FAKULTAS KEDOKTERAN
UNIVERSITAS TRISAKTI

HETERO

The Role of Tyrosine Kinase Inhibitor (TKI) the 2nd Generation focus in Afatinib

in Management of Lung Cancer (NSCLC)

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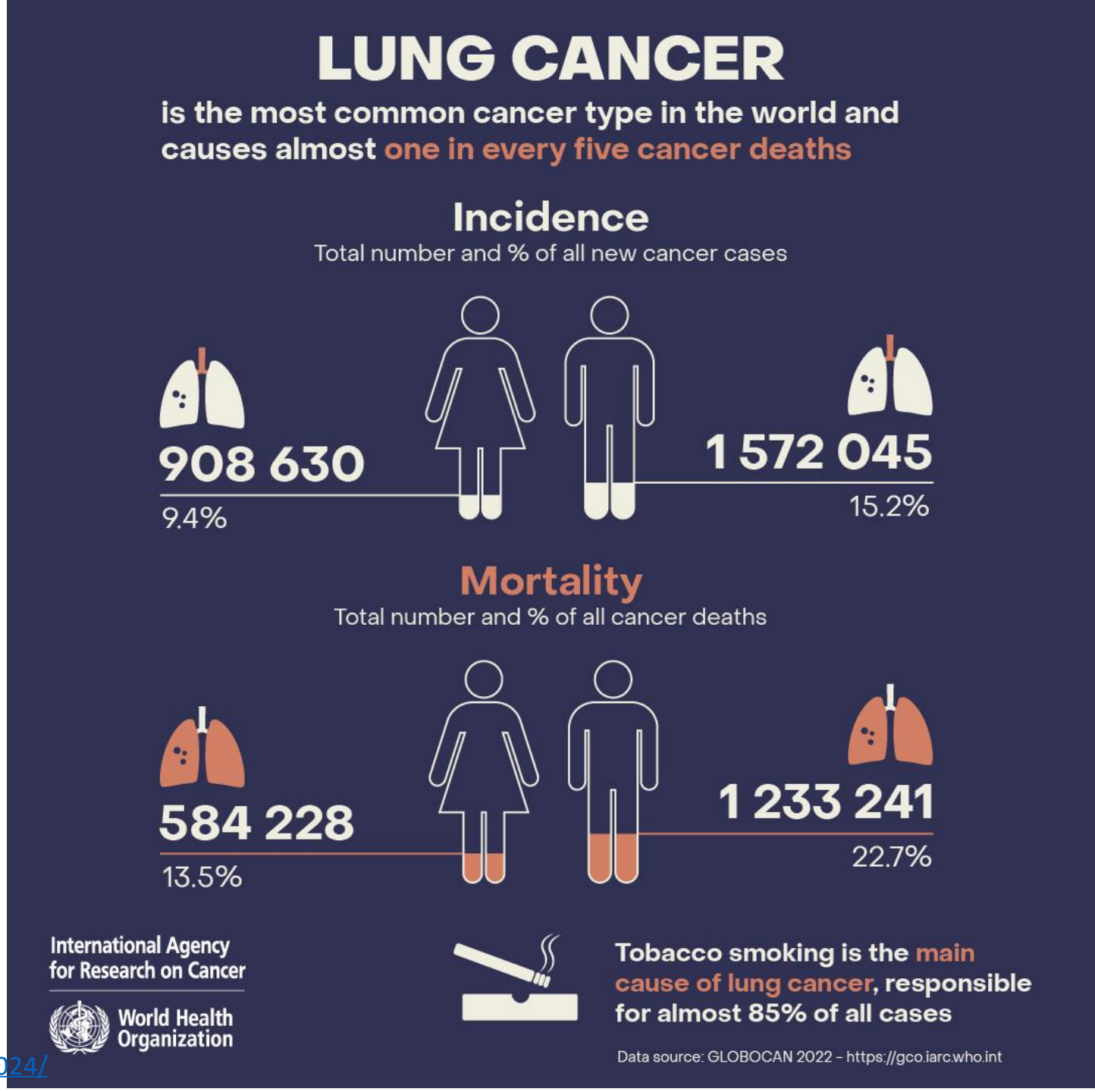
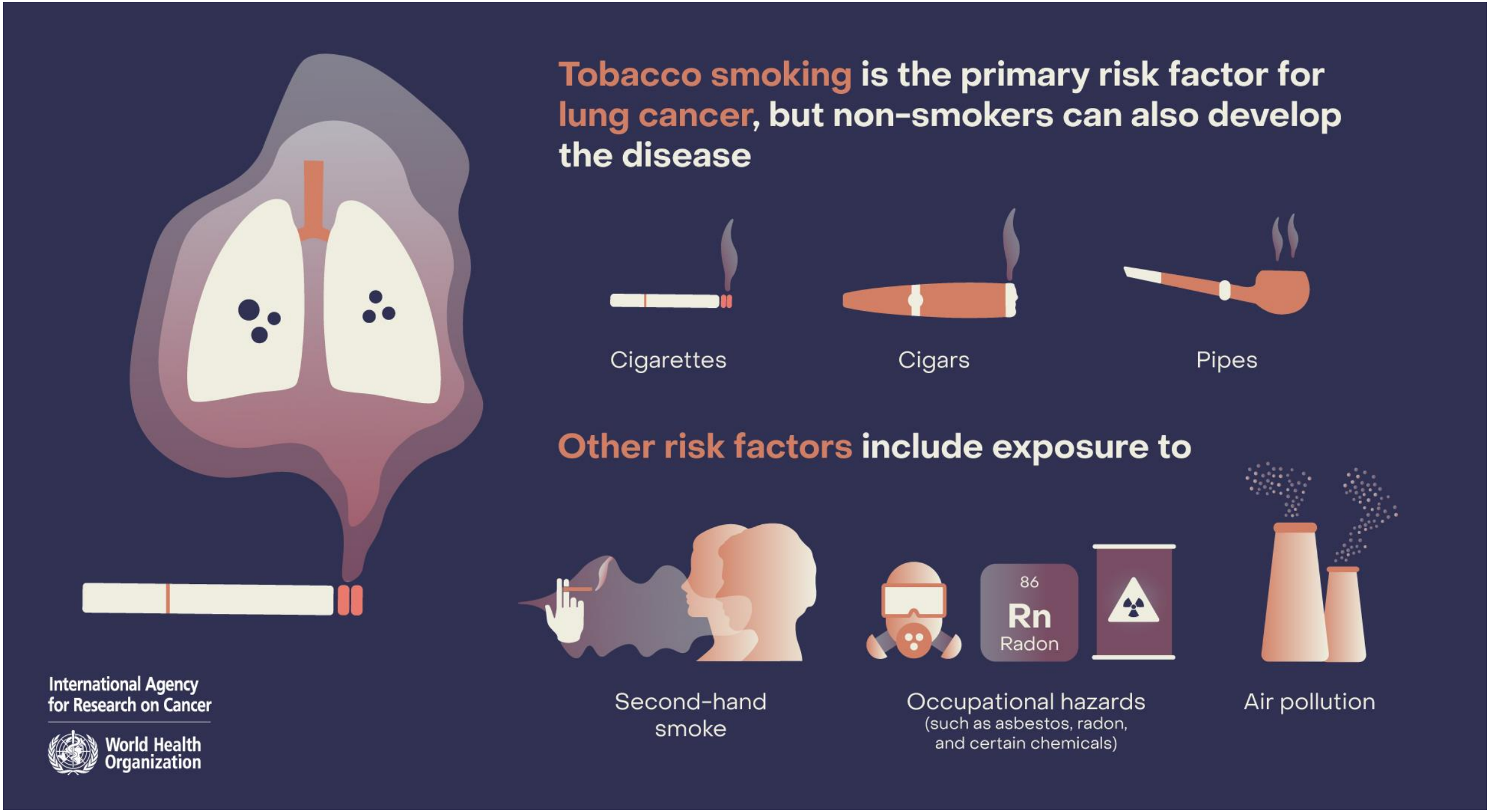
Lung Cancer Facts

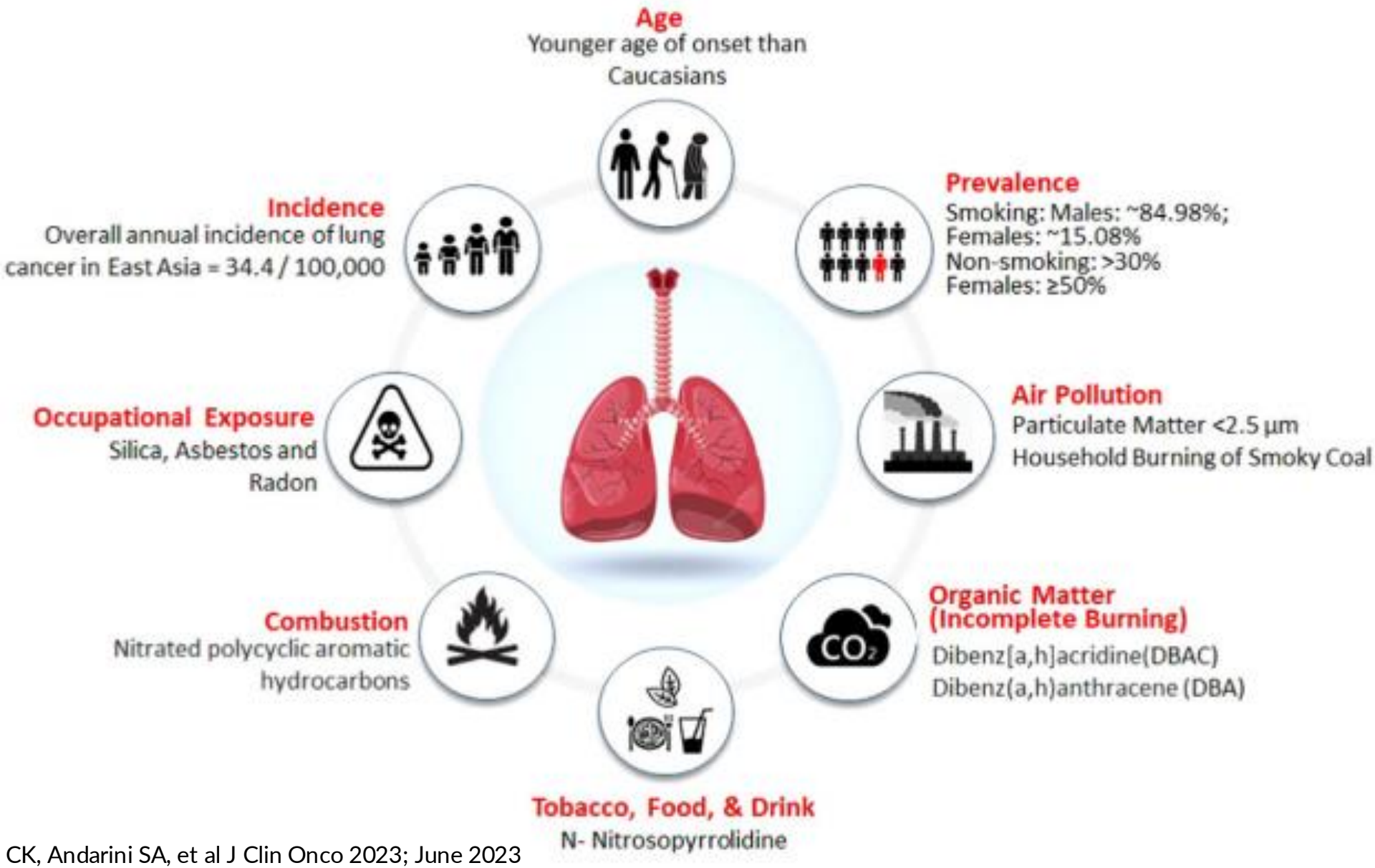


https://www.iarc.who.int/infographics/lung-cancer-awareness-month-2024/



https://www.iarc.who.int/infographics/lung-cancer-awareness-month-2024/

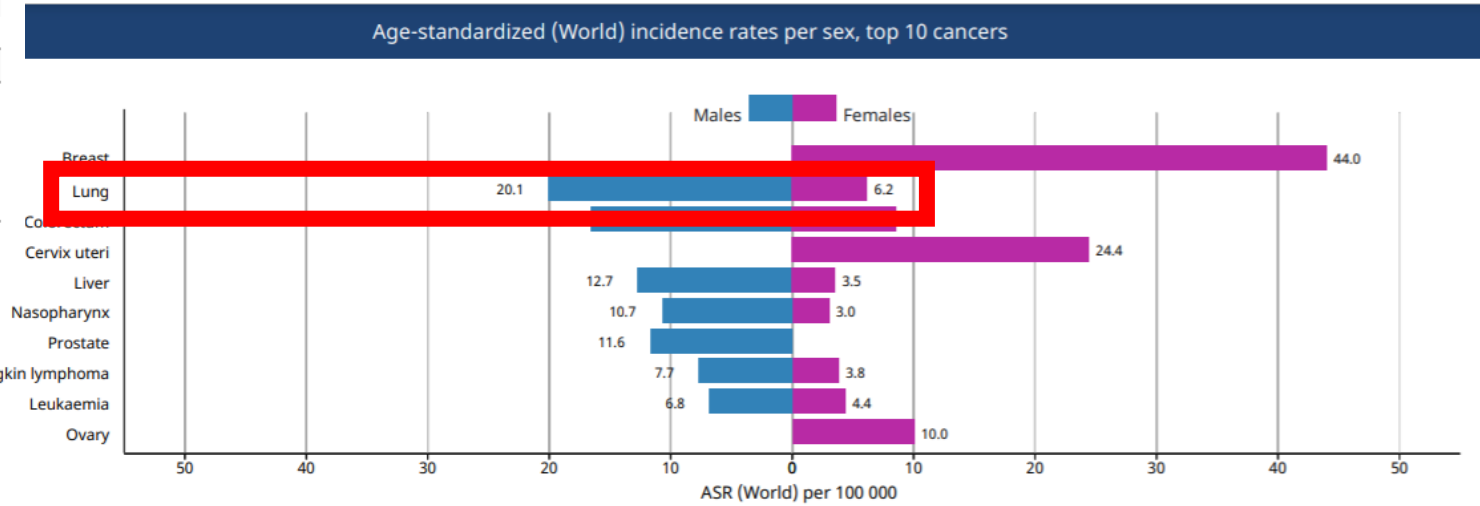
Gambaran Epidemiologi dan Faktor Risiko Kanker Paru di Asia

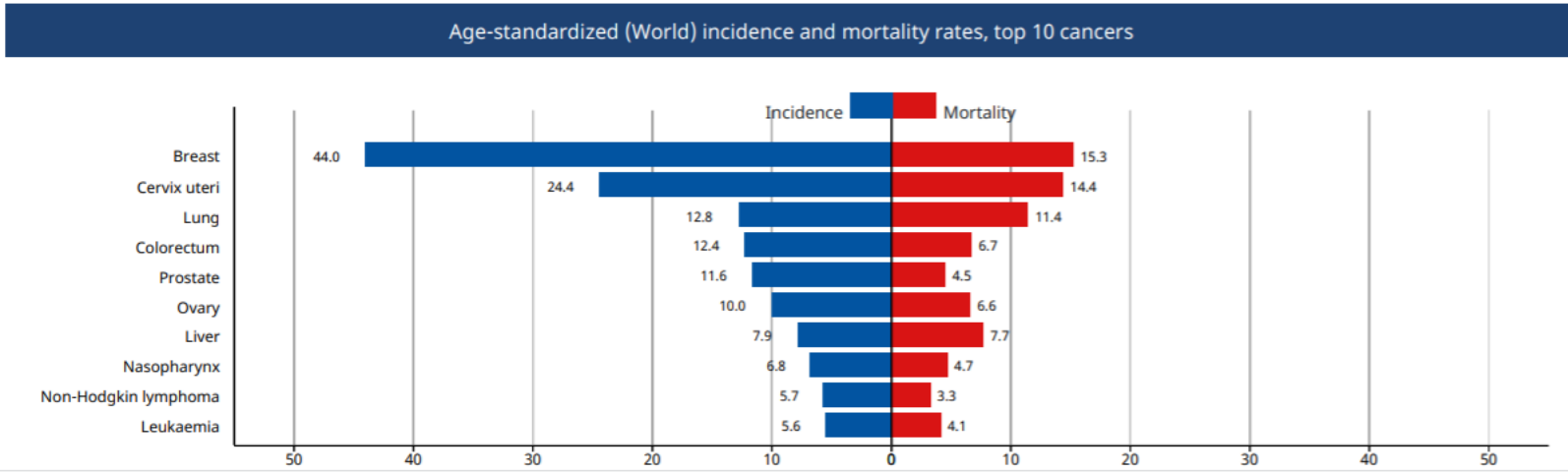


Lam DC, Liam CK, Andarini SA, et al J Clin Onco 2023; June 2023

Lung Cancer - Indonesia

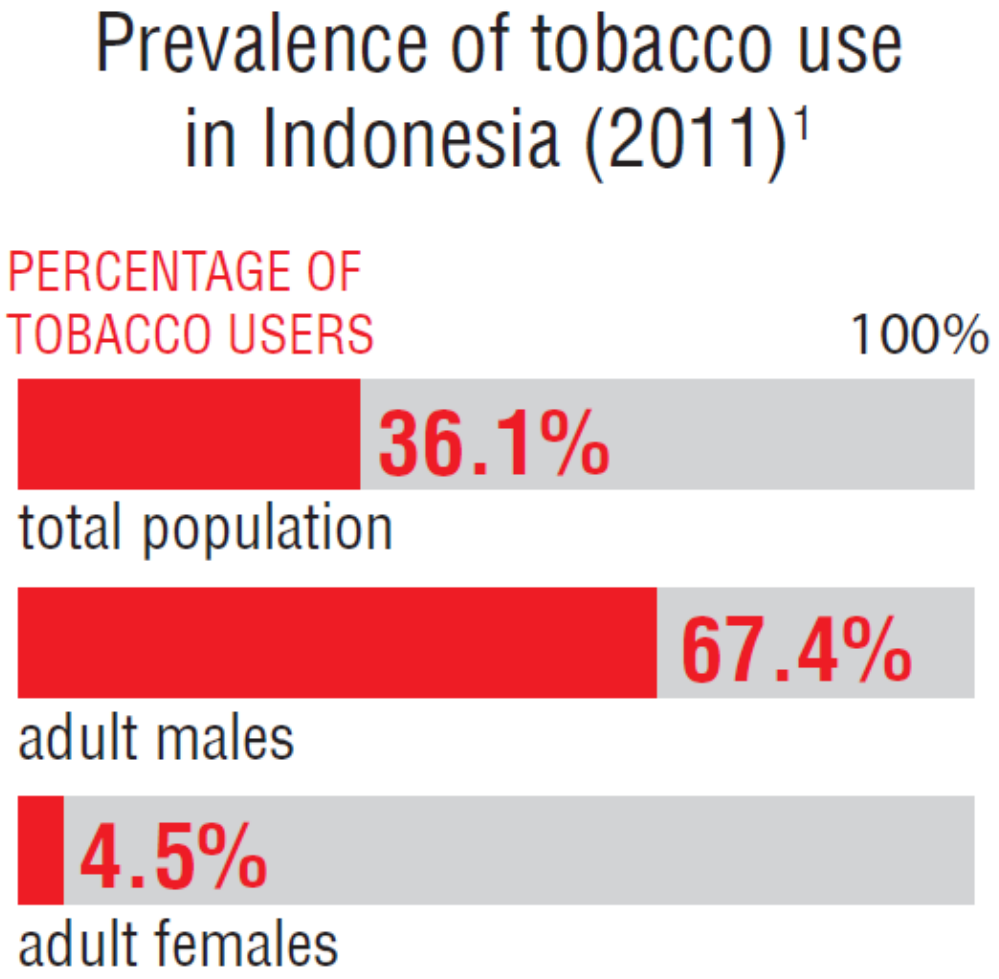
	Males	Females	Both sexes
Population	137 717 861	135 805 760	273 523 621
Number of new cancer cases	183 368	213 546	396 914
Age-standardized incidence rate (World)	138.9	145.4	141.1
Risk of developing cancer before the age of 75 years (%)	15.0	14.9	14.9
Number of cancer deaths	124 698	109 813	234 511
Age-standardized mortality rate (World)	96.3	75.9	85.1
Risk of dying from cancer before the age of 75 years (%)	10.5	8.3	9.4
5-year prevalent cases	389 640	556 448	946 088
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Liver Nasopharynx Prostate	Breast Cervix uteri Ovary Colorectum Thyroid	Breast Cervix uteri Lung Colorectum Liver





WHO, IARC globocan 2021

Main Risk Factor : SMOKING

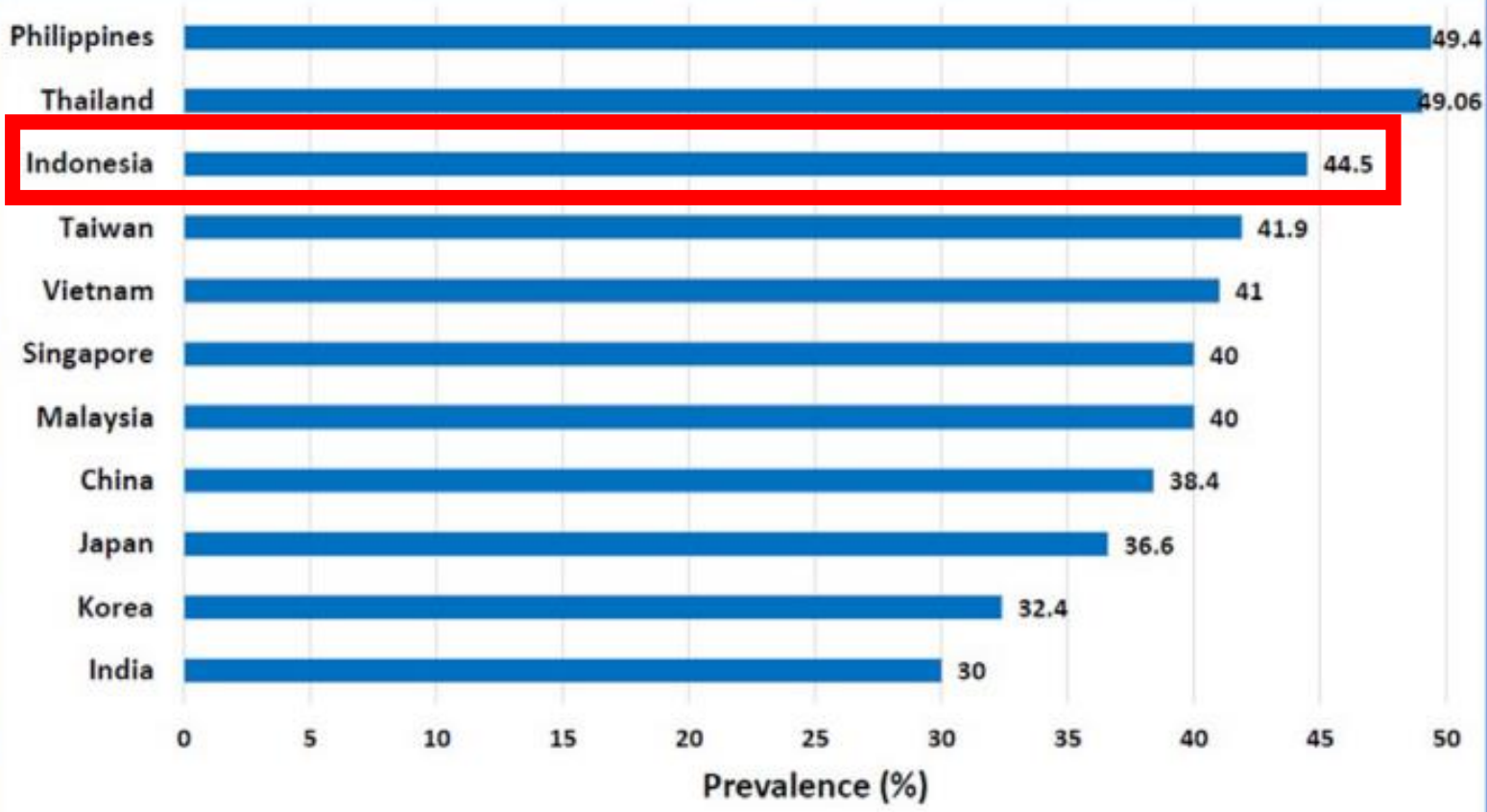


Profil Mutasi EGFR pada Populasi Asia

Genetic Features of Lung Cancer in Asia

- High prevalence of *EGFR* mutations (40–55%)
- Most common *EGFR* mutations: exon 19 deletion, L858R
- Prevalence of *EGFR* mutations in non-smoking females: 63%
- Low prevalence of *KRAS* mutations (8–12%)
- Most common *KRAS* mutation: G12C
- Other common mutations: *TP53* and *RBM 10*

Prevalence of EGFR Mutations in Lung Cancer in Asian Countries



Lam DC, Liam CK, Andarini SA, et al J Clin Onco 2023; June 2023

General Approach to Lung Cancer

- Surgery
- Chemotherapy
- Radiotherapy
- **Targeted therapy**
  - Small molecules targeted therapy
  - Bispecific Monoclonal Antibody
- Immunotherapy

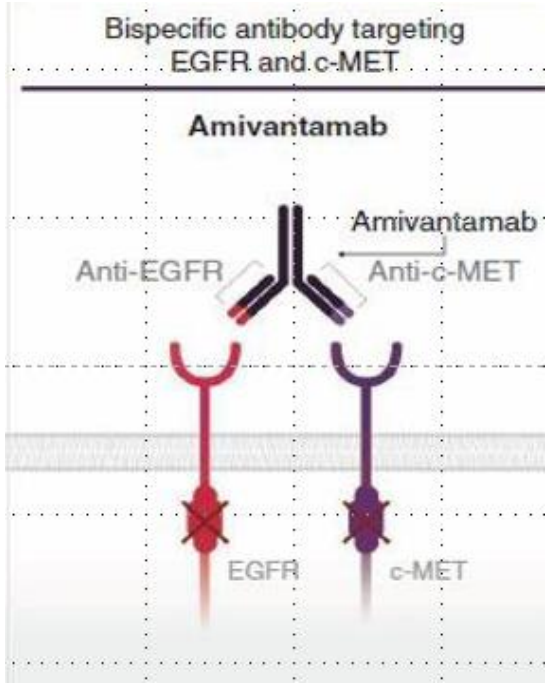
Targeted Therapy

Small Molecules Targeted therapy (Tablet)

EGFR TKI (**gefitinib, erlotinib**, osimertinib, **afatinib**, dacomitinib),
ALK-inhibitor (alectinib, brigatinib, lorlatinib)

Bispecific monoclonal antibody

Amivantamab



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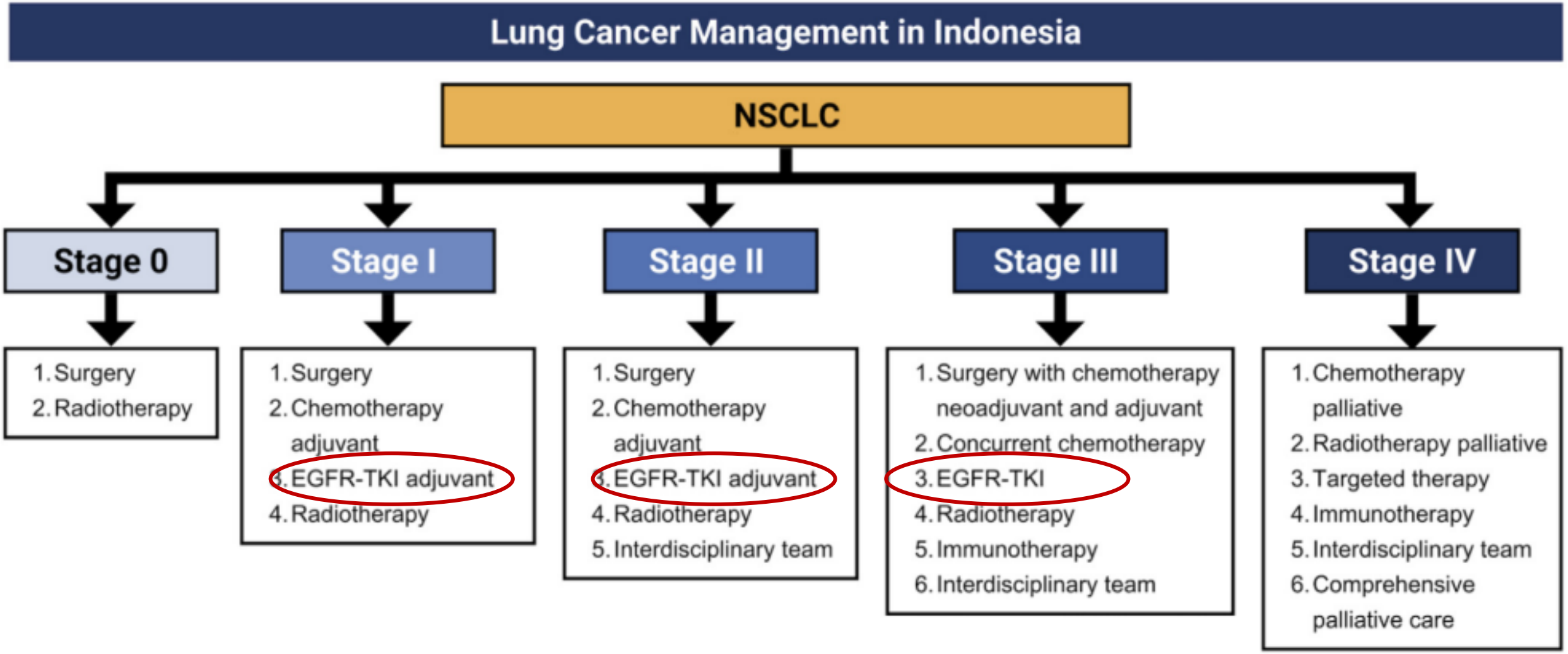
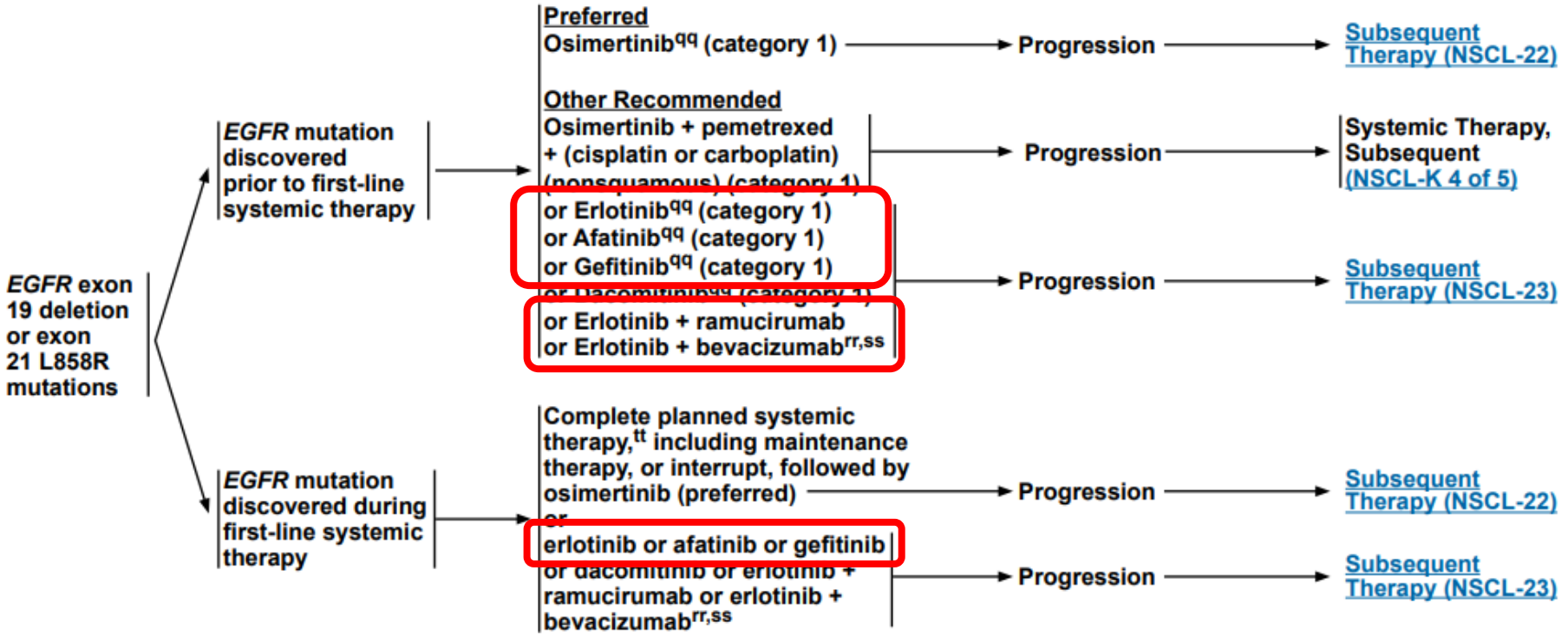


https://www.sciencedirect.com/science/article/abs/pii/S1556086423006317

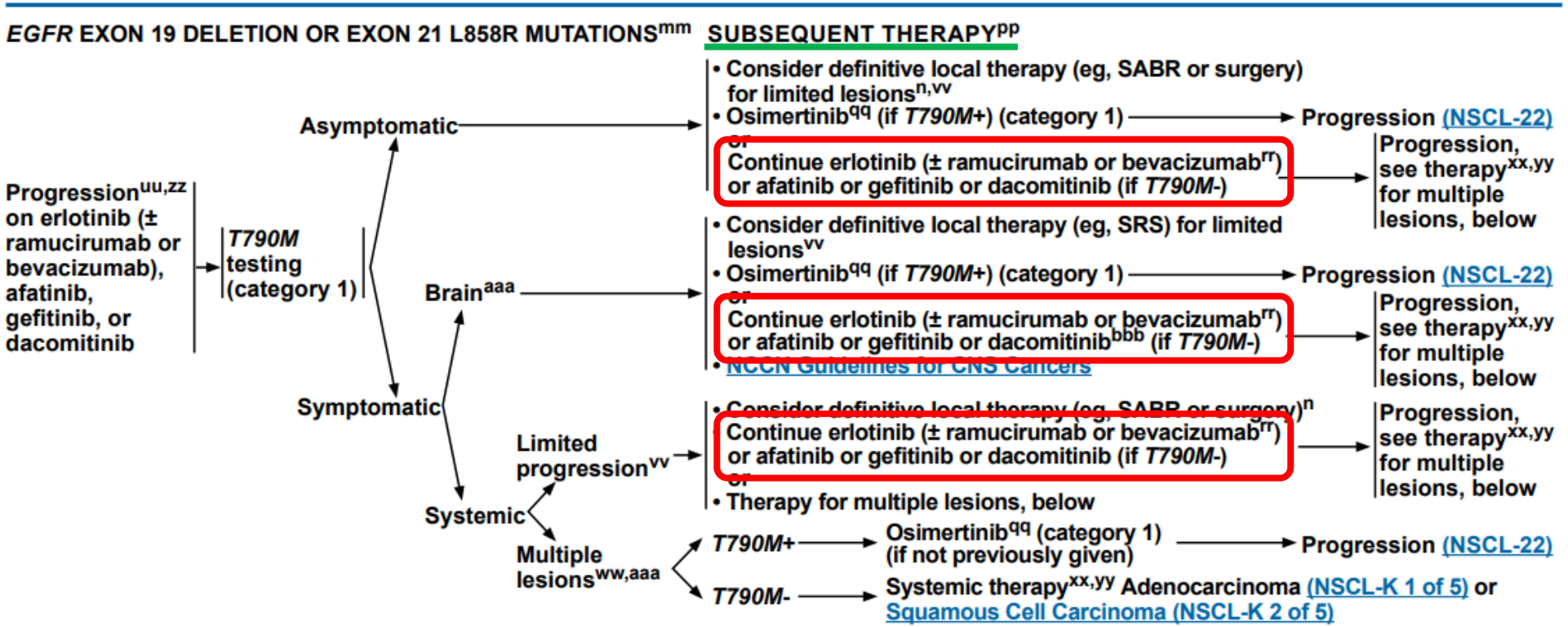
EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[mm]

FIRST-LINE THERAPY[pp]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[rr] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. The rate of side effects (pneumonitis) is higher within 3 months. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[rr] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.

[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Clinical trials have included up to 3 to 5 progressing sites.

[ww] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. NCCN Guidelines for Small Cell Lung Cancer.

[xx] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or exon 21 L858R, *ALK*+ NSCLC.

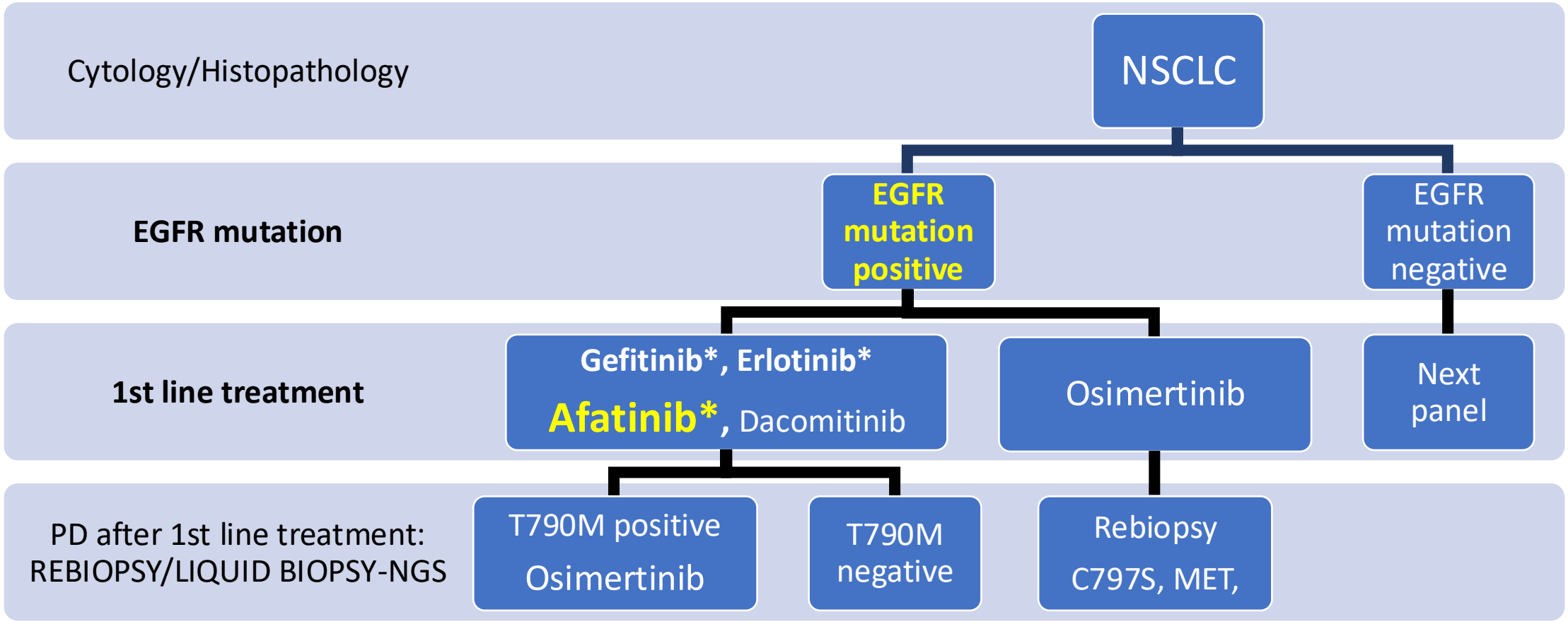
[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression, for the T790M mutation and other genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

[aaa] Consider osimertinib (regardless of T790M status) for progressive CNS disease or leptomeningeal disease. In the BLOOM study, osimertinib was used at 160 mg once daily for patients with leptomeningeal disease.

[bbb] In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PDPI 2022 : EGFR mutation positive



*available on BPJS

Classification of the Approved EGFR-TKIs

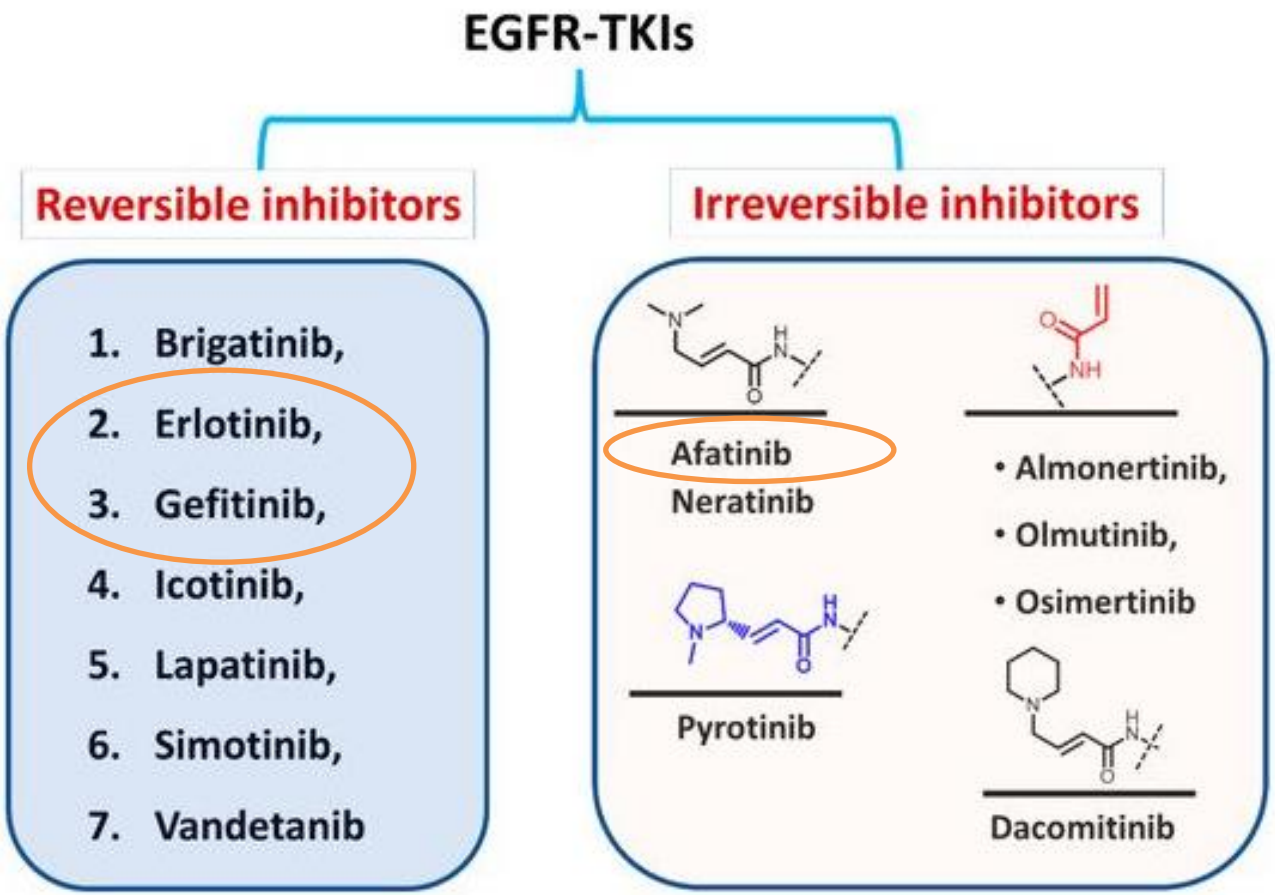


Figure 2. Classification of EGFR-TKIs based on the nature of inhibition of EGFR.

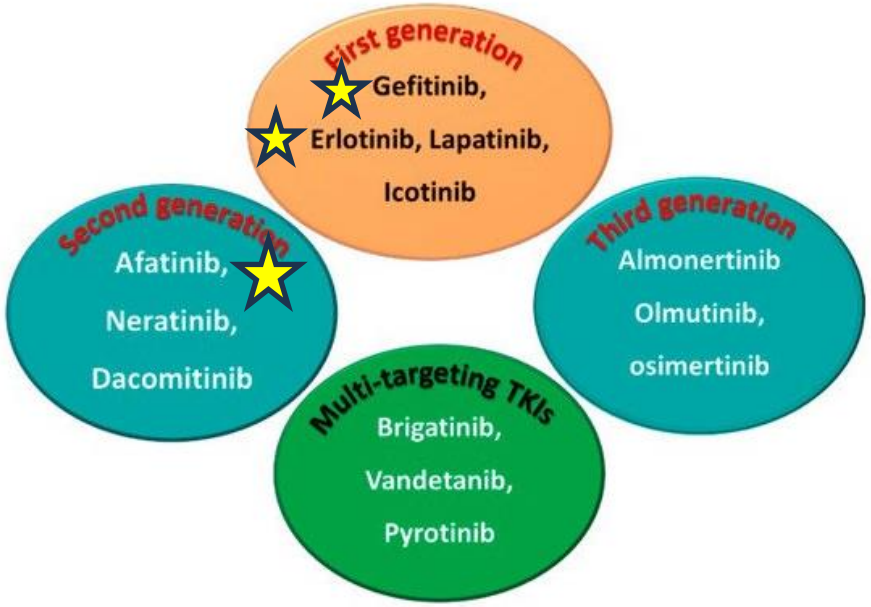
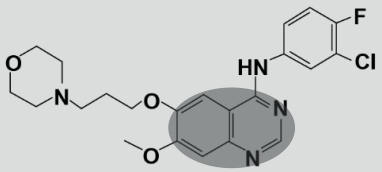
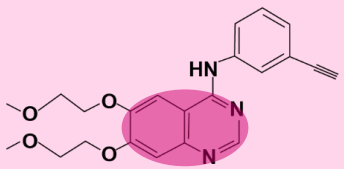
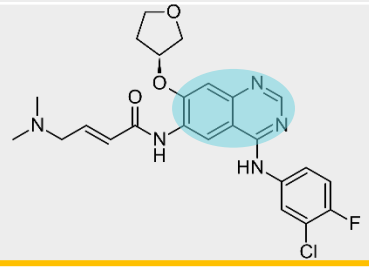
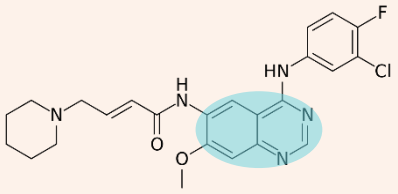
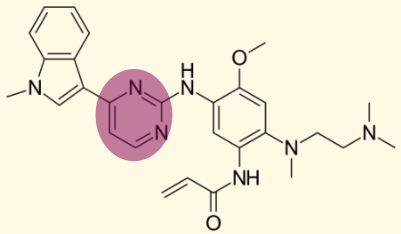


Figure 3. First-, second-, and third-generation EGFR-TKIs and the multi-targeting inhibitors.

Profiles of EGFR TKIs[1]

	First generation		Second generation		Third generation
Drug	**Gefitinib[2,3,4]**	**Erlotinib[5,6,7]**	**Afatinib[8-12]**	**Dacomitinib[12-15]**	**Osimertinib[12,16-18]**
Company	AstraZeneca	Roche	Boehringer Ingelheim	Pfizer	AstraZeneca
Status	Approved	Approved	Approved	Approved	Approved
EGFR inhibition	Reversible	Reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
Primary Target	wt-EGFR, EGFR: ex19del, L858R	wt-EGFR, EGFR: ex19del, L858R	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, HER2 amp, HER4[a]	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, mutant-HER2, HER2 amp, HER4[a]	EGFR: L858R, ex19del, T790M
Chemical structure (backbone highlighted)					

amp, amplification; EGFR = epidermal growth factor receptor; ex19del = exon 19 deletion; HER2 = human epidermal growth factor receptor 2; HER4 = human epidermal growth factor receptor 4; TKI = tyrosine kinase inhibitor; wt = wild type.

[a]Preclinical targeting of T790M; table adapted from Sullivan I, Planchard D. *Front Med (Lausanne)*. 2017;3:76.

References in slide notes.

Monitoring EGFR-TKI Patient

DIAGNOSIS

- X-ray +Thorax CT
- Biopsy : proven cytology or histopatology
- Only Adenoca underwent EGFR mutation testing (supported by pharma company)

1st EGFR-TKI administered

Covered by Indonesia National Health Insurance :

- **Gefitinib**
- **Erlotinib**
- **Afatinib**

MONITORING

Monthly assessment:

a. Clinical response
b. Side effects and Toxicity effect

3-monthly assessment:

a. Clinical response
b. Side effect and toxicity effect
c. CT scan

PROGRESSIVE DISEASE

Determined by:

1. Clinical PD
2. Radiological PD

❖ All advanced lung adenocarcinoma patients should be tested for EGFR & ALK regardless of clinical characteristics (e.g. age, race, smoking status)
❖ Nonsquamous, non-small-cell histology
❖ Any non-small-cell histology when clinical features indicate a higher probability of an oncogenic drive (e.g. young age [<50 years]; light or absent tobacco exposure)

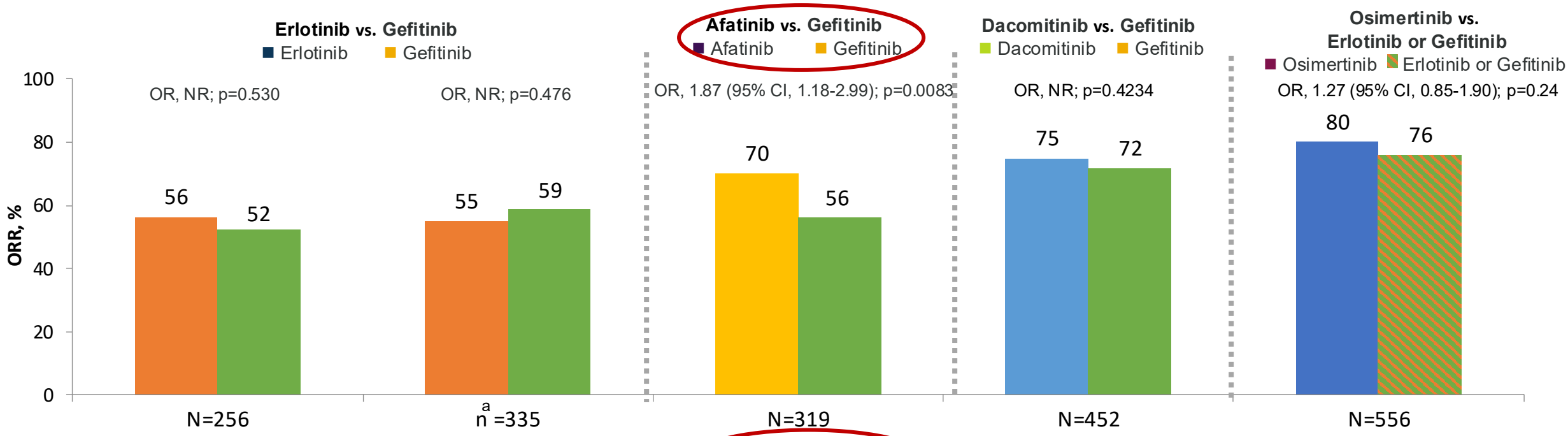
Arch Path Lab Med 2018;142(3):321

Summary - EGFR TKI Monotherapy Studies with Results

Study	Study Design	Treatment Arms	Primary Outcome	Results
IPASS[1]	Phase III, open-label, 1L advanced adenocarcinoma; EGFR+ subgroup; (n=261)	Gefitinib vs CARBO+PAC	PFS	• **In EGFR+ group, PFS significantly longer following gefitinib** (HR, 0.48; 95% CI, 0.36–0.64; p<0.001) • **In EGFR- group (n=176) PFS significantly longer following chemotherapy** (HR 2.85; 95% CI, 2.05 to 3.98; p<0.001)
EURTAC[2]	Phase III, open-label, 1L advanced EGFR+; (n=174)	Erlotinib vs standard chemotherapy	PFS	• **mPFS 9.7 vs 5.2 months, erlotinib vs chemotherapy** (HR, 0.37; 95% CI, 0.25–0.54; p<0.0001)
ARCHER 1050[3]	Phase III, open-label 1L EGFR+ Stage III / IV NSCLC; (n=452)	Dacomitinib vs gefitinib	PFS	• **mPFS 14.7 vs 9.2 months, dacomitinib vs gefitinib** (HR, 0.59; 95% CI, 0.47–0.74; p<0.0001)
LUX-Lung 3[4]	Phase III, Stage IIIB / IV EGFR+ adenocarcinoma; (n=345)	**Afatinib** vs CIS+PTX	PFS	• **mPFS for patients with exon 19 deletions and L858R *EGFR* mutations (n=308) 13.6 vs 6.9 months** (HR, 0.47; 95% CI, 0.34–0.65; p=0.001)
LUX-Lung 6[5]	Phase III, open-label 1L EGFR+ Stage IIIB / IV NSCLC; (n=364)	Afatinib vs GEM+CIS	PFS	• **mPFS 11.0 vs 5.6 months, afatinib vs GEM+CIS** (HR, 0·28; 95% CI, 0.20–0.39; p<0.0001)
LUX-Lung 7[6]	Phase IIB, open-label, 1L EGFR+ Stage IIIB / IV NSCLC; (n=319)	**Afatinib** vs gefitinib	PFS, TTF, OS	• **mPFS 11.0 vs 10.9 months, afatinib vs gefitinib** (HR, 0.73; 95% CI, 0.57–0.95; p=0.017) • **Median TTF 13.7 vs 11.5 months, afatinib vs gefitinib** (HR, 0.73; 95% CI, 0.58–0.92; p=0.0073)
FLAURA[7,8]	Phase III, double-blind, 1L, EGFR+, advanced NSCLC; (n=556)	Osimertinib vs SoC EGFR TKI	PFS	• **mPFS 18.9 vs 10.2 months, osimertinib vs standard TKI** (HR, 0.46; 95% CI, 0.37–0.57; p<0.001)

1. Mok TS, et al. *N Engl J Med* 2009;361:947–957; 2. Rosell R, et al. *Lancet Oncol* 2012;13:239–246; 3. Wu YL, et al. *Lancet Oncol* 2017;18:1454–1466; 4. Sequist LV, et al. *J Clin Oncol* 2013;31:3327;
5. Wu YL, et al. *Lancet Oncol* 2014:15;213–222; 6. Park K, et al. *Lancet Oncol* 2016:17;577–589; 7. Soria JC, et al. *N Engl J Med* 2018:378;113–125; 8. Ramalingam SS, et al. Presented at: ESMO; 27 September-1 August 2019; Barcelona, Spain. Oral presentation LBA5.

Head-to-head TKI clinical trials in advanced EGFRm NSCLC: ORR results



Study:	**CTONG 0901[1] Phase III**	**WJOG 5108L[2] Phase III**	**LUX-Lung 7[3] Phase IIB**	**ARCHER 1050[4] Phase III**	**FLAURA[5,6] Phase III**
Prior Therapy:	TKI naïve (35% previously treated[b])	TKI naïve, previously treated[b]	Treatment naïve	Treatment naïve	Treatment naïve
Brain metastases:	Unstable brain metastases excluded	Symptomatic brain metastases excluded	Symptomatic brain metastases, LM excluded	CNS metastases excluded	Symptomatic and unstable brain metastases excluded[c]

CNS = central nervous system; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; LM = leptomeningeal metastasis; NR = not reported; NSCLC = non-small cell lung cancer; OR = odds ratio; ORR = objective response rate; TKI = tyrosine kinase inhibitor.

[a]Subset analysis of enrolled patients with EGFR mutations; [b]Previously treated with chemotherapy; [c]Patients with symptomatic and unstable brain metastases were permitted if they had completed definitive therapy, were not on steroids, and had a stable neurological status for ≥2 weeks after completion of definitive therapy and steroids.[6]

1. Yang JJ et al. *Br J Cancer*. 2017;116:568-574. 2. Urata Y et al. *J Clin Oncol*. 2016;34:3248-3257. 3. Park K et al. *Lancet Oncol*. 2016;17:577-589. 4. Wu YL et al. *Lancet Oncol*. 2017;18:1454-1466. 5. Soria JC et al. *N Engl J Med*. 2018;378:113-125. 6. Soria JC et al. Supplementary protocol. *N Engl J Med*. 2018;378:113-125.

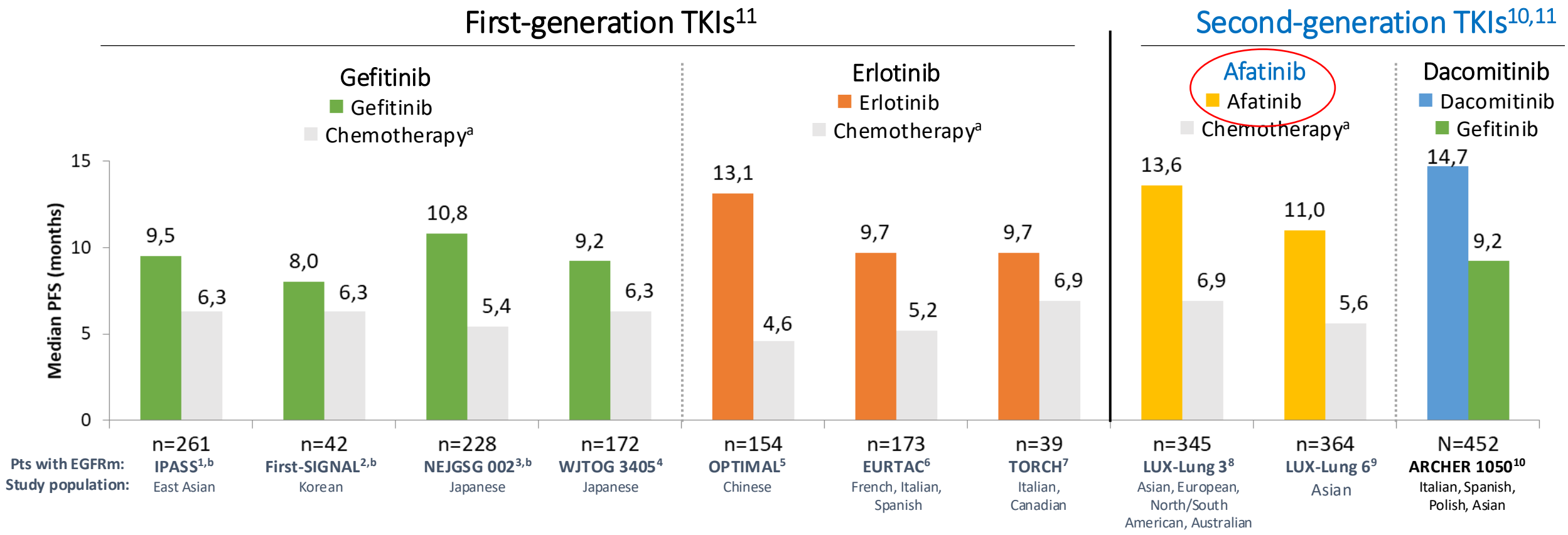
First-line efficacy of 2nd/3rd gen EGFR-TKIs in patients with EGFRm NSCLC

	Study	ORR, % (independently assessed)	Median PFS, months (HR [95% CI]) (independently assessed)	Median OS, months (HR [95% CI])
EGFR TKI vs. chemotherapy				
Afatinib	LUX-Lung 3[1,2] (vs. cisplatin/pemetrexed) N=345	**56** vs. 23 (p=0.001)	**11.1** vs. 6.9 (0.58 [0.43-0.78]; p=0.001)	**28.2** vs. 28.2 (0.88 [0.66-1.17]; p=0.39)
Afatinib	LUX-Lung 6[2,3] (vs. cisplatin/gemcitabine) N=364	**66.9** vs. 23.0 (p<0.0001)	**11.0** vs. 5.6 (0.28 [0.20-0.39]; p<0.0001)	**23.1** vs. 23.5 (0.93 [0.72-1.22]; p=0.61)
Afatinib	LUX-Lung 3 and 6 combined[2]	Not reported	Not reported	**25.8** vs. 24.5 (0.91 [0.75-1.11]; p=0.37)
EGFR TKI vs. EGFR TKI				
Afatinib	LUX-Lung 7[4,5] (vs. gefitinib) N=319	**70** vs. 56 (p=0.0083)	**11.0** vs. 10.9 (0.73 [0.57-0.95]; p=0.017)	**27.9** vs. 24.5 (0.86 [0.66-1.12]; p=0.2580)
Dacomitinib	ARCHER 1050[6,7] (vs. gefitinib) N=452	**75** vs. 72 (p=0.4234)	**14.7** vs. 9.2 (0.59 [0.47-0.74]; p<0.0001	**34.1** vs. 26.8 (0.760 [0.582-0.993]; p=0.0438[a])
Osimertinib	FLAURA[8,9] (vs. standard EGFR-TKIs)	**80** vs. 76 (p=0.24) (investigator assessed)	**18.9** vs. 10.2 (0.46 [0.37-0.57]; p<0.001) (investigator assessed)	**38.6** vs. 31.8 (0.80 [0.64-1.00[b]]; p=0.046[c])

EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; HR = hazard ratio; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

[a]The hierarchical statistical testing order: PFS→ORR →OS. There was no formal testing of OS, since ORR was not statistically significant;[10] [b]95.05% CI reported for HR for OS;[9] [c]For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required.[9]

PFS among first- and second-generation EGFR-TKIs



The majority of patients treated with EGFR-TKIs ultimately progress with an average PFS of 8-14 months

EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

[a]Chemotherapy is platinum doublet chemotherapy; [b]In patients with any EGFR mutation. All other studies are in patients with common EGFRm (L858R and/or exon 19 deletions/mutation).

Real World Evidence Data Afatinib in Indonesia

Clinical characteristics and real-world progression-free survival of patients with EGFR mutation positive non-small cell lung cancer treated with afatinib as first-line : **A retrospective cohort study from Indonesia**

Background: The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) afatinib, demonstrated superiority to chemotherapy as a first-line treatment and improved survival in non-small cell lung cancer (NSCLC) patients with EGFR mutations. This study aimed to investigate the clinical risk factors affecting progression-free survival (PFS) of patients treated with first-line afatinib in Indonesia.

Methods: This is a retrospective cohort study. Clinical characteristics and data were collected from medical records from 14 respiratory service centers nationwide between January 2017 and December 2021. The Kaplan-Meier method and log-rank test were used to estimate PFS, and the Cox proportional hazards model was used for multivariate analyses.

Results

A total 106 patients treated with **first-line afatinib** were enrolled. The median age was 59 years (range: 18-81) and **54.3%** were female. Patients with smoking history were 34.3% while 22.9% were with ECOG performance status (PS) ≥2 and 98.1% with EGFR common mutations. Median PFS was 12 months (95% CI: 10.5-13.5).

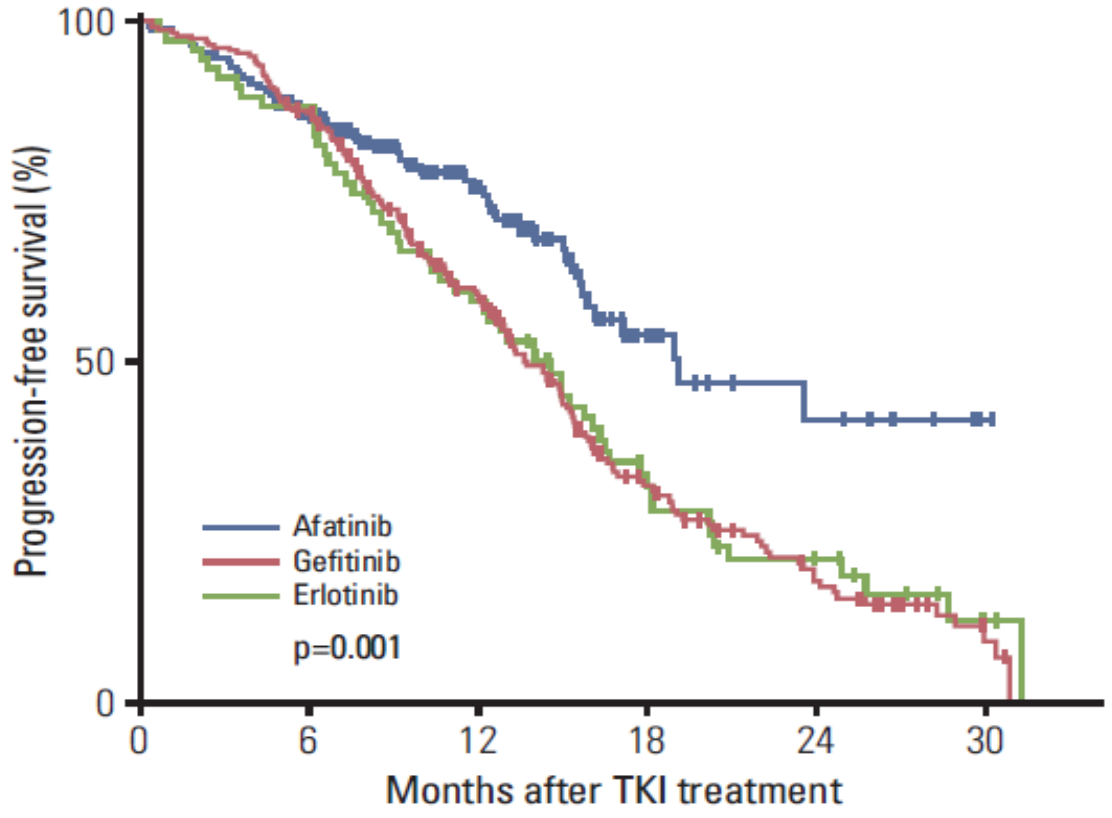
Patients with exon 19 deletion, never smoker, and ECOG PS 1 had the longest PFS of 13 months, and those with poor ECOG PS were with the shortest PFS of 8 months

This retrospective cohort study showed that **smoking history** and **poor ECOG PS** are **independent factors associated with poor PFS** in EGFR mutation positive NSCLC with first-line afatinib treatment. Other demographic characteristics had **no impact in PFS** including **gender, race, history of family cancer, history of tuberculosis, staging, pleural effusion, brain metastasis,** and **EGFR mutations**.

https://www.annalsofoncology.org/article/S0923-7534(22)04530-6/fulltext

Real World Evidence Data Afatinib in South Korea

- Korean real-world data showed that **Afatinib significantly improved PFS** vs. Gefitinib or Erlotinib



The median PFS times for :

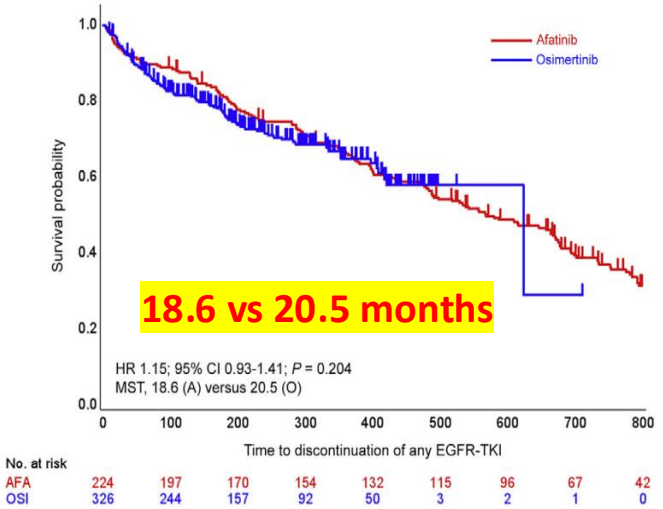
Afatinib
- **19.1** months (95% CI, 12.3 to 25.9)
Gefitinib,
- 13.7 months (95% CI, 12.3 to 15.1)
Erlotinib
-14.0 months(95% CI, 11.3 to 16.8)
respectively (p=0.001)

Kim Y et al. Cancer Res Treat. 2019;51(2):502-509.

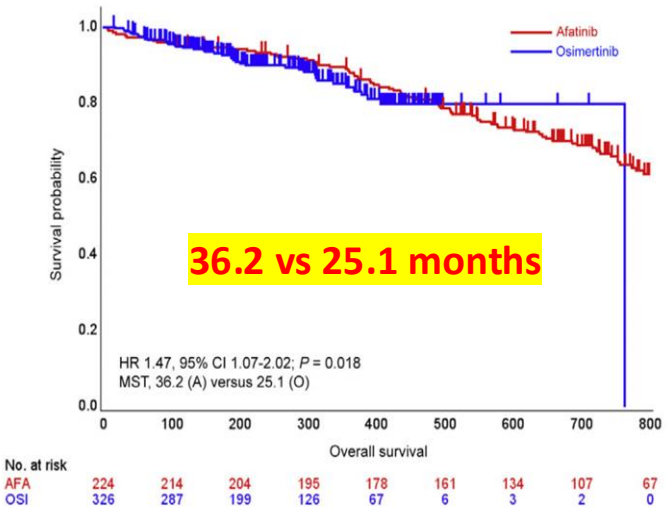
Real World Practice of 1st Line Afatinib vs Osimertinib from Japan

- The subgroup analysis with the propensity score method revealed that **afatinib had a strong trend of prolonged TD-TKI and OS over** osimertinib in patients with the L858R mutation

TD-TKI adjusted by propensity score



OS adjusted by propensity score



Outcomes	TTD*		OS*	
	Median (95% CI)	p-Value	Median (95% CI)	p-Value
Afatinib cohort (with 25% Afa-Osi sequence)	18.6 (15.8-22.0)	0.204	36.2 (30.6-55.3)	0.018
Osimertinib cohort (with <1% Osi-Afa sequence)	20.5 (13.8-not estimated)		25.1 (not estimated)	

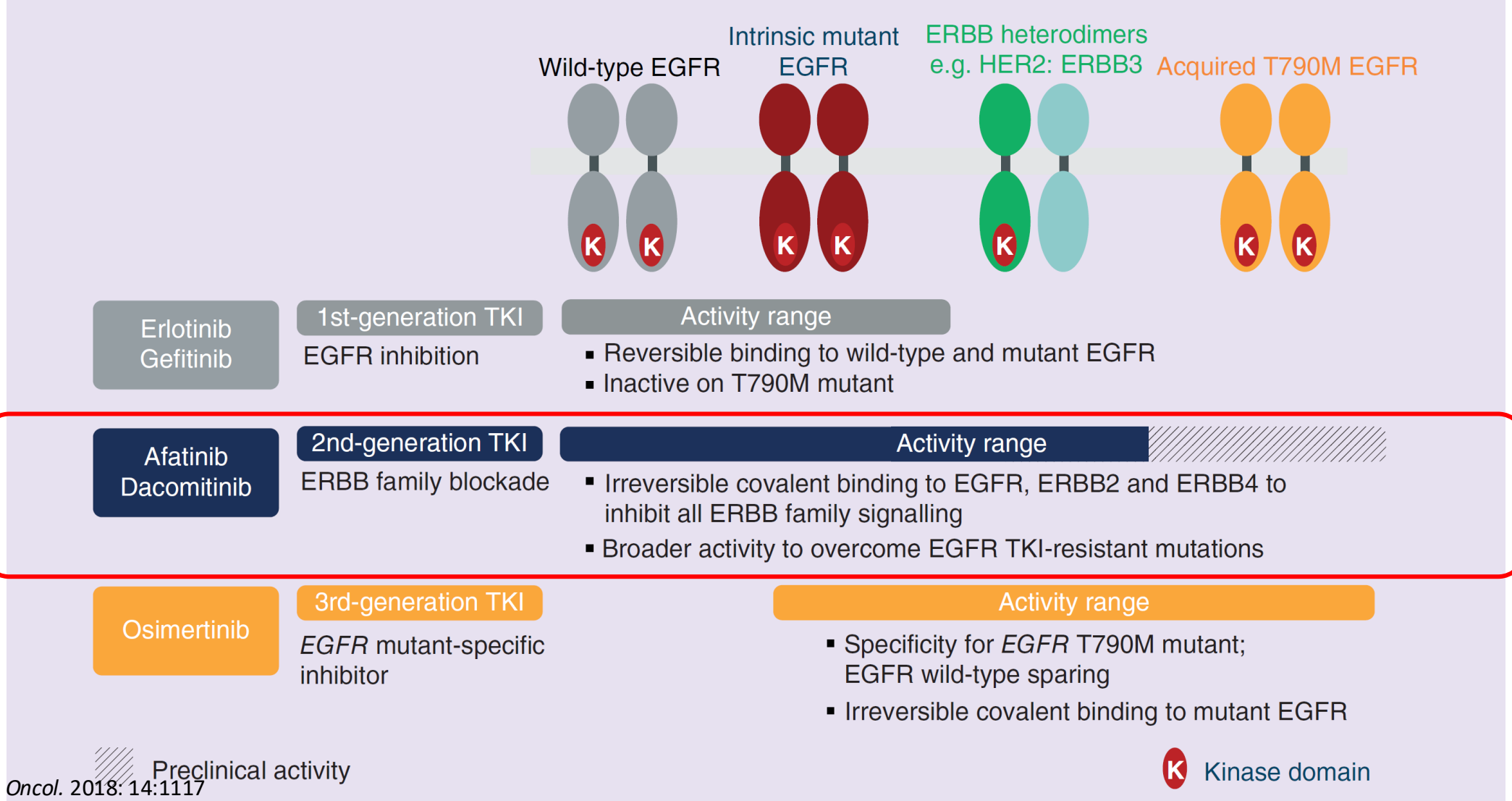
RWD – Real-world data; TD-TKI – Time to discontinuation of any EGFR TKI; 2G – 2nd-generation; 3G – 3rd-generation.

Ito K, et al. *ESMO Open*. 2021 May 10;6(3):100115

EGFR TKIs are not Equal:
Afatinib 2nd Generation Irreversible TKI

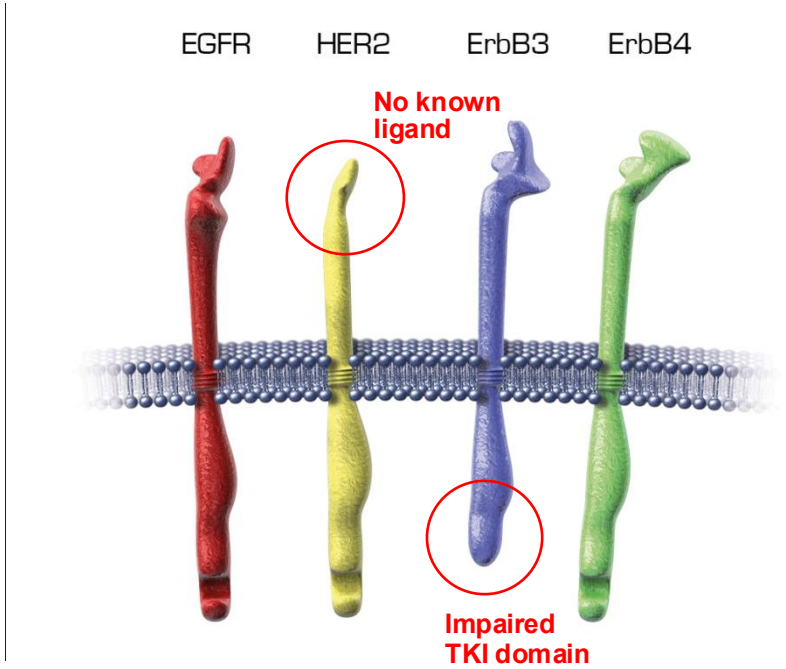
What is Afatinib?

- ErbB family consists: EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4
- **Afatinib** are EGFR TKI irreversible blockade signaling in all ErbB receptor family



Girard N. *Future Oncol.* 2018: 14:1117

The ErbB family of receptors has 4 members



Adapted from Yarden and Pines 2012.[1]

The receptors are responsible for essential functions in homeostasis of healthy tissues. However, they can upregulate proliferation and metastasis of various tumours.[1]

EGFR (ErbB1)

- Mutation frequency in NSCLC: 10% of white and 50% of Asian patients[2]
- Common mutations: exon 19 (deletion) and exon 21 (point mutation L858R)[3]

HER2 (ErbB2)

- Preferred partner for dimerisation for all receptors of the ErbB Family[4]
- Mutation frequency in NSCLC: 2%-4%[5,6]

ErbB3

- Acts as heterodimer with HER2 as the most potent oncogene[7]

ErbB4

- Increasing relevance in dysregulation of the ErbB Family signal cascade[8]
- Mutation frequency in NSCLC: 2%-5%[8,9]

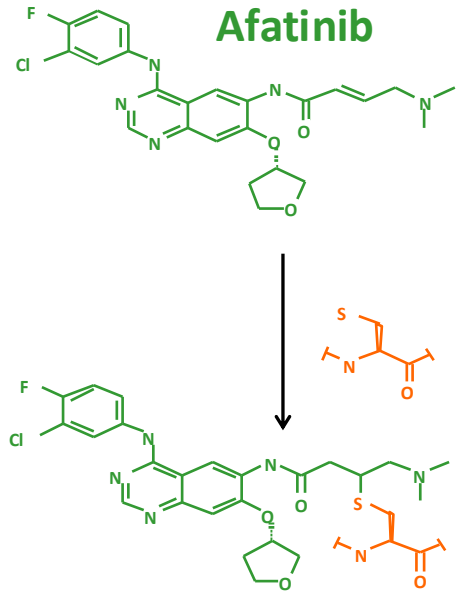
ErbB = proto-oncogene B of the avian erythroblastosis virus.

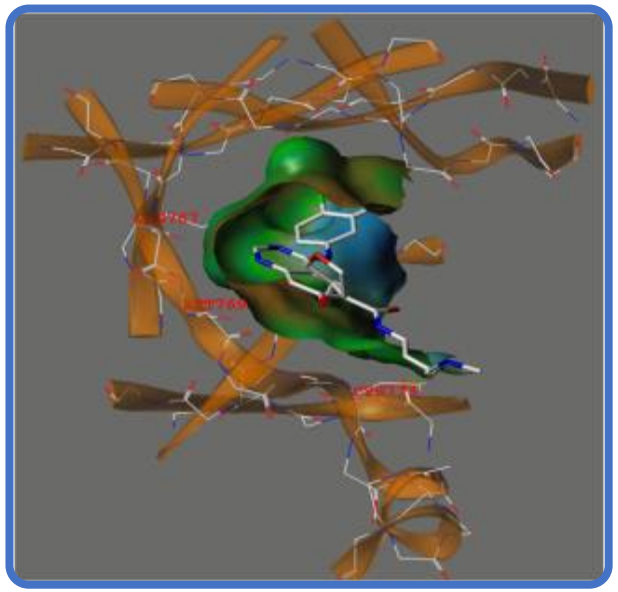
1.Yarden and Pines. *Nat Rev Cancer*. 2012;12:553; 2. Hirsch and Bunn. *Lancet Oncol*. 2009;10:432; 3. Rosell et al. *N Engl J Med*. 2009;361:958; 4.Tzahar et al. *Mol Cell Biol.* 1996;16:5276; 5. Stephens et al. *Nature.* 2004;431:525; 6. Shigematsu et al. *Cancer Res.* 2005;65:1642; 7. Hellyer et al. *J Biol Chem.* 2001;276:42153; 8. Rudloff and Samuels. *Cell Cycle*. 2010;9:1487; 9. Soung et al. *Int J Cancer*. 2006;118:1426.

Afatinib, Structure & Binding

Afatinib irreversibly blocks EGFR, HER2 and ErbB4

Afatinib was designed to covalently bind, and therefore irreversibly block the ErbB Family





Afatinib covalently bound to EGFR, HER2 or ErbB4

Li D, et al. *Oncogene* 2008;27:4702–11; Solca F, et al. *J Pharmacol Exp Ther* 2012. Epub ahead of print.

Drug Safety Report

E-mail : drugsafety@Amaroxpharma.com or call center : 08118115993.

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