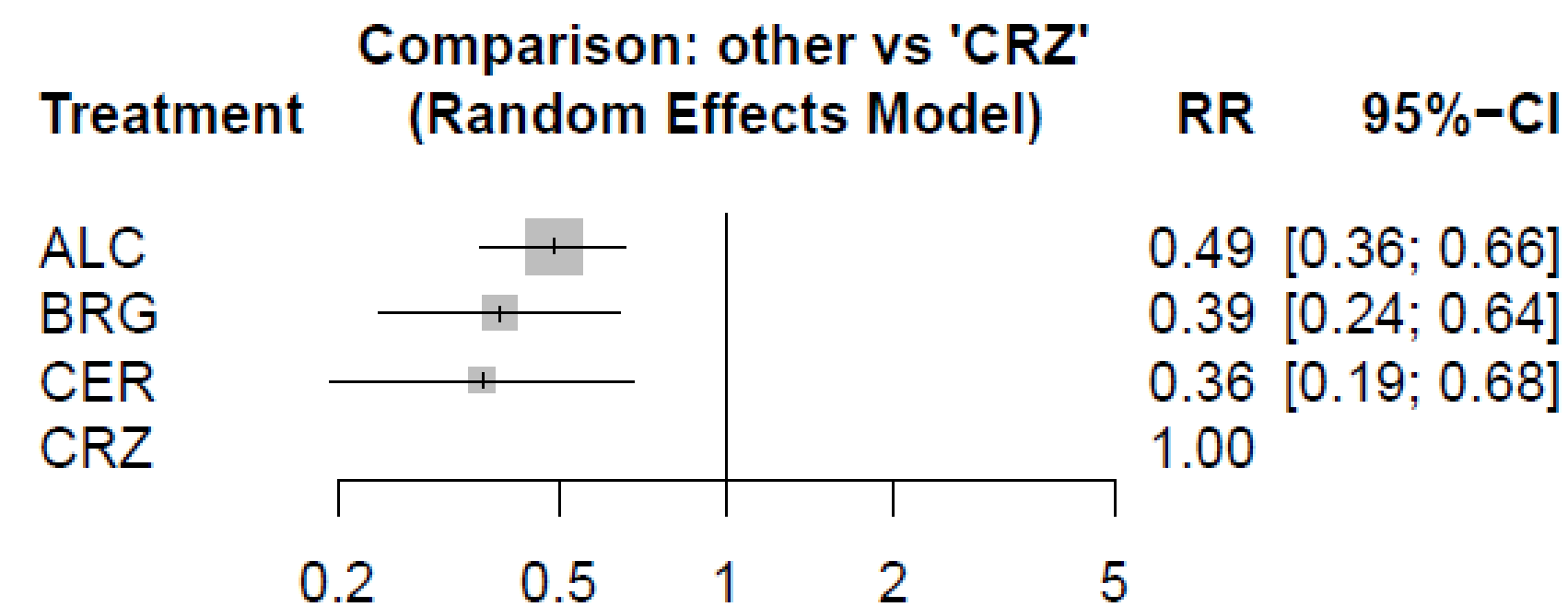


Figure 3- Relative treatment effects in ranked order for all studies.

Treatments are ranked from best to worst along the leading diagonal. Above the leading diagonal are estimates from pairwise meta-analyses, below the leading diagonal are estimates from network meta-analyses

CER				0.36 [0.19; 0.68]
0.93 [0.42; 2.07]	BRG			0.39 [0.24; 0.64]
0.74 [0.37; 1.49]	0.80 [0.45; 1.43]	ALC		0.49 [0.36; 0.66]
0.36 [0.19; 0.68]	0.39 [0.24; 0.64]	0.49 [0.36; 0.66]	CRZ	

Figure 4- Ranking for all studies with probability of each treatment to be the best (Bayesian Analysis)

	Rank 1	Rank 2	Rank 3	Rank 4
ALC	0.12450	0.34296	0.51648	0.01606
BRG	0.39300	0.35383	0.21806	0.03511
CER	0.48224	0.29506	0.18996	0.03274
CRZ	0.00026	0.00815	0.07550	0.91609

Rank	Intervention
1	
2	BRG CER
3	ALC
4	CRZ

References

- Hida, T et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390(10089):29-39.
- Peters, S et al. Alectinib versus Crizotinib in untreated ALK-positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;377(9):829-838.
- Camidge, D et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;379(21):2027-2039.
- Zhou, C et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *Lancet Respir Med* 2019;7(5):437-446.
- Costa, D et al. Clinical experience with Crizotinib in patients with advanced ALK-rearranged Non-Small-Cell Lung Cancer and brain metastases. *J Clin Oncol* 2015;33:1881-1888.
- Kim, D et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol* 2016;17(4):452-463.
- Crinò, L et al. Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2. *J Clin Oncol* 2016;34(24):2866-73.
- Tan D, et al. Comparative Efficacy of Ceritinib and Crizotinib as Initial ALK-Targeted Therapies in Previously Treated Advanced NSCLC: An Adjusted Comparison with External Controls. *J Thorac Oncol* 2016;11(9):1550-7.

Disclosures

The above authors have no conflicts of interest or relevant financial relationships to disclose.