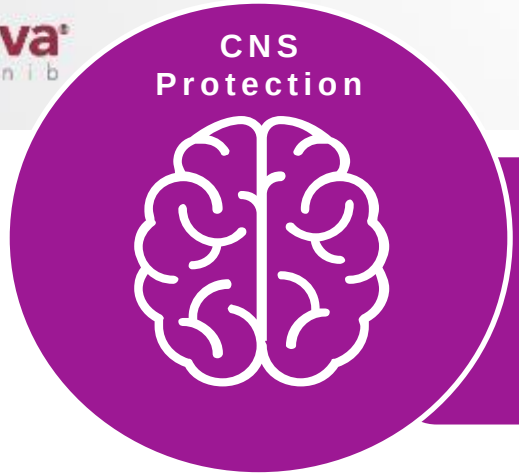
EXPERIENCE BRINGS Confidence

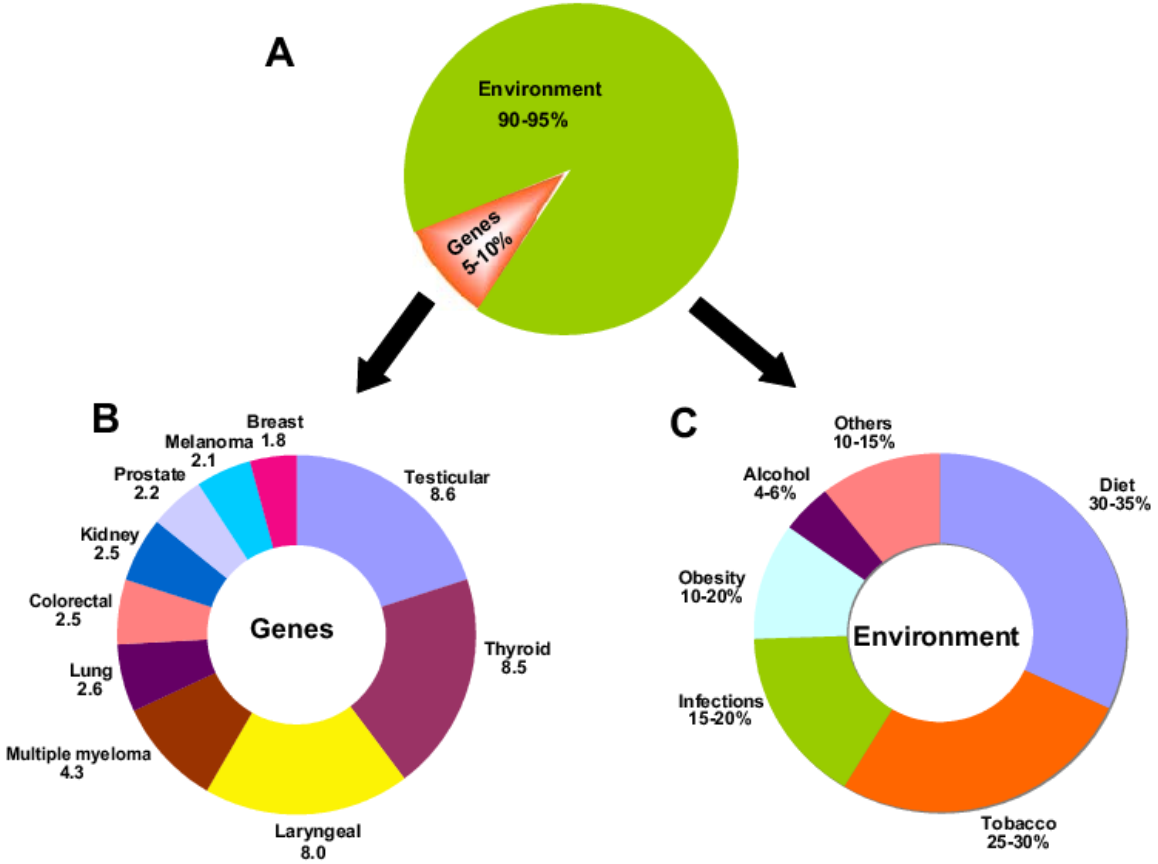
Tarceva erlotinib



Protecting EGFR Mut+ Patients from CNS Metastases in NSCLC with erlotinib (Erlotinib)

By Dr Arif Santoso Sp. P(K), Ph.D, FAPSR

ENVIRONMENT AND LUNG CANCER



CENTRAL NERVOUS SYSTEM METASTASES

Brain metastases and leptomeningeal disease often occur at the same time and can be termed Central Nervous System (CNS) metastases, although the two conditions remain distinct.[1] In patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer, CNS metastases can occur in up to 44% of patients[2], with median overall survival varying between 4.5[3] and 18 months.[2,4]

BRAIN METASTASES

is a common complication of advanced cancer **(in 20 to 40% of patients)** where the cancer spreads from the original site around the body and starts to regrow in the brain[5]

Lung is the most common type of cancer to spread to the brain.[5] For patients with lung cancer who develop brain metastases, this is often within **2.6 months** of first diagnosis of advanced cancer[6]

Brain metastases are notoriously hard to treat; whilst radiotherapy, surgery and chemotherapy may reduce tumour size and steroids may control symptoms, **metastases are rarely cured by these treatments** and the treatment options themselves cause serious side-effects[7]

LEPTOMENINGEAL DISEASE

(LM) is a rare complication of cancer in which the disease spreads to the meninges **surrounding the brain and spinal cord**[9]

LM occurs in approximately 5% of people with cancer and is usually fatal. If left untreated, **median survival is 4-6 weeks;** if treated effectively, median survival is currently 2-3 months[9]

LM is incurable and difficult to treat. Current therapy options include radiation therapy and intrathecal chemotherapy[9]

The most common cancers to spread to the leptomeninges are:

Breast (35%)[5]

Lung (24%)[5]

Hematologic malignancies (16%)[5]

Symptoms of brain metastases[7] and LM[8] include:

- **Nausea**
- **Difficulty thinking**
- **Double vision**
- **Headaches**
- **Difficulty speaking or swallowing**
- **Pain**
- **Seizures**
- **Weakness and/or lack of coordination in your arms and legs**

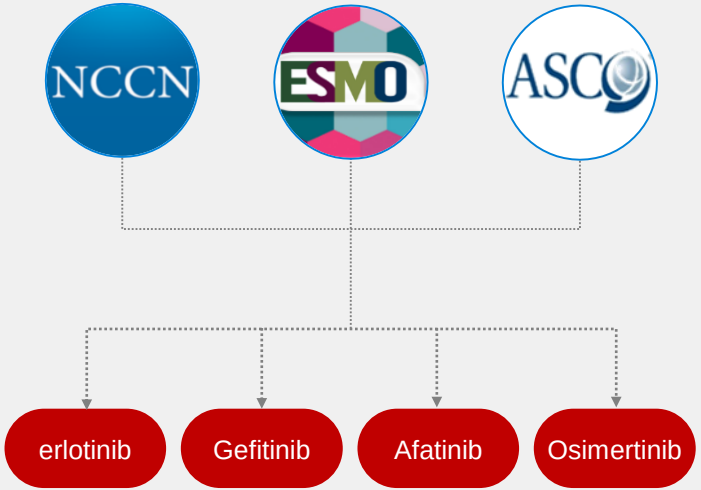
1: BRAINMETSBC.ORG. Leptomeningeal Metastases. Available at: http://www.brainmetsbc.org/en/content/leptomeningeal-metastases-1. Accessed November 2016. 2: Eichler et al. EGFR mutation status and survival after diagnosis of brain metastasis in non-small cell lung cancer Neuro-Oncology. 2010;12:1193-1199 3: Liao et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Non–Small-Cell Lung Cancer Patients with Leptomeningeal Carcinomatosis. Journal of Thoracic Oncology. 2015; 10(12): 1754-61 4: Umemura et al. Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group. Lung Cancer. 2012;77:134-139 5: National Institutes of Health. Adult Central Nervous System Tumors Treatment–Health Professional Version (PDQ®) Metastatic Brain Tumors. Available here: https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#link/_1167_toc Accessed November 2016. 6: Kong XT, Alexandru D & Bota DA. Epidemiology of Central Nervous System Metastases, in Brain Metastases From Primary Tumours. Epidemiology, Biology and Therapy. Vol 1. Ed. Hayat MA. 2014. 7: MacMillian Cancer Support. Secondary Brain Tumours. Available at: http://www.macmillan.org.uk/Information-and-support/brain-tumours-secondary#1556559 Accessed November 2016. 8: Memorial Sloan Kettering Cancer Center. Leptomeningeal Metastases. Available at: https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#link/_1167_toc Accessed November 2016. 9: Schneck MJ et al. Leptomeningeal Carcinomatosis. Practice Essentials. Available at: http://emedicine.medscape.com/article/1156338-overview. Accessed November 2016.

Date of preparation: November 2016 Date of expiry: November 2017 ATLAS ID: 1023420.011

AstraZeneca

Erlotinib is a widely used standard of care with recommendations by all major international guidelines, extensive clinical data and clinical experience

Guidelines for first-line treatment of *EGFR* Mut+ advanced NSCLC[1–3]



>1.7 million

patients **TREATED** with erlotinib

worldwide since **2004**[4]

MEDIAN **PFS IN PHASE III** STUDIES:

EURTAC[5]	OPTIMAL[6]	ENSURE[7]
10.4 Months	13.7 Months	11.0 Months

Median **time-to-next treatment in real-world setting**:

Flatiron Health Database (USA): **13.2** months[8]

EGFR = epidermal growth factor receptor; Mut+ mutation positive; NSCLC = non-small-cell lung carcinoma; PFS = progression-free survival

1. NCCN 2018; 2. Novello, et al. Ann Oncol 2016; 3. Hanna, et al. J Thorac Oncol 2017; 4. Roche Data on file
5. Costa, et al. Clin Cancer Res 2014; 6. Chen, et al. Ann Oncol 2013; 7. Wu, et al. Ann Oncol 2015; 8. Li, et al. WCLC 2017

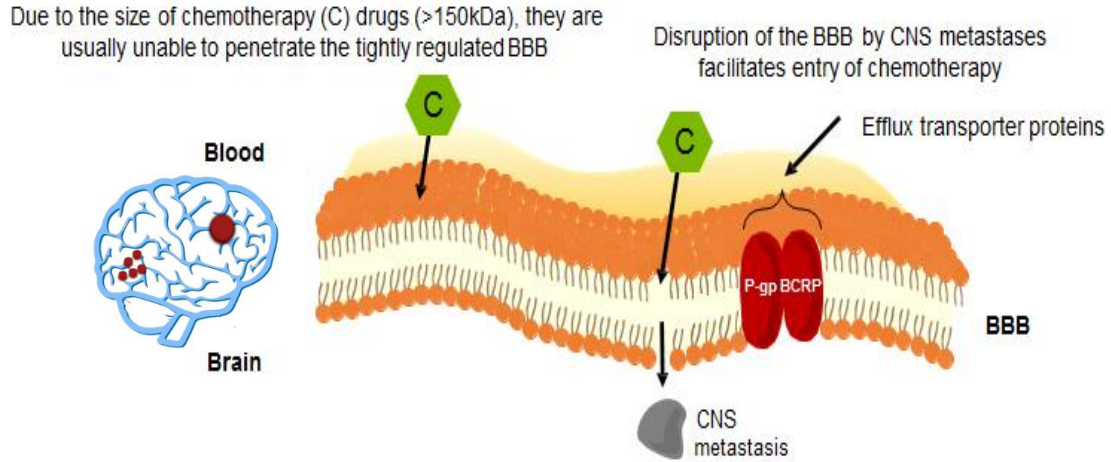
CNS Protection

CNS Metastases are common in patients with EGFR Mut-Positive NSCLC

As many as **20–40%** of patients with NSCLC develop brain metastases during treatment[3]

Approximately **10–20%** of patients with NSCLC present with brain metastases at initial diagnosis[3]

CNS metastases are common in patients with EGFR mutation-positive NSCLC and are associated with **worse quality of life and prognosis**[1,2]



1. Levy et al. Eur J Cancer. 2018;93:37-46
2. Li et al. BMC Cancer. 2017;17:245
3. Proto et al. Transl Lung Cancer Res. 2016;5(6):563-578

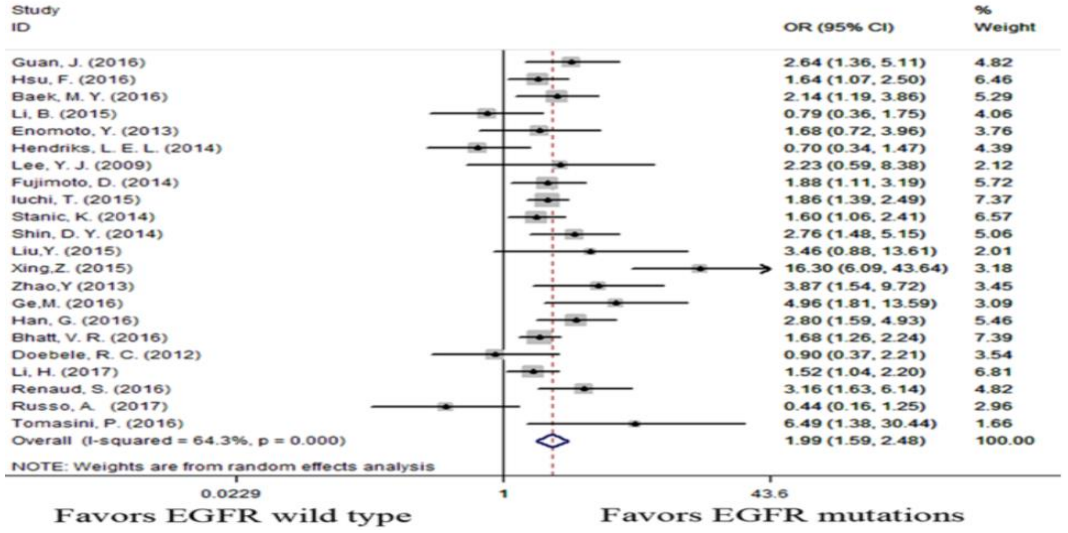
The Incidence of Brain Metastasis is higher in EGFR-mutant patients compared to EGFR-wild type

EGFR mutation status showed a concordance rate of 93.3% (14 of 15 patients) between the primary lung lesions and corresponding brain metastasis[1]

Incidence of CNS Metastasis from primary lung ca by subtype[2]

Histologic subtype	Incidence of CNS metastasis
Small cell lung cancer	13.5-59%
Adenocarcinoma	6.6-43%
Squamous cell carcinoma	5.2-13%
Large cell carcinoma	8.3%
Undifferentiated	41.0%
NSCLC-NOS	7.4%

The Incidence of Brain Metastasis is higher in EGFR-mutant patients compared to EGFR-wild type[1]



1. Li et al, *J Thorac Dis* 2017;9(8):2510-2520
2. Whitsett et al, Transl Lung Cancer Res 2013:2(4):273-283

Symptoms and Clinical Presentation

CNS METASTASES ARE ASSOCIATED WITH POOR SURVIVAL AND REDUCED QUALITY OF LIFE

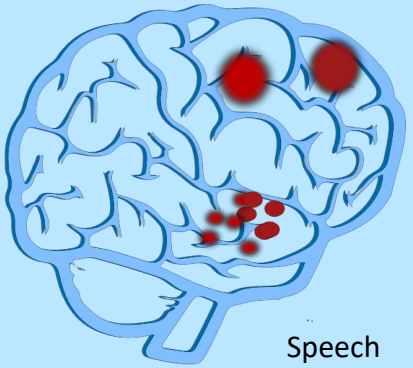
Survival times for patients with brain metastases are low[1-3]

Without treatment*: **4–11 weeks**
With treatment*: **4–15 months**

*Treatment encompasses systemic and intrathecal chemotherapy and radiotherapy

1. Wong, et al. Curr Oncol 2008; 2. Lee, et al. J Thoracic Oncol 2013
3. Tsakonas, et al. Cancer Treatment Review 2017

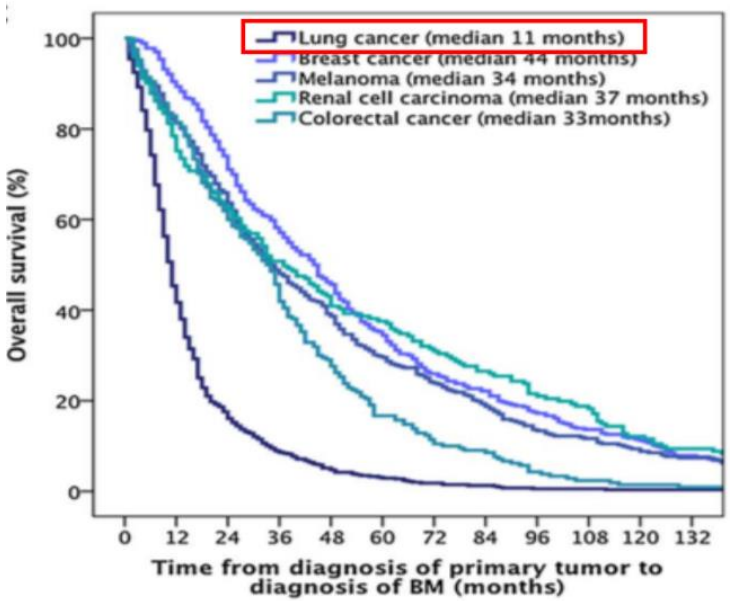
Debilitating symptoms resulting in anxiety and loss of independence in brain metastases patients[1-3]

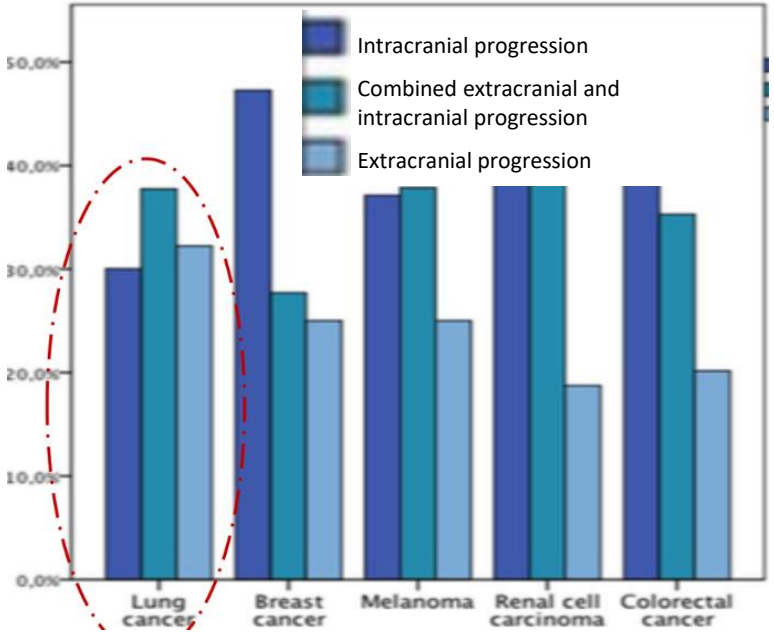


What do patients brain metastasis die of ?

Patients with lung cancer presented with the **shortest time** from diagnosis of primary tumour to brain metastasis development, with **median of 11 months**[1]

In the end of life period, **combined extracranial and intracranial progression** was most frequent in patients with lung cancer **(36.6%)**[1]

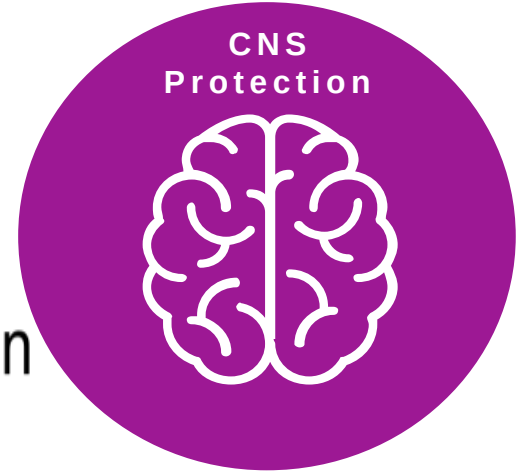




1. Berghoff AS, et al. ESMO Open 2016 :1

Goals of Lung Cancer Brain Metastasis Treatment

- Optimizing quality of life (QOL)
- Maximizing duration of disease control
- Maintain neurological and cognitive function



Arvold et al, Neuro-Oncology 18(8), 1043–1065, 2016

Brain Metastasis Treatment Modality

Treatment Modality of CNS Metastasis

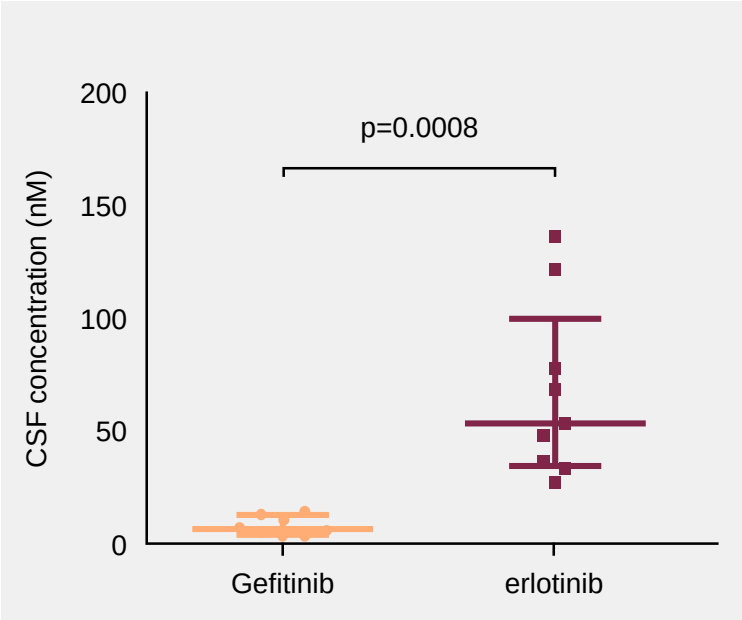
1. Neurosurgery
2. Radiotherapy
   - Whole brain radiotherapy (WBRT)
   - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
3. Systemic therapy
   - Chemotherapy
   - Targeted therapies, e.g. tyrosine kinase inhibitors
4. Supportive therapy
   - Edema control
   - Anticonvulsants
   - Pain

Arvold et al, Neuro-Oncology 18(8), 1043–1065, 2016

erlotinib demonstrates Higher CSF Concentration than other first-/second-generation TKIs

erlotinib achieves a **higher CSF Concentration** than gefitinib[1]

	CSF* Concentration (nM)
Gefitinib	8,2 ± 4,3
Erlotinib	**66,9 ± 39,0**



CNS = central nervous system; CSF = cerebrospinal fluid

1. Togashi, et al. Cancer Chemother Pharmacol 2012

erlotinib demonstrates Greater CNS Penetration Rate than other first-/second-generation TKIs

erlotinib has a higher CSF Penetration Rate than gefitinib and afatinib[1]

Publications	TKI	Dose (mg/day)	Mean CSF Penetration (range, %)
Zhao, et al. 2013	Gefitinib	250	0.36–1.3
Togashi, et al. 2012			
Zeng, et al. 2015			
Togashi, et al. 2012	erlotinib	75–150	2.7–6.2
Masuda, et al. 2011			
Togashi, et al. 2011			
Deng, et al. 2014			
Hoffknecht, et al. 2015	Afatinib	50	0.6

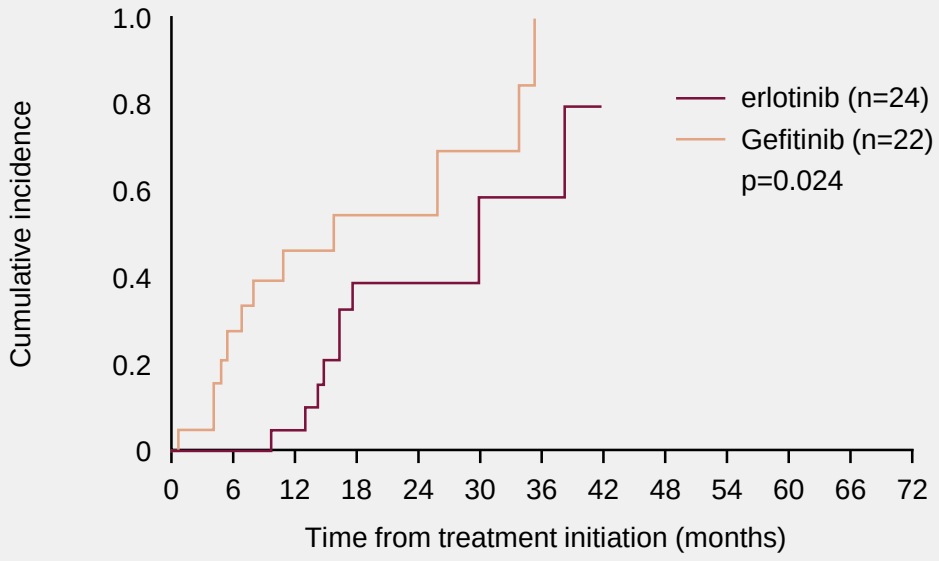
erlotinib has demonstrated mean CSF Penetration Rates ranging from 2.7% to 6.2%

which is higher than the rates reported for gefitinib (0.36–1.34%) and afatinib (0.6%)[1]

CNS = central nervous system; CSF = cerebrospinal fluid

1. Metro, et al. Expert Opin Pharmacother 2015

First-line erlotinib delays the onset of CNS metastases in patients without prior CNS metastases

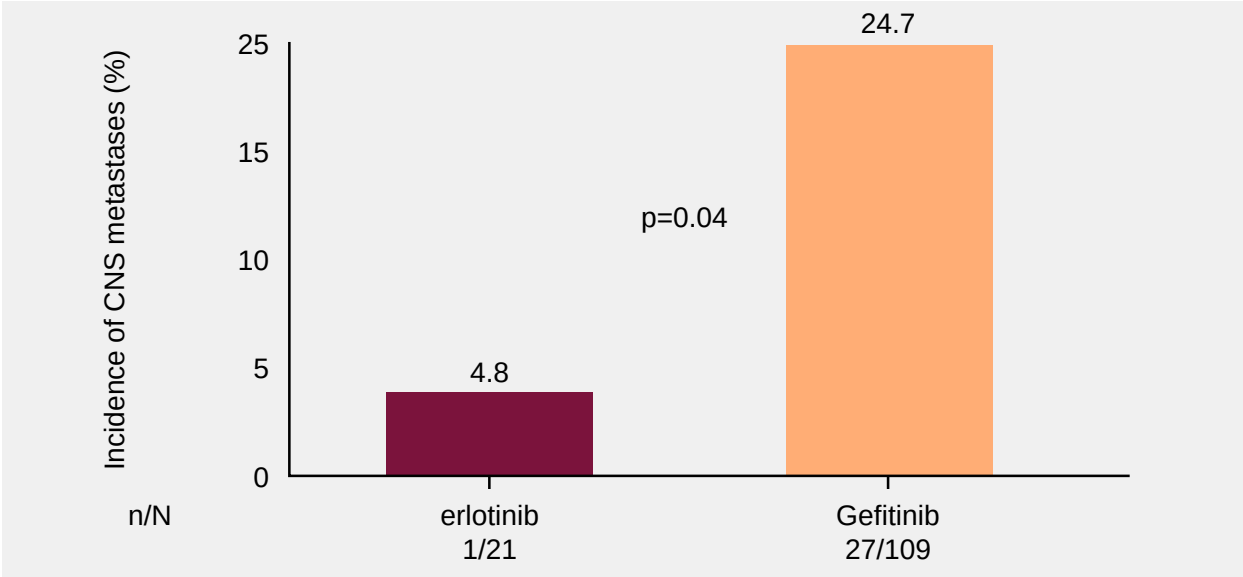


erlotinib significantly prolongs time to CNS progression in comparison with gefitinib

(median 30 months vs 15.8 months; p=0.024)[1]

1. Li, et al. BMC Cancer 2017

First-line erlotinib reduces the risk of CNS progression in patients without prior CNS metastases



Overall incidence of new CNS metastases was lower witherlotinib than gefitinib

A retrospective analysis of 175 patients with *EGFR* Mut+ NSCLC without prior CNS metastases[1]

1. Yoshida, et al. WCLC 2016

Clinical Data of Efficacy of EGFR TKI in EGFR Mut+ Brain Metastasis[1,2]

Author	Country	EGFR TKI	N	Study	EGFR Status	Intracranial Response Rate (icRR)	TTP / PFS	OS
Porta (2011)	Spain	Erlotinib	17	Retro	EGFR Mutants	82.4%	11.7 m	12.9 m
Park (2012)	Korea	Gefitinib/ Erlotinib	28	Pros	EGFR Mutants	83%	6.6 m	15.9 m
Wu (2013)	China	Erlotinib	48	Pros	80% NS 93% ade	75% M+ vs 55% uk/wild	10.1 m (for brain)	18.9 m
Hotta (2004)	Japan	Gefitinib	14	Retro	EGFR Mutants	43%	9.1 m	NA
Gerber (2014)	USA	Erlotinib	63	Retro	EGFR Mutants	NR	17 m	24 m
		Afatinib	81	Pooled Analysis	EGFR Mutants	21%	8.2 m	NA

1. Myung-Ju Ahn, WCLC 2017
2. Curr. Treat. Options in Oncol. (2017) 18:22

Gefitinib to achieve equivalent drug concentrations to erlotinib, patients would need 3 times the recommended dose[1,2]

	erlotinib (150mg/day)	Gefitinib (225mg/day)	Gefitinib (525mg/day)	Gefitinib (700mg/day)
C_{max} (ng/mL)	2,120	307	903	2,146
AUC_{0-24} (ng•hour/mL)	38,420	5,041	14,727	36,077

erlotinib is dosed to achieve effective plasma concentrations

For Gefitinib to achieve equivalent drug concentrations to erlotinib, patients would need to take >3 times the recommended 250mg dose

C_{max} = maximum plasma concentration
AUC = area under the curve

1. Hidalgo et al. 2001
2. Ranson et al. 2002

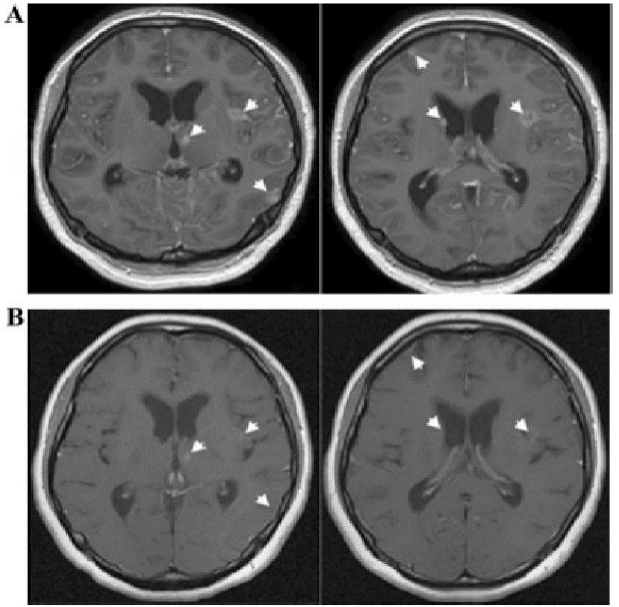
Patient - Case Reports

EGFR Mut+ and CNS Metastases

A 32-year-old woman with EGFR mutation-positive NSCLC and CNS metastases[1]

A 32-year-old patient with NSCLC and multiple brain metastases was treated with first-line erlotinib®. EGFR mutations were determined by analysing a fine-needle lung tumour biopsy taken before the treatment. A PET/CT of the brain was performed during treatment, and a MRI of the head and a CT of the chest were performed pre- and post-treatment.

The primary lung tumour displayed a erlotinib®-sensitive exon 19 deletion in the EGFR gene, and [^{11}C]-erlotinib® PET/CT showed accumulation in the brain metastases. An MRI scan three weeks after starting treatment revealed a near-complete remission of brain metastases.



(A) Imaging of the brain before the treatment
(B) 3 weeks after start of treatment
Arrows indicate positions of brain metastases

1. Weber, et al. J Thorac Oncol. 2011;6: 1287–1289

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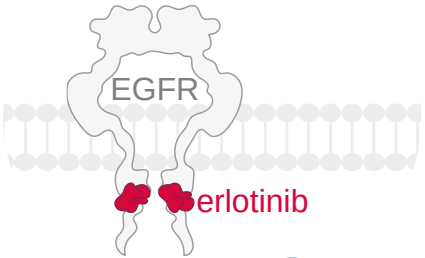
Tarceva erlotinib

TAKE HOME MESSAGES



erlotinib shows benefit in Controlling CNS metastases in EGFR mut+ patients[1-3]

erlotinib provides EGFRmut+ patients an optimal balance of efficacy and safety compared with other first-/ second-generation EGFR TKIs[4-7]

1. Li, et al. BMC Cancer 2017
2. Togashi, et al. Cancer Chemother Pharmacol 2012
3. Yoshida, et al. WCLC 2016
4. Zhang Y, et al. Oncotarget. Vol. 7, No. 15 (2016)
5. Zhou C, et al. Lancet Oncol. 12: 735–42 (2011)
6. Takeda M, et al. Lung Cancer. 88 : 74–79 (2015)
7. BPOM Product Information erlotinib (Erlotinib) December 2018

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Any **untoward medical occurrence** in a patient or clinical investigation subject administered a pharmaceutical drug and **which does not necessarily have a causal relationship with this treatment.**

Example: any unfavorable and unintended sign and symptom (including an abnormal laboratory finding), and pregnancy.

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