Molecular Detection of EGFR ex20ins in NSCLC: Why, When, and How?

Satellite Symposium Sponsored by Janssen

HKIAP Scientific Meeting Fall 2023

Approval code: EM-143197

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Disclaimer

- This meeting is organized and sponsored by Janssen, a division of Johnson & Johnson (HK) Ltd
- This scientific program is intended for educational purposes and for healthcare professionals only.
- The views expressed are those of the individual speaker and do not necessarily reflect the views of Janssen. They are not intended as an endorsement of any usage not contained in the Hong Kong Prescribing Information. Please refer to the approved Hong Kong Prescribing Information before making treatment decision.
- The presentation may include discussion on investigational compounds and/or off-label use of drugs in Hong Kong. Physicians may refer to the product prescribing information before making treatment decision

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Dr Molly LI

Clinical Assistant Professor

- **Department of Clinical Oncology, The Chinese University of Hong Kong**

Dr Molly Li received his MBBS from the University of Hong Kong with distinction in medicine and psychiatry.

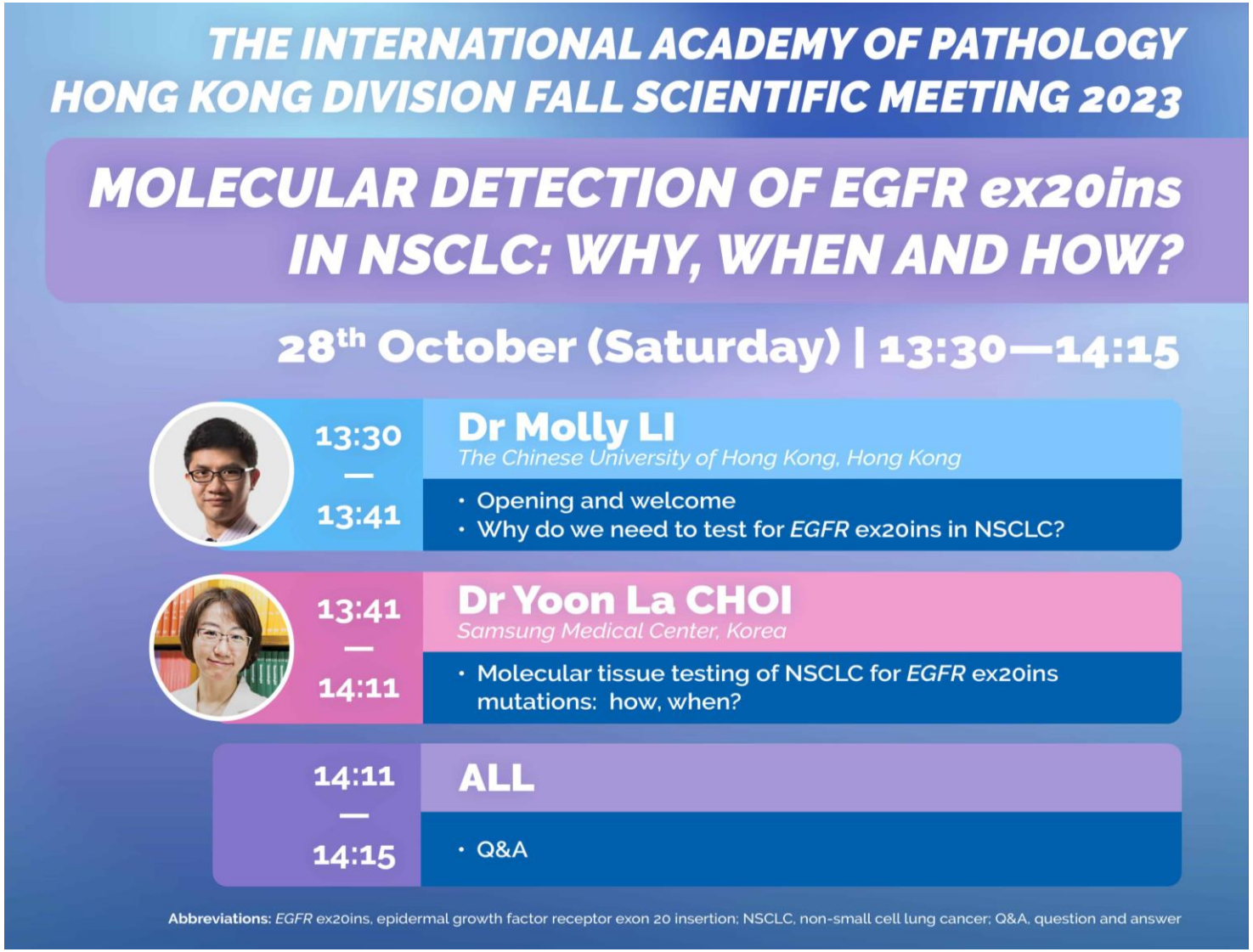
Principal investigator or co-investigator of over 15 lung cancer clinical trials

Principal investigator of a number of translational studies:

- *Resistance mechanism and tumour immune microenvironment of EGFR-mutation positive lung cancer after osimertinib failure*
- *Intratumoral heterogeneity of ALK-mutated lung cancer)*
- *preclinical studies testing novel drug combinations in cell lines and patient derived xenograft models*

Selected as a participant of the ASCO Leadership Development Programme Asia Pacific 2023-2024.

Agenda


THE INTERNATIONAL ACADEMY OF PATHOLOGY
HONG KONG DIVISION FALL SCIENTIFIC MEETING 2023
MOLECULAR DETECTION OF EGFR ex20ins IN NSCLC: WHY, WHEN AND HOW?
28th October (Saturday) | 13:30—14:15
13:30 — 13:41
Dr Molly LI
The Chinese University of Hong Kong, Hong Kong
• Opening and welcome
• Why do we need to test for EGFR ex20ins in NSCLC?
13:41 — 14:11
Dr Yoon La CHOI
Samsung Medical Center, Korea
• Molecular tissue testing of NSCLC for EGFR ex20ins mutations: how, when?
14:11 — 14:15
ALL
• Q&A
Abbreviations: EGFR ex20ins, epidermal growth factor receptor exon 20 insertion; NSCLC, non-small cell lung cancer; Q&A, question and answer

Symposium Objectives:

- To highlight the clinical importance of molecular identification of EGFRex20ins in NSCLC
- To reflect on the recent evidence on the treatment of NSCLC with EGFRex20ins
- To demonstrate the limitation of molecular identification of EGFRex20ins by conventional methodologies (ie. PCR)
- To demonstrate the opportunities and challenges of identifying patients with EGFRex20ins by next generation sequencing (NGS)

香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Calling for EGFR exon 20 insertion testing in NSCLC

Molly SC Li
MBBS (HK), MRCP (UK), FHKCP, FHKAM
Clinical Assistant Professor, Department of Clinical Oncology, CUHK

Email: molly@clo.cuhk.edu.hk
Twitter/X: @mollylisc

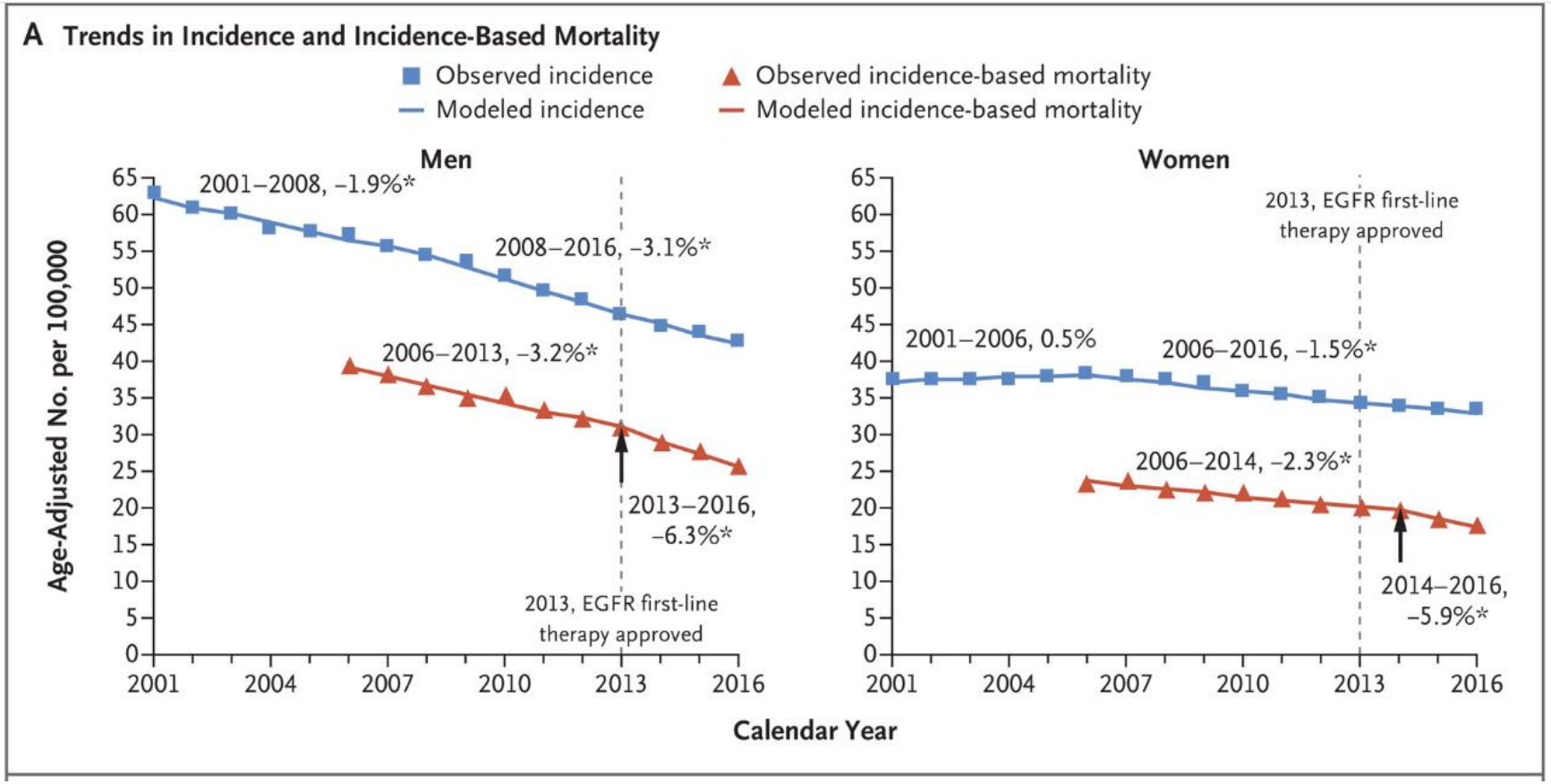
Disclosure

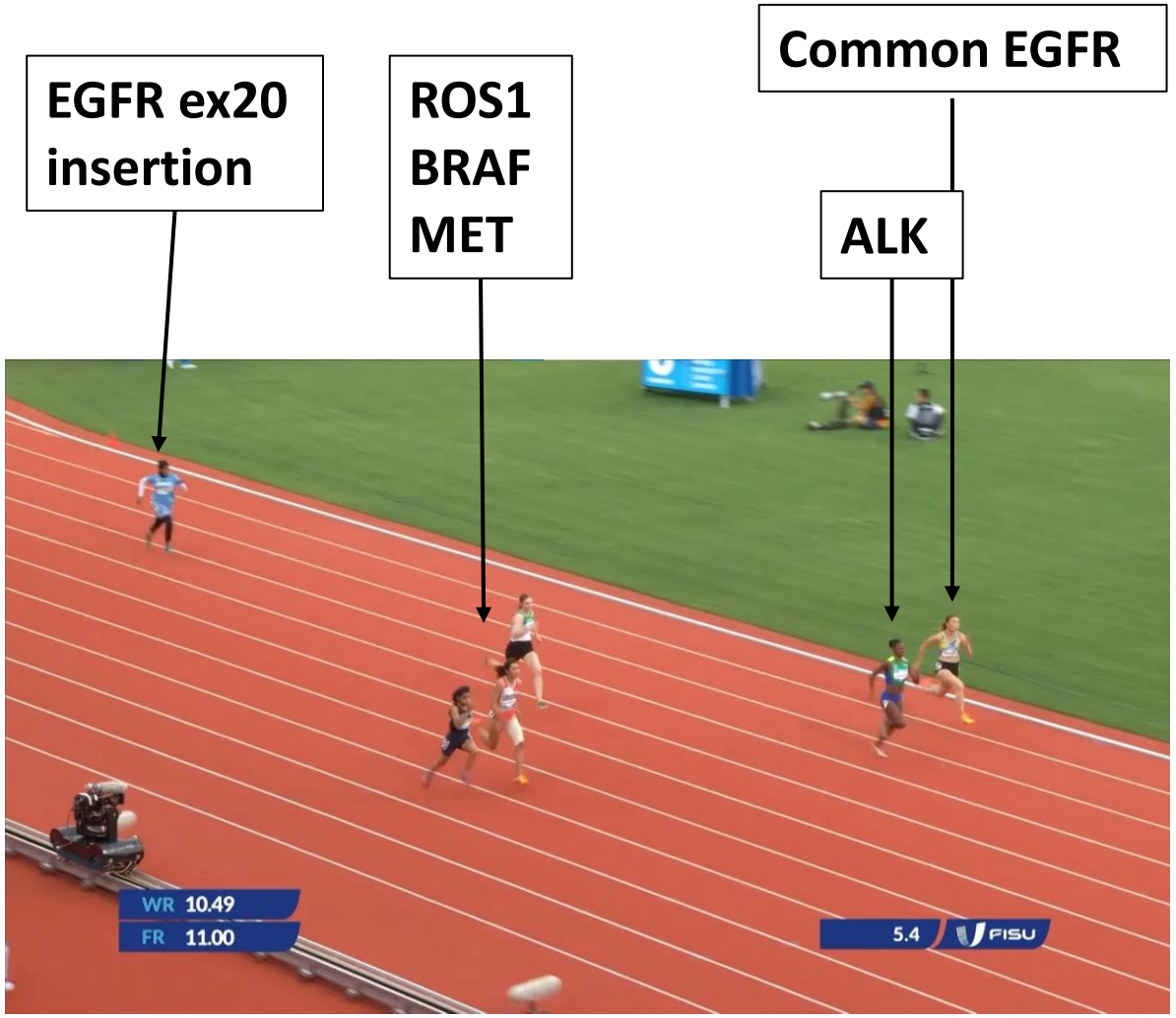
Honorarium	AstraZeneca Novartis Amgen Pfizer Takeda ACE Oncology
Advisory Board	Amgen AnHeart AstraZeneca Pfizer Takeda
Research Funding	Gilead MSD Takeda

Disclaimer

- This meeting is organized and sponsored by Janssen, a division of Johnson & Johnson (HK) Ltd
- This scientific program is intended for educational purposes and for healthcare professionals only.
- The views expressed are those of the individual speaker and do not necessarily reflect the views of Janssen. They are not intended as an endorsement of any usage not contained in the Hong Kong Prescribing Information. Please refer to the approved Hong Kong Prescribing Information before making treatment decision.
- The presentation may include discussion on investigational compounds and/or off-label use of drugs in Hong Kong. Physicians may refer to the product prescribing information before making treatment decision

Personalized medicine is the cornerstone of Lung Cancer Treatment



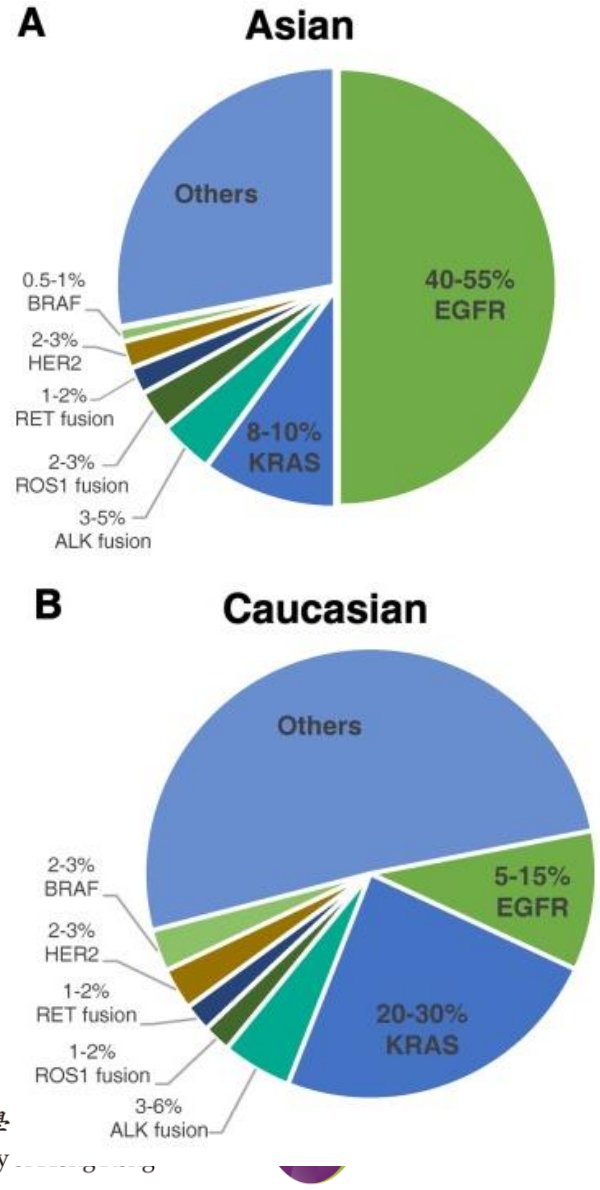


Why?

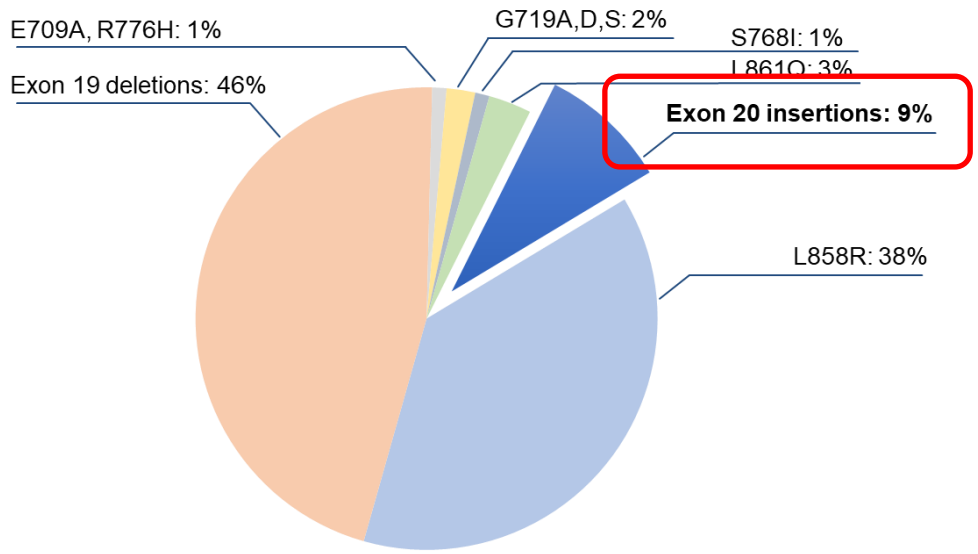
- It is a rare mutation
- EGFR ex20 ins are “TKI resistant”
- Approved EGFR PCR tests (more intended to capture common EGFR) can also detect EGFR exon 20 insertion

No harm in missing a case of EGFR exon 20ins?

EGFR exon 20 insertion is not rare in Asia!



Frequency of *EGFR* Mutations in NSCLC[1]

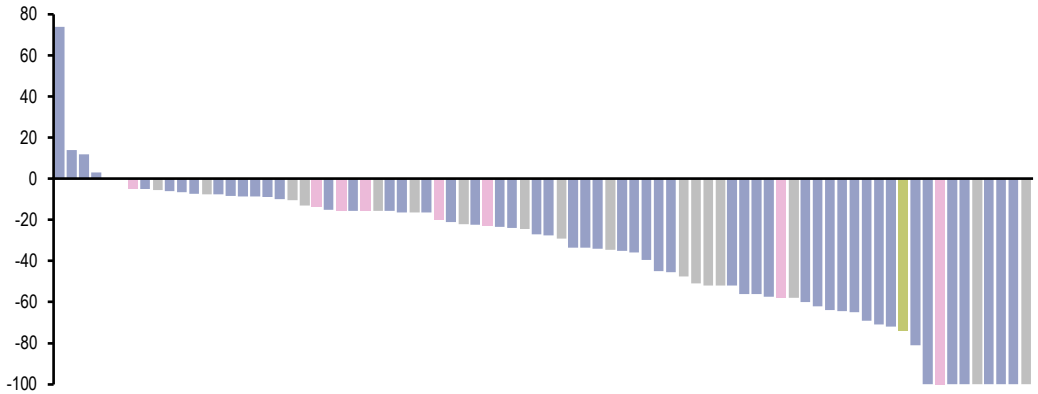


EGFR exon 20 ins is the **3rd** most prevalent type of primary EGFR mutation in NSCLC

1. Oncol Rep. 2017 Mar; 37(3): 1347–1358;
2. Arcila ME. *Mol Cancer Ther*. 2013;12(2):220-229

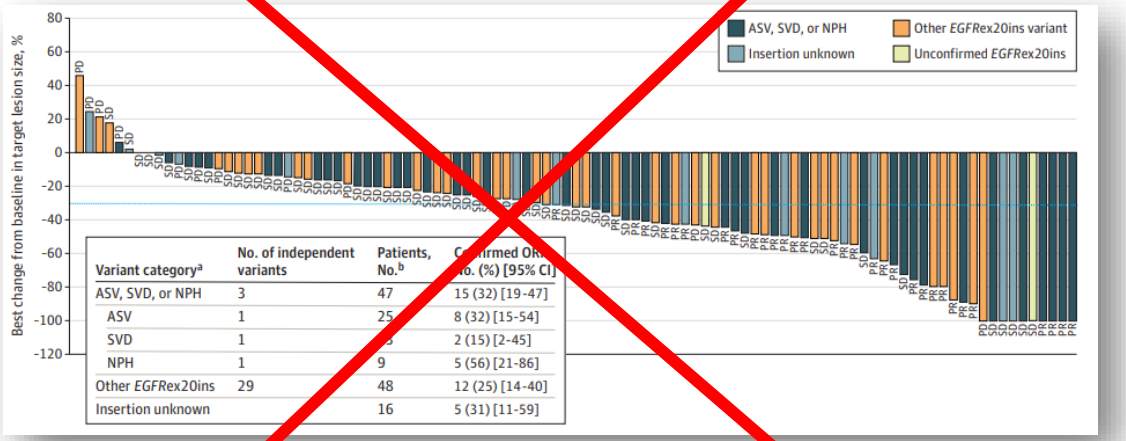
Amivantamab and Mobocertinib are approved for patients with NSCLC harbouring EGFR ex20 ins

Amivantamab



n=81, ORR=40%, mPFS=8.3m, mOS=22.8m

Mobocertinib



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	8	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

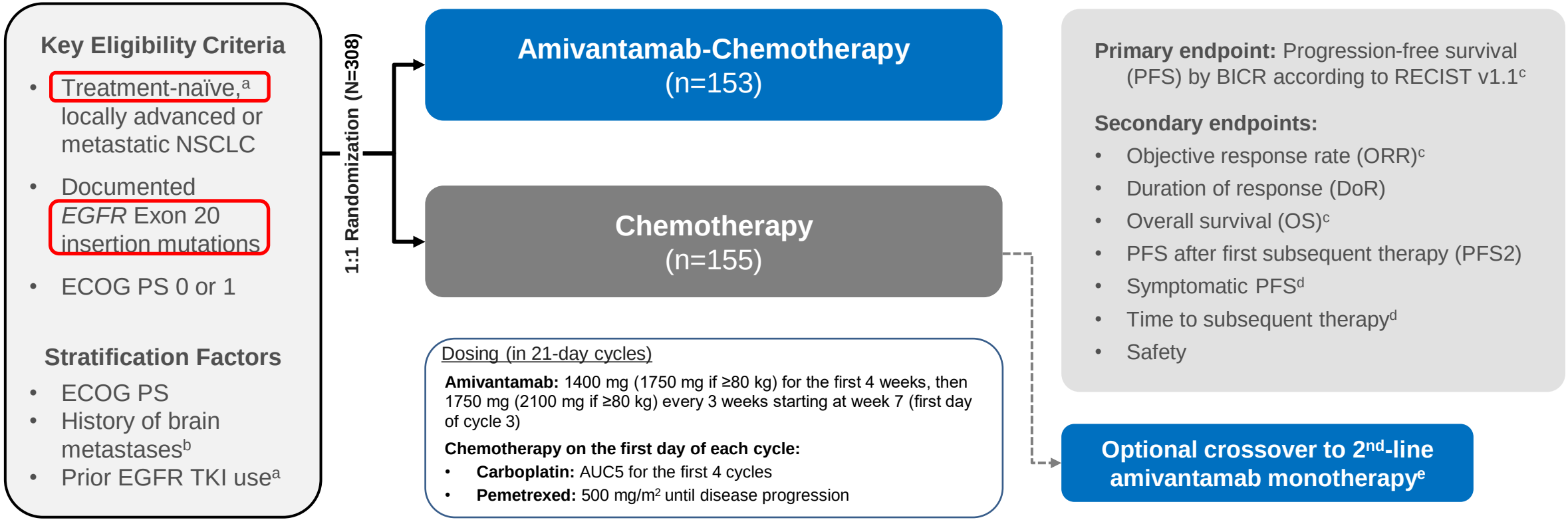
n=96, ORR=28%, mPFS=7.3m, mOS=24.0m

香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

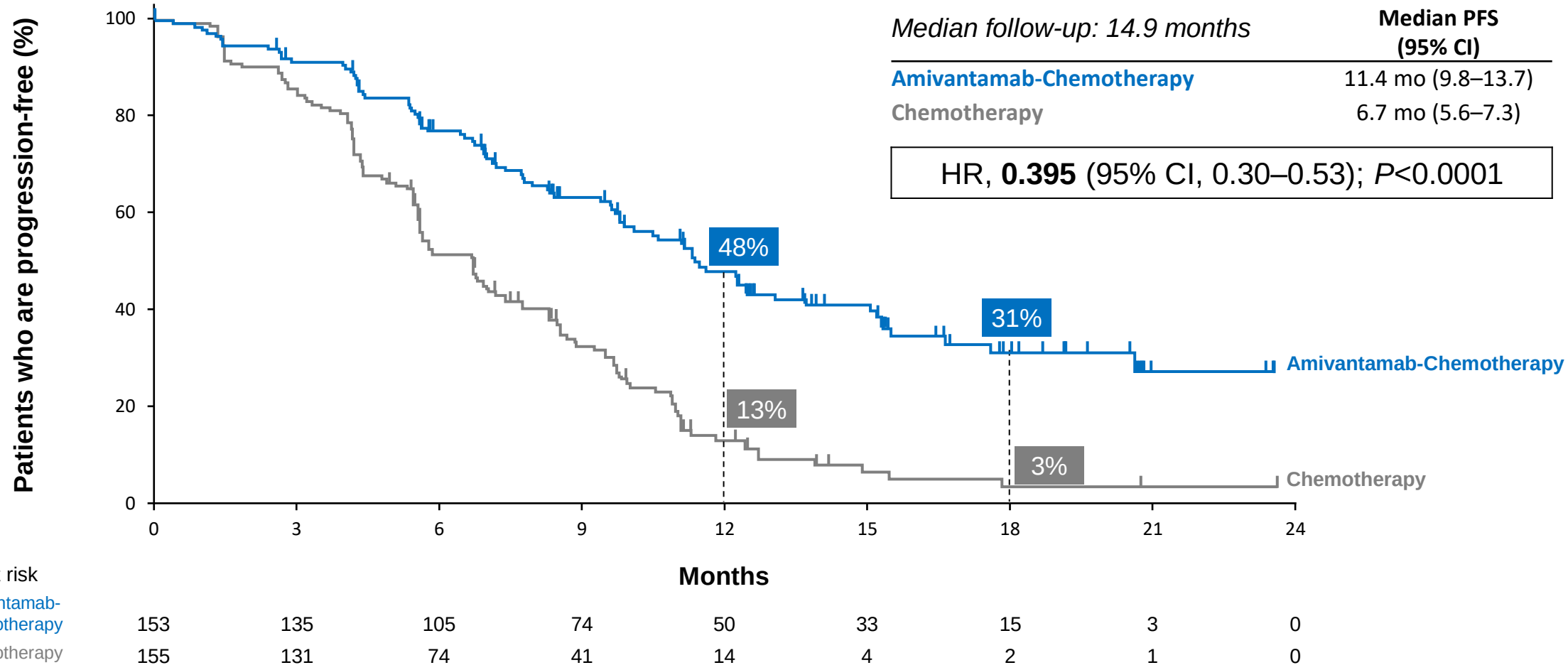
Park et al. JCO 2021; Zhou et al. JAMA Oncol 2021

PAPILLON: Phase 3 Study Design



Girard et al. ESMO 2023

Primary Endpoint: Progression-free Survival by BICR



Girard et al. ESMO 2023

Targeted therapy efficacy in different driver oncogenes

Gene	Targeted Therapy	Median PFS	ORR	Ref
EGFR	Gefitinib	10.9m	71%	Mok et al NEJM 2009
ALK	Crizotinib	10.9m	74%	Solomon et al NEJM 2014
BRAF V600E	Dabrafenib + Trametinib	10.2m	64%	Planchard et al. JTO 2022
MET ex14	Tepotinib	8.5m	46%	Paik et al. NEJM 2020
ERBB2 ex20	Trastuzumab Deruxtecan	8.2m	55%	Li et al NEJM 2022
EGFR ex20ins	Amivantamab + Chemotherapy	11.4m	73%	Girard et al. ESMO 2023

The field of EGFR exon 20ins is advancing rapidly

Efficacy and Toxicity Cross-comparison in pretreated pts

			Efficacy		Toxicity		
Drug	**Class**	**N**	**ORR (95% CI)**	**mPFS (95% CI)**	**Rash all / gr 3**	**Diarrhoea**	**Other**
Amivantamab	EGFR-MET bispecific mAb	81	40% (29-51%)	8.3 (6.5-10.0)	86% / 4%	12% / 4%	Infusion reactions, edema
Mobocertinib	EGFR TKI	114	28% (20-37%)	7.3 (5.5-9.2)	45% / 0%	91% / 21%	
Poziotinib	EGFR TKI	42	31% (19-46%)	5.5 (5.4-10.4)	90% / 34%	92% / 22%	
Sunvozertinib	EGFR TKI	104	61% (50-71%)	n.a.	80% / 1%	20% / 3%	
Zipalertinib	EGFR TKI	73	38% (27-49%)	10 (6-12)	80% / 1%	30% / 3%	
Furmonertinib	EGFR TKI	26	46% (27-67%)	n.a.	21% / 0%	86% / 0%	

De Langen et al WCLC 2023

Any harm in missing EGFR ex20ins NSCLC?

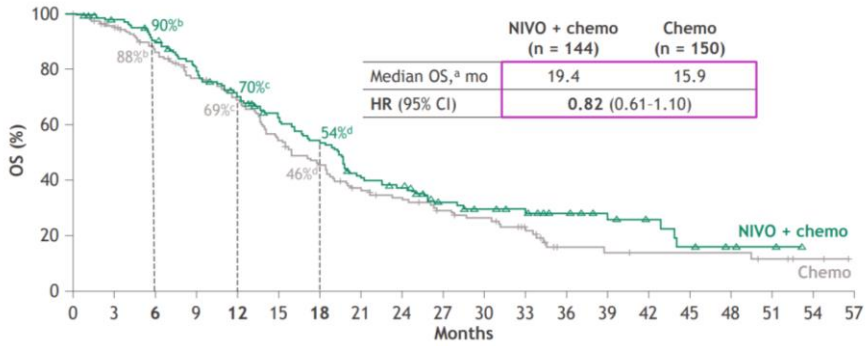
70yo/F, non-smoker
p/w massive pleural effusion
Cytology: TTF1+ adenocarcinoma

Multiplex PCR: EGFR/ALK/ROS1/BRAF/MET/RET/KRAS -ve
PD-L1 TPS (22C3): 60%

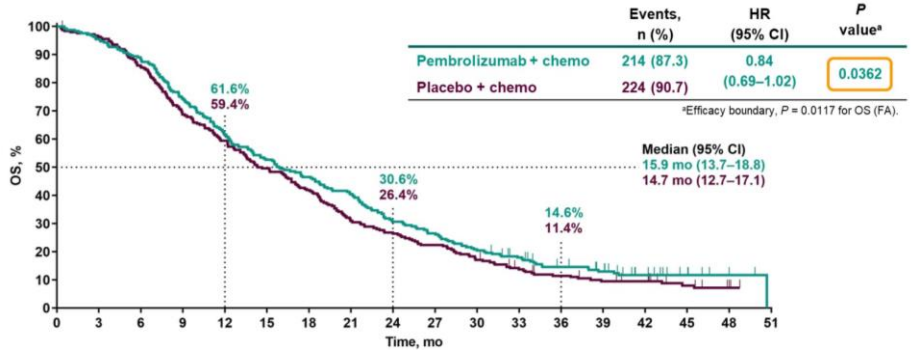
1st line: Pembrolizumab monotherapy
Further disease progression after 3 cycles

NGS testing: EGFR exon 20 H773_V774dup

Switched to 2nd line chemotherapy → responded



CM722 – nivolumab+chemo vs chemo. Mok et al. ESMO Asia 2022



KN789 – pembrolizumab+chemo vs chemo. Yang et al ASCO 2023

Take Home Message

Call for EGFR exon 20 insertion testing in NSCLC

- Its not uncommon! (more common than ROS-1, RET, BRAF V600E…)
- There is approved targeted therapy
- Moving EGFR exon 20ins targeted therapy to the 1L setting
- May harm patients in missing EGFR exon 20 ins – offering immunotherapy inappropriately

Professor Yoon-La (Yuna) CHOI

Professor

- **Department of Pathology & Translational Genomics, Samsung Medical Centre**
- **Department of Health Science and Technology, Samsung Advanced Institute for Health Science and Technology**

Professor Choi obtained her M.D. and Ph.D in the Seoul National University College of Medicine. She has over 30 selected publication in high impact factor peer-reviewed journal. Her research interest include:

- *molecular diagnostics development and validation,*
- *biomarker development and validation,*
- *companion diagnostics for target therapy and immunotherapy,*
- *cancer genomics and molecular pathology*

Molecular tissue testing for NSCLC for EGFRex20ins mutations: How, when? Perspective of Pathologist

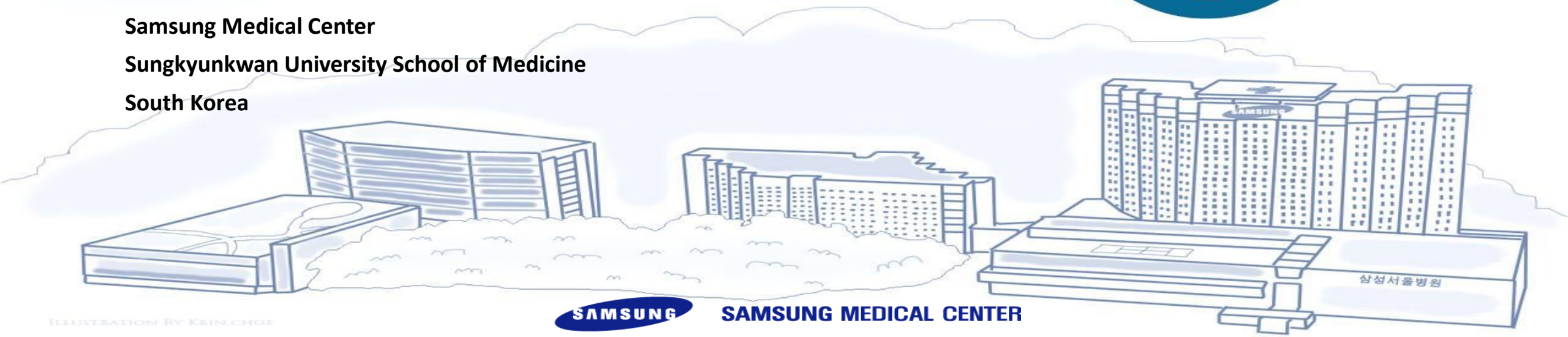
Yoonla Choi

Department of Pathology & Translational Genomics

Samsung Medical Center

Sungkyunkwan University School of Medicine

South Korea



SAMSUNG MEDICAL CENTER

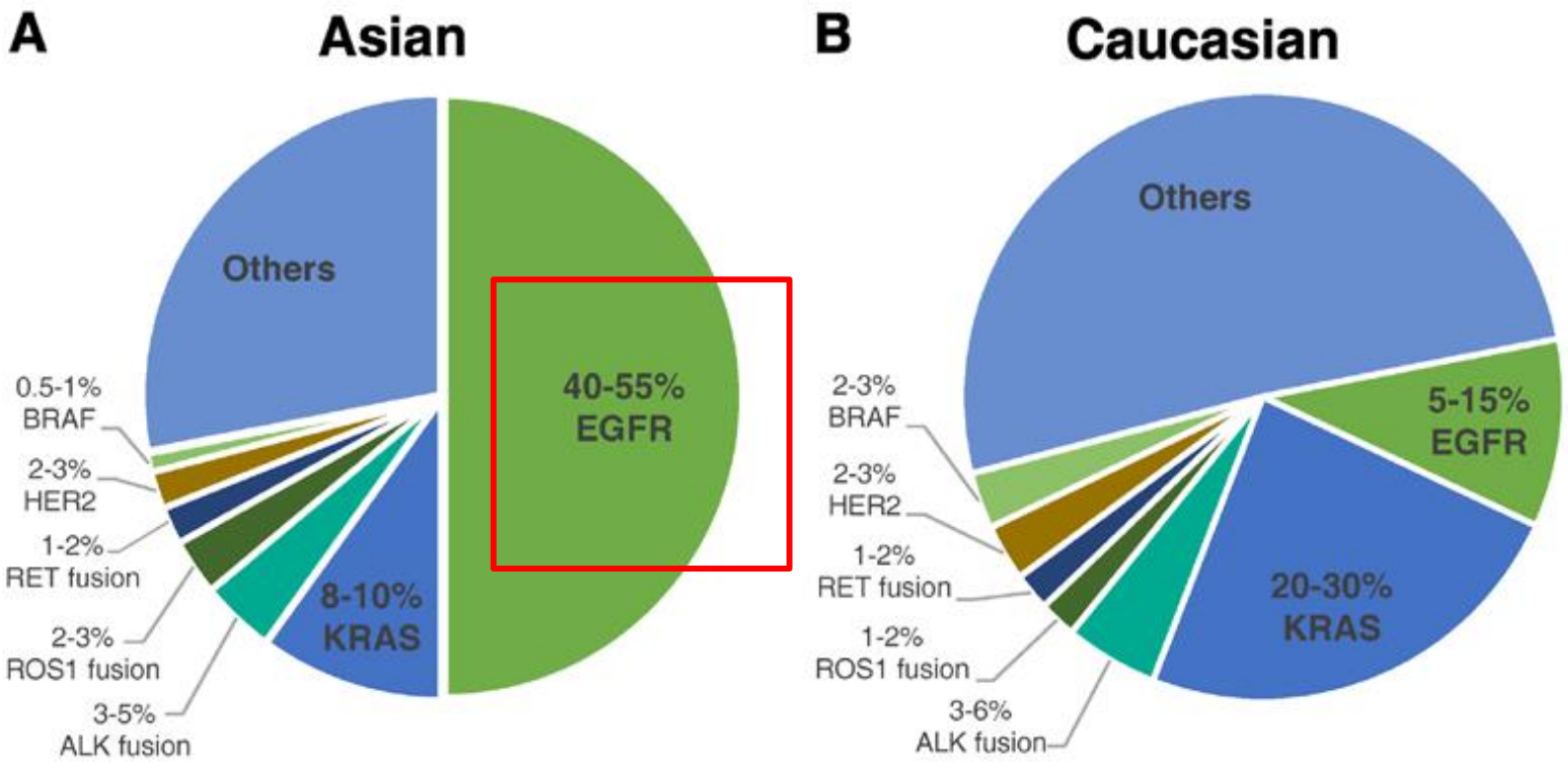
DECLARATION OF INTERESTS

Lectures, Advisory boards, Consultant and Research support to institute

AstraZeneca, Roche, Novartis, Takeda, Janssen, MSD, Bayer, Merk, Pfizer,
LG chemical, Yuhan, Panagene, Gencurix, Genecast

CONTENTS

Frequency of oncogene-driven genes in NSCLC patients of Asian and Caucasian



- Asians display a 40-55% prevalence of EGFR mutation.
- This elevated frequency underscores the critical importance of EGFR testing in Asian NSCLC patients, emphasizing tailored treatment approaches for this population.
- Furthermore, when adjuvant TKI therapy is considered for NSCLC at an early stage, we need to test for EGFR mutations as well.

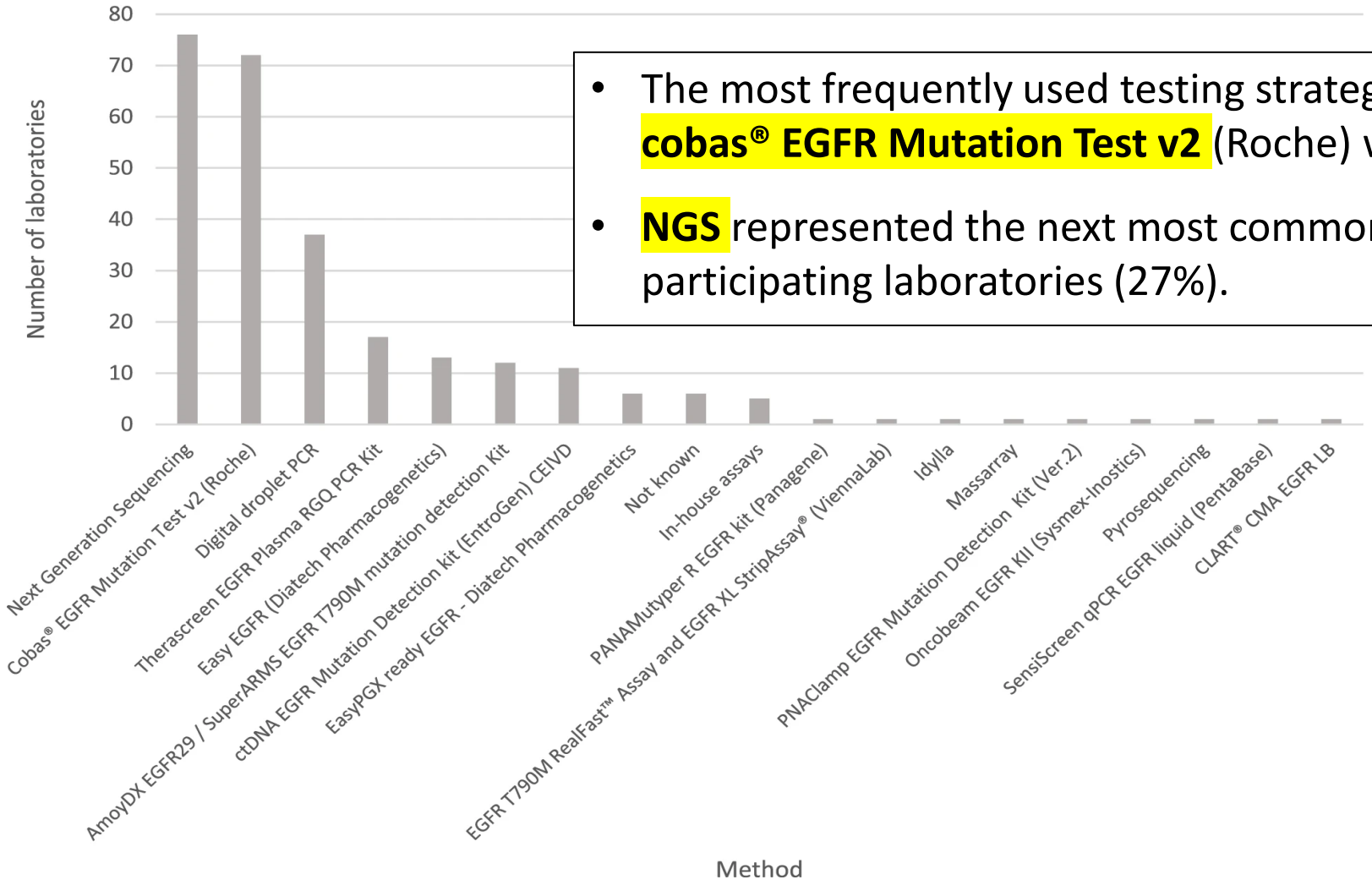
Oncol Rep, 2017

Molecular biomarker analysis : Testing methodologies

- **NGS**
  - Broad-based genomic testing approaches that efficiently utilize limited biopsy tissue while maximizing diagnostic genomic information are most commonly NGS-based.
- **PCR (RT-PCR, real-time PCR, digital PCR)**
  - Only those specific alterations that are targeted by the assay are assessed and the potential for mutations outside of the testing scope of the specific assay must be considered.
- **Sanger sequencing**
  - Requires the greatest degree of tumor enrichment
  - Not appropriate for assays in which identification of subclonal events (eg, resistance mutations)

EGFR testing methods among 264 laboratories from 45 countries

Summary of testing methods used by participating laboratories



- The most frequently used testing strategy was **Real-Time PCR (51%)** : **cobas® EGFR Mutation Test v2** (Roche) was the most common test (27%).
- **NGS** represented the next most common testing strategy used by participating laboratories (27%).

BMC Cancer 22, 2022

Usage of epidermal growth factor mutation testing and impact on treatment patterns in non-small cell lung cancer: An international observational study

Janakiraman Subramanian [a,*,1], Natasha B. Leighl [b,2], Yoon-La Choi [c,3], Teh-Ying Chou [d,4], Jeffrey Gregg [e,5], Rina Hui [f,6], Antonio Marchetti [g,7], Mark Silvey [h,8], Rebecca Makin [h,9], Liane Gillespie–Akar [h,10], Aliki Taylor [i,11], Doreen A Kahangire [i,12], Tom Bailey [h,13], Maiyan Chau [j,14], Neal Navani [k,15]

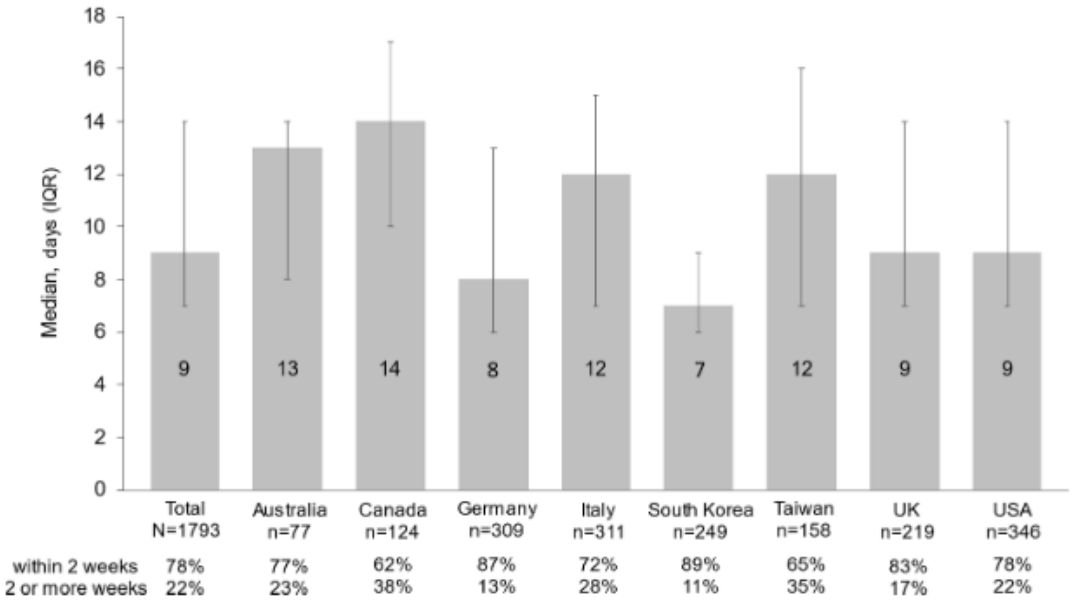
- A cross-sectional **medical chart review** was completed May–August 2020 in Australia, Canada, Germany, Italy, South Korea, Taiwan, UK, and USA.
- **1,793** patients with advanced (stage IIIb/IIIc/IV) NSCLC
- **78 %** of EGFRm test results were received **≤ 2 weeks (7-14d)** from order to result
- Median time **from Dx to EGFRm test** result : **18 d**(10–22 d)
- **37 %** of patients received a systemic treatment prior to EGFRm result;

Lung Cancer 2023;175: 47-56

Real world EGFR testing patterns

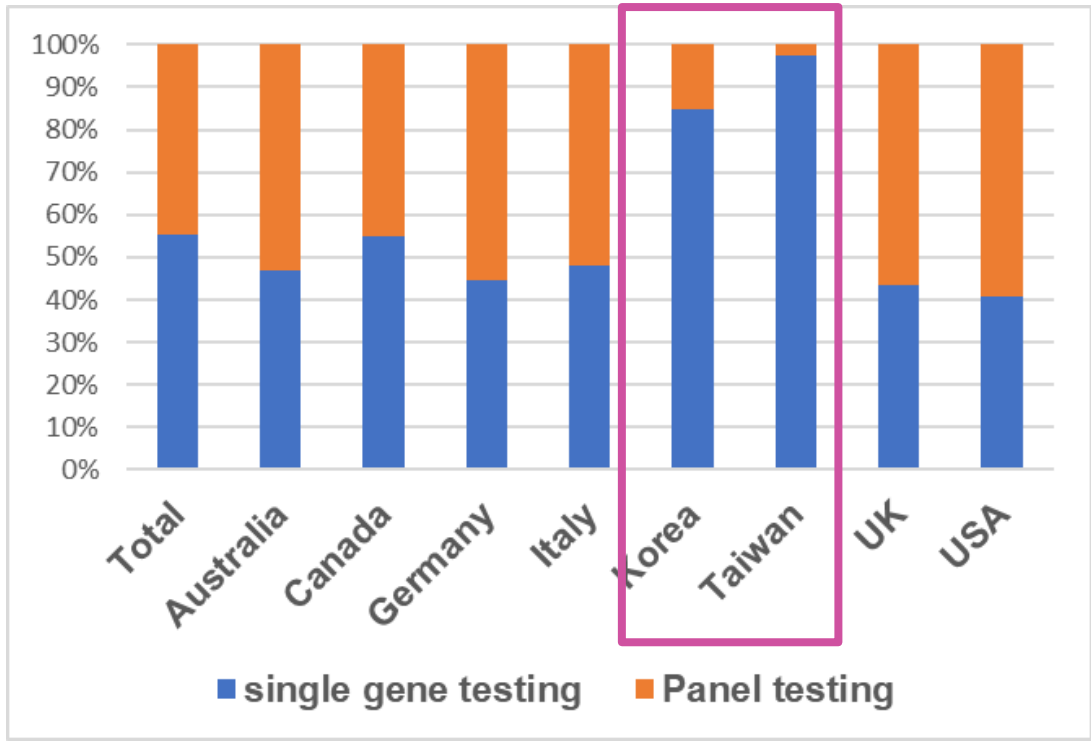
Time from EGFR mutation test request to receipt of test result in patients with NSCLC

Time from EGFRm test request to receipt of test result in patients with NSCLC



It took 7 to 14 days to get the results after requesting the test.

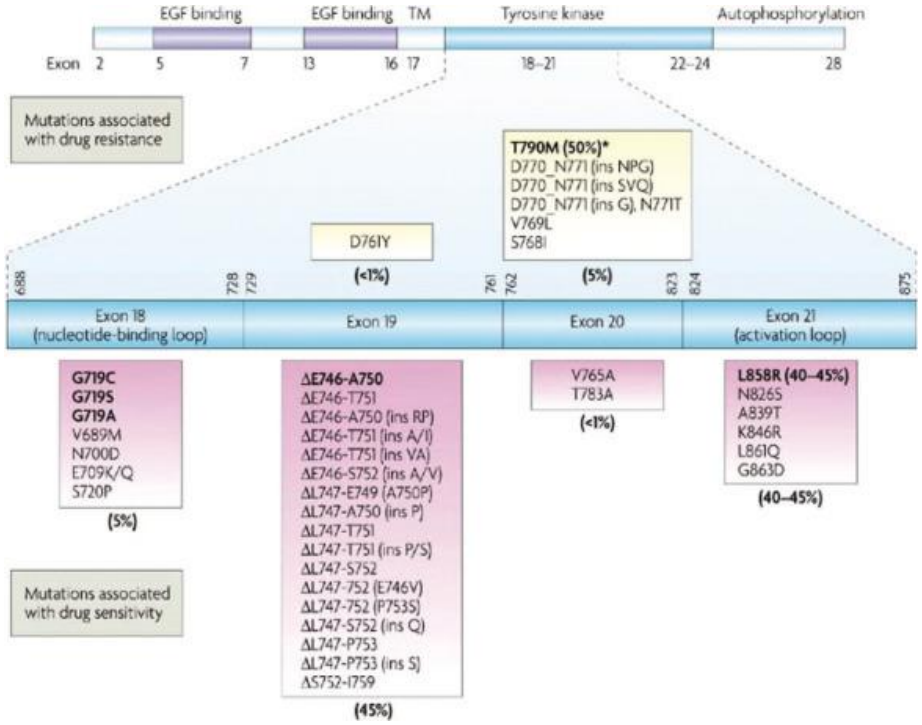
Single gene test vs. Panel test

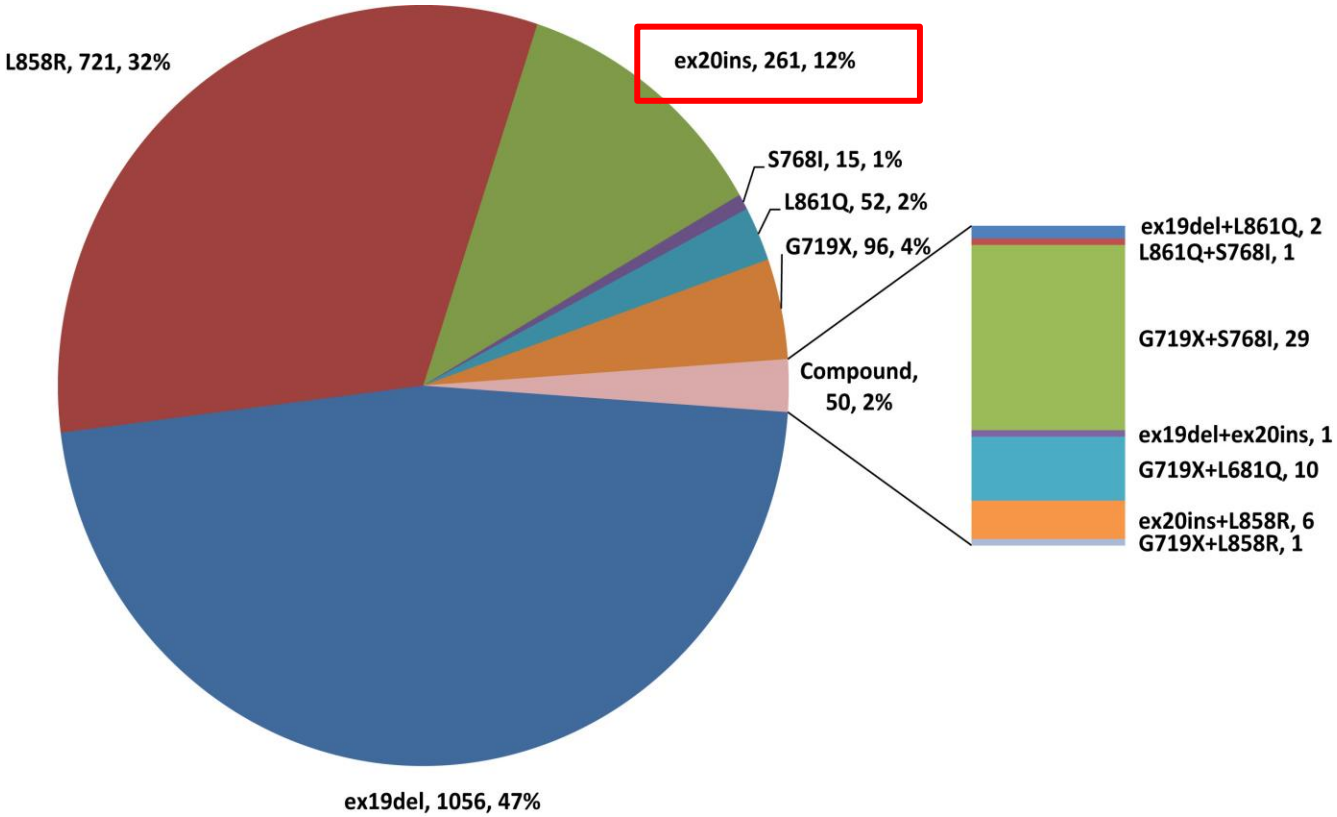


While panel and single gene tests are equally prevalent in other countries, Korea and Taiwan are more likely to perform single gene tests.

Lung Cancer 2023;175: 47-56

EGFRex20ins are the third most common type of EGFR mutation

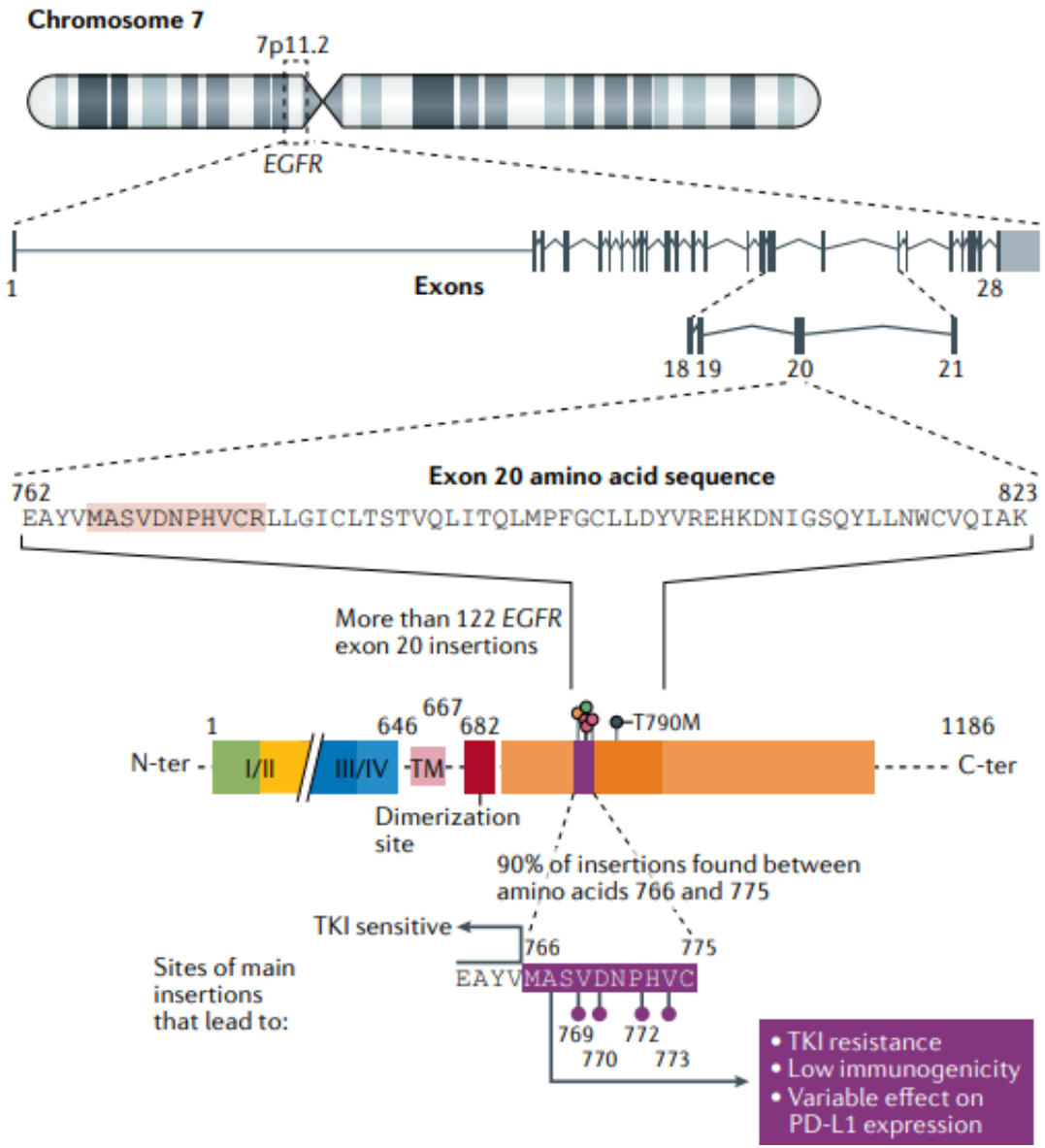




- Detected following *EGFR* exon 19 deletions (47%) and EGFR L858R (32%).
- CGP performed on 14,483 NSCLC cases in the course of clinical care identified 2251 cases with *EGFR* mutations.
- 263 of these cases were *EGFR*ex20ins, representing **12%** of all *EGFR*-mutant NSCLC and **1.8%** of all NSCLC cases tested.

J Thoracic Oncology 2018: 13; 1560
Nat Rev cancer 2007: 7(3); 169

EGFR gene and protein domain organization and summary of exon 20 ins



- In EGFR exon 20, in addition to p.T790M mutation, in-frame insertions and 3–21-bp duplications (corresponding to 1–7 amino acid) can occur within amino acids 762 and 774.
- At least 122 different EGFR exon 20 insertions have been identified, with ~90% occurring in the region comprising amino acids 766–775.
- Different insertion sites are associated with differing disease phenotypes and patient characteristics, sensitivity to current therapies and, potentially, tumour immunogenicity.

Nat Rev Clin Oncol . 2022 Jan;19(1):51-69.

EGFR mutation testing in NSCLC 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Non-Small Cell Lung Cancer

TESTING RESULTS[ll,mm]

EGFR **exon 19 deletion or exon 21 L858R mutation positive**	NSCL-20
EGFR **S768I, L861Q, and/or G719X mutation positive**	NSCL-23
EGFR **exon 20 insertion mutation positive**	NSCL-24
KRAS **G12C mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
ERBB2 (HER2) **mutation positive**	NSCL-35
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

- A recent guideline lists several specific mutation variants of EGFR based on the therapeutic value of each variant.

EGFR exon20 insertion : Patient characteristics

Table 1: Characteristics of Exon 20 insertion patients vs common EGFR mutations

		All		EGFR Exon 20 insertion		Common EGFR Mutation		
		N	%	N	%	N	%	*p*-value*
Cohort Size	N	2209	100.00%	53	2.40%	1978	89.5%	
Age at advanced NSCLC diagnosis	Mean (SD)	62.44 (11.15)		58.83 (13.15)		62.30 (10.93)		0.023
	Median (Q1-Q3)	62.00 (55.00-71.00)		58.00 (50.0-70.0)		62.00 (55.0-70.0)		
	Min-Max	26.00 - 94.00		26.00 - 82.00		28.00 - 94.00		
Gender	Female	1321	59.80%	28	52.83%	1198	60.57%	0.320
	Male	888	40.20%	25	47.17%	780	39.43%	
Smoking Status	Never smoker	1451	65.69%	30	56.60%	1314	66.43%	0.221
	Former	505	22.86%	13	24.53%	450	22.75%	
	Current	246	11.14%	10	18.87%	208	10.52%	
	Unknown	7	0.32%	0	0.00%	6	0.30%	
Performance Score ECOG at diagnosis	0	521	23.59%	10	18.87%	471	23.81%	0.134
	1	1157	52.38%	29	54.72%	1037	52.43%	
	2	143	6.47%	5	9.43%	123	6.22%	
	3	31	1.40%	3	5.66%	26	1.31%	
	4	5	0.23%	0	0.00%	3	0.15%	
	Unknown	352	15.93%	6	11.32%	318	16.08%	
TNM Classification	IIIB/C	126	5.70%	4	7.55%	108	5.46%	0.533
	IV	2083	94.30%	49	92.45%	1870	94.54%	
Histology	NSQ	2139	96.83%	50	94.34%	1923	97.22%	0.040
	SQ	33	1.49%	0	0.00%	26	1.31%	
	Other specified	13	0.59%	<3	<5.66%	9	0.46%	
	NOS	24	1.09%	<3	<5.66%	20	1.01%	

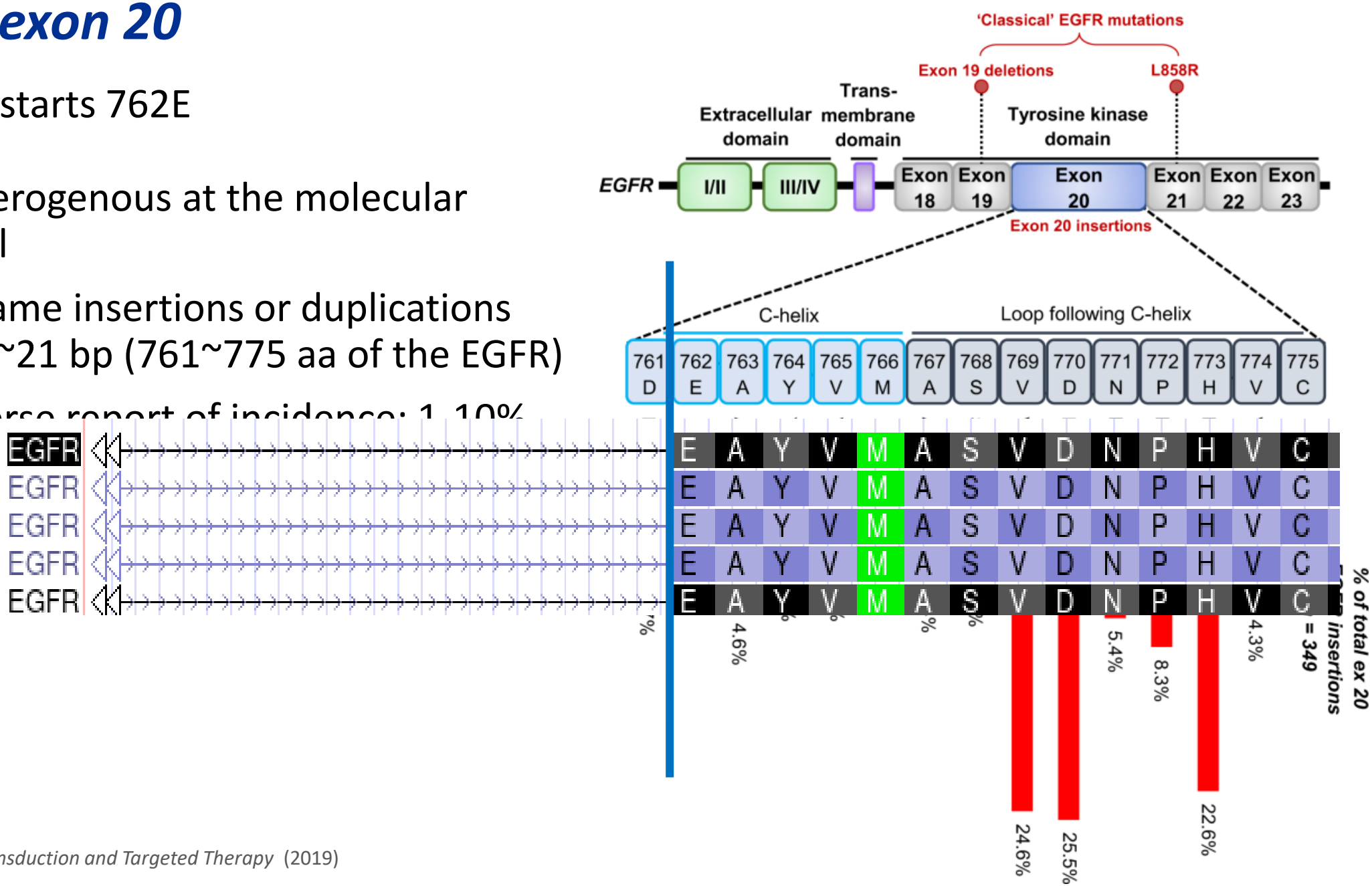
NSCLC, Non-small cell lung cancer; SD, standard deviation; NSQ, Non-squamous cell carcinoma; SQ, squamous cell carcinoma; NOS, Not otherwise specified.
**Student's t-test was used to compare age at advanced NSCLC diagnosis between groups. For categorical variables, Chi-square test or Fisher exact test when any of expected cell count < 5 was used.*

Annals of Oncology. 2022;33:S56. doi: 10.1016/j.annonc.2022.02.059.

EGFR exon 20

Exon20 starts 762E

- Heterogenous at the molecular level
- Inframe insertions or duplications of 3~21 bp (761~775 aa of the EGFR)
- Diverse report of incidence: 1-10%

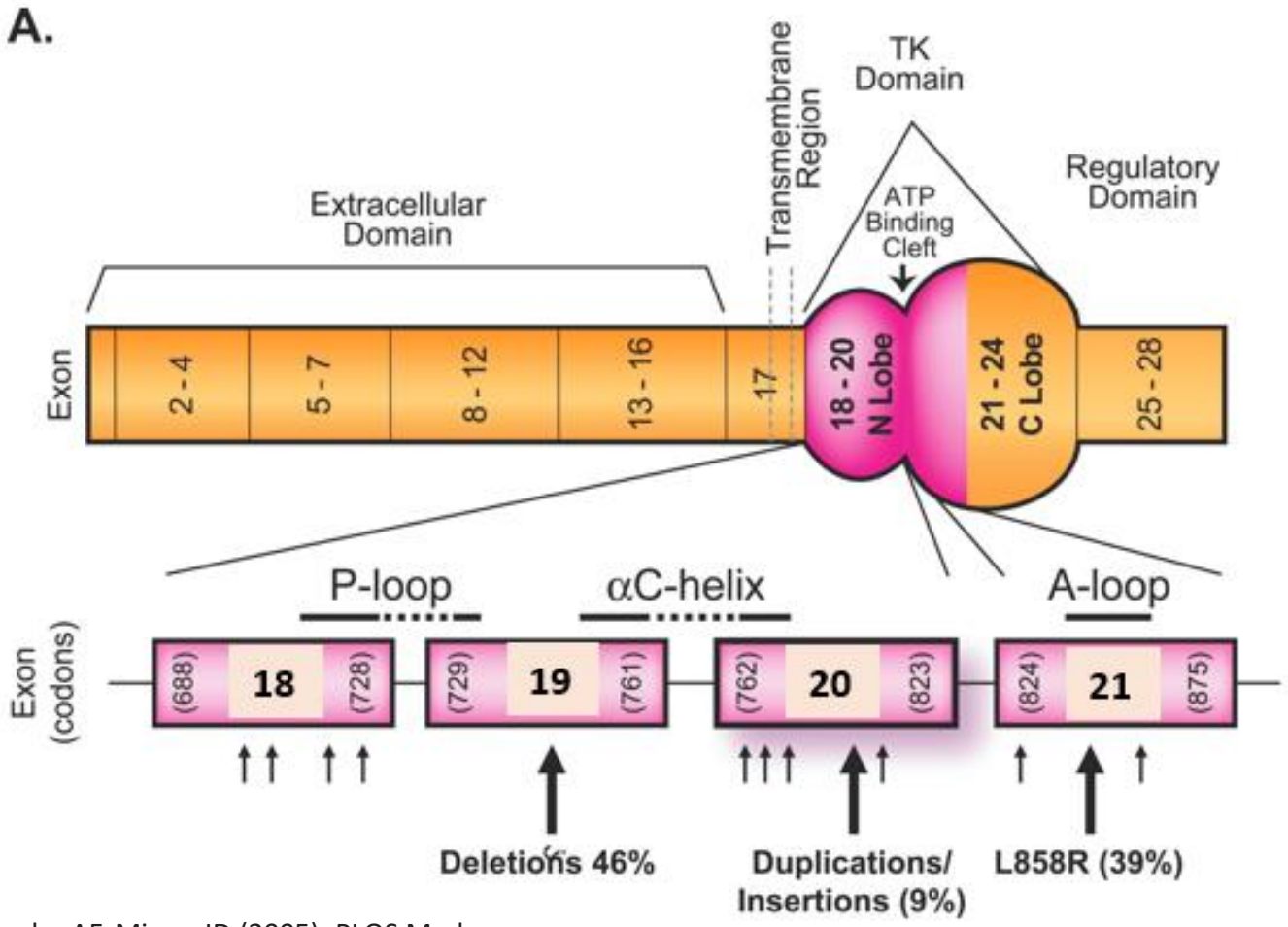


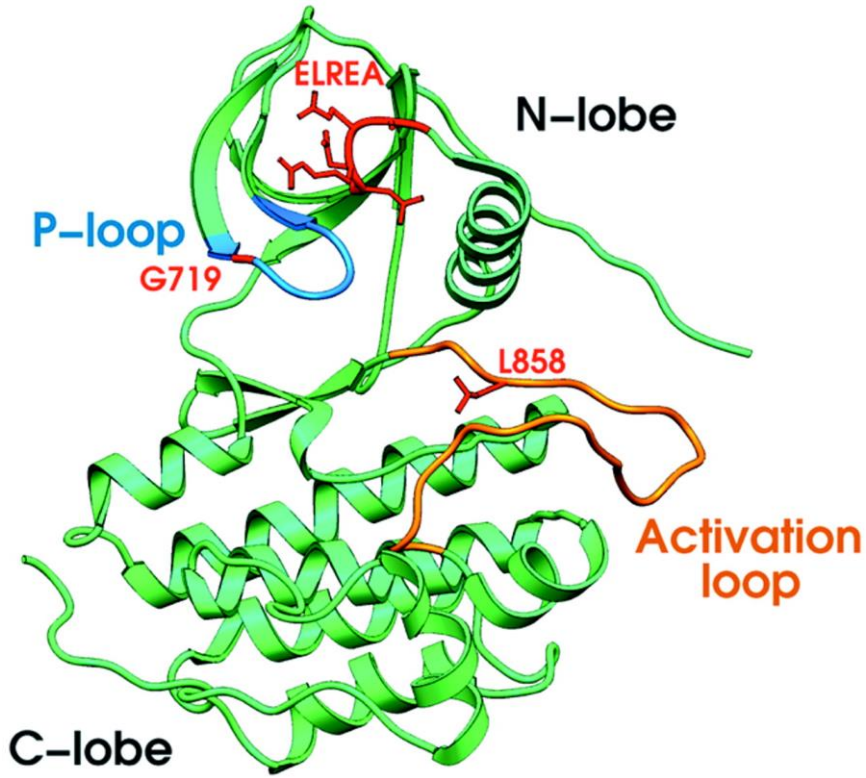
Signal Transduction and Targeted Therapy (2019)

EGFR exon 20

C-helix : **761**-766

Exon20 : **762**-823





Gazdar AF, Minna JD (2005) PLOS Med

Heterogeneity of EGFR exon20 insertion mutations in NSCLC

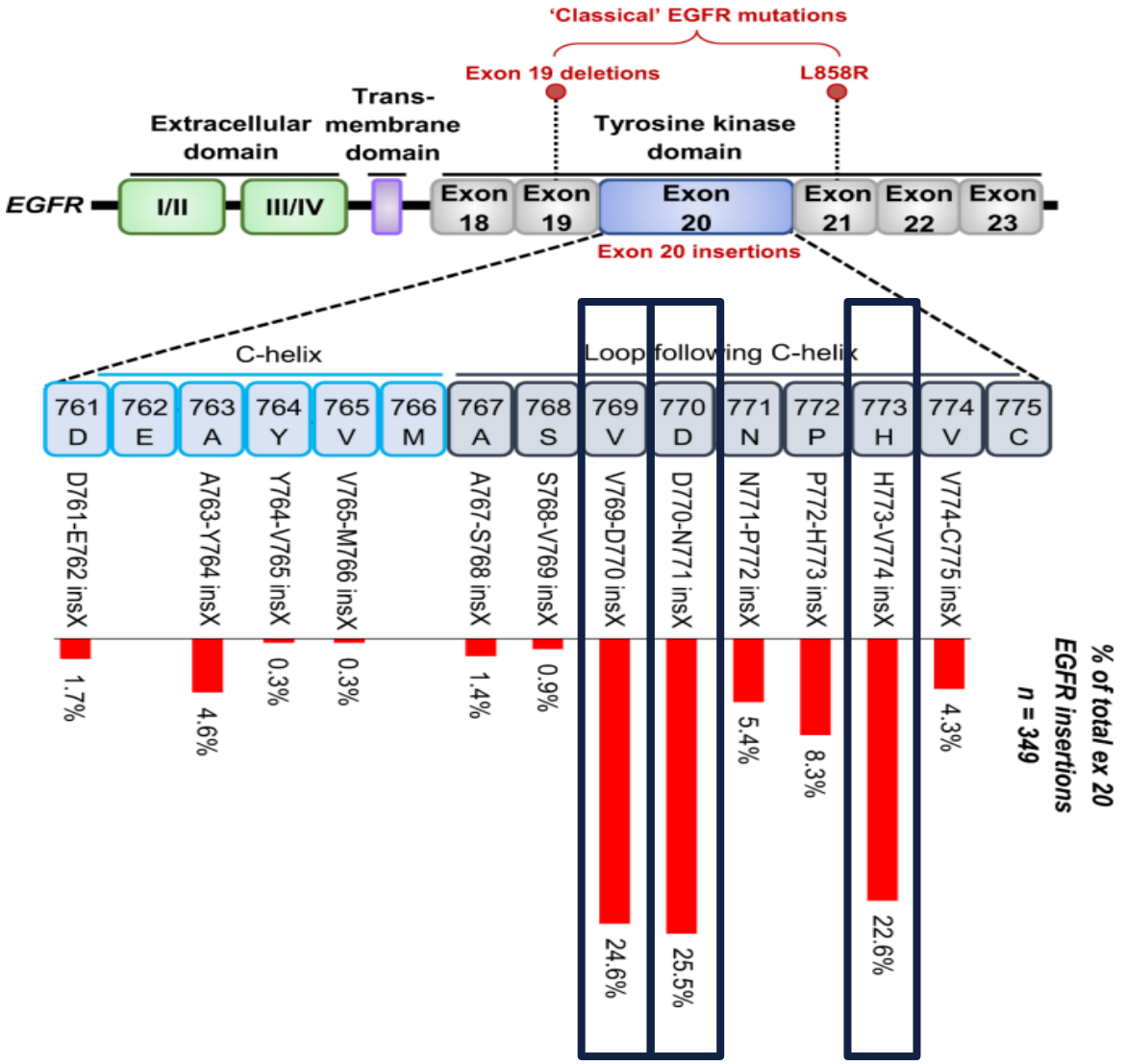
- Over 100 different *EGFR* exon 20 insertion mutations have been reported in NSCLC
- The majority are composed of 1 to 4 AA insertions located in the loop following the C-helix

Crit Rev Oncol Hematol. 2022 Jan:169:103536.

EGFR exon20 insertion

cobas® EGFR Mutation Test v2

p.V769_D770insASV
p.D770_N771insSVD
p.D770_N771insG
p.H773_V774insH



EGFR exon20 insertion CDx

Only three diagnostic products are CDx for Exon20 insertion mutations

Diagnostic name	Method	Drug	Biomarker
• Oncomine Dx Target Test	Amplicon NGS	Rybrevant(amivantamb)	Exon 20 insertion mutations
• Guardant360 CDx	Hybridization NGS	Rybrevant(amivantamb)	Exon 20 insertion mutations
• FoundationLiquid CDx	Hybridization NGS	Exkivity (mobocertinib)	Exon 20 insertion mutations

- Cobas EGFR Mutation Test v2
- FoundationOne CDx
- ONCO/Reveal Dx Lung & Colon Cancer Assay
- therascreen EGFR RGQ PCR Kit

→ Exon 19 deletion or exon 21 L858R substitution mutation
T790M mutation

EGFR exon20 insertion Testing: RWD

6. Which *EGFR* mutations does your laboratory report?	Freq*
Exon 18 G719X [c.2156G>C p.G719A or c.2155G>A p.G719S or c.2155G>T p.G719C, associated with sensitivity to anti-*EGFR* therapy]	138
Exon 19 (in-frame deletion, associated with sensitivity to anti-*EGFR* therapy]	141
Exon 20 [c.2303G>T p.S768I, associated with low sensitivity to anti-*EGFR* therapy]	134
Exon 20 [c.2369C>T p.T790M, associated with resistance resistance to anti-*EGFR* therapy]	141
Exon 20 (insertion/duplication, typically associated with resistance to anti-*EGFR* therapy)	131
Exon 21 [c.2573T>G p.L858R, associated with sensitivity anti-*EGFR* therapy]	142
Exon 21 [c.2582T>A p.L861Q, associated with sensitivity sensitivity to anti-*EGFR* therapy]	137
Any mutation in exons 18-21	21
Other mutations, specify:	5

5. If your laboratory uses an FDA-cleared or approved companion diagnostic for *EGFR*, specify the manufacturer:	Freq (63)
Roche cobas *EGFR* Mutation Test	-
Roche cobas *EGFR* Mutation Test v2	50
Qiagen therascreen *EGFR* RGQ PCR Kit	13

9. If your laboratory-developed test uses primers or probes by a commercial vendor, specify:	Freq (148)
AmoyDx	2
Applied Biosystems	2
Biocartis Idylla	50
DxS *EGFR* mutation	-
EntroGen	4
Illumina	5
Integrated DNA Technologies	5
Qiagen PCR	-
Qiagen Pyro	-
Qiagen RGQ PCR	6
Roche	14
Sequenom Oncocarta	-
Thermo Scientific	4
TrimGen	1
Other, specify:	8
Not applicable (N/A)	47

cobas® EGFR Mutation Test v2 – Potential for false positive results

Updated 11/08/2022

Device Indication for a Specific Group of Oncology Therapeutic Products

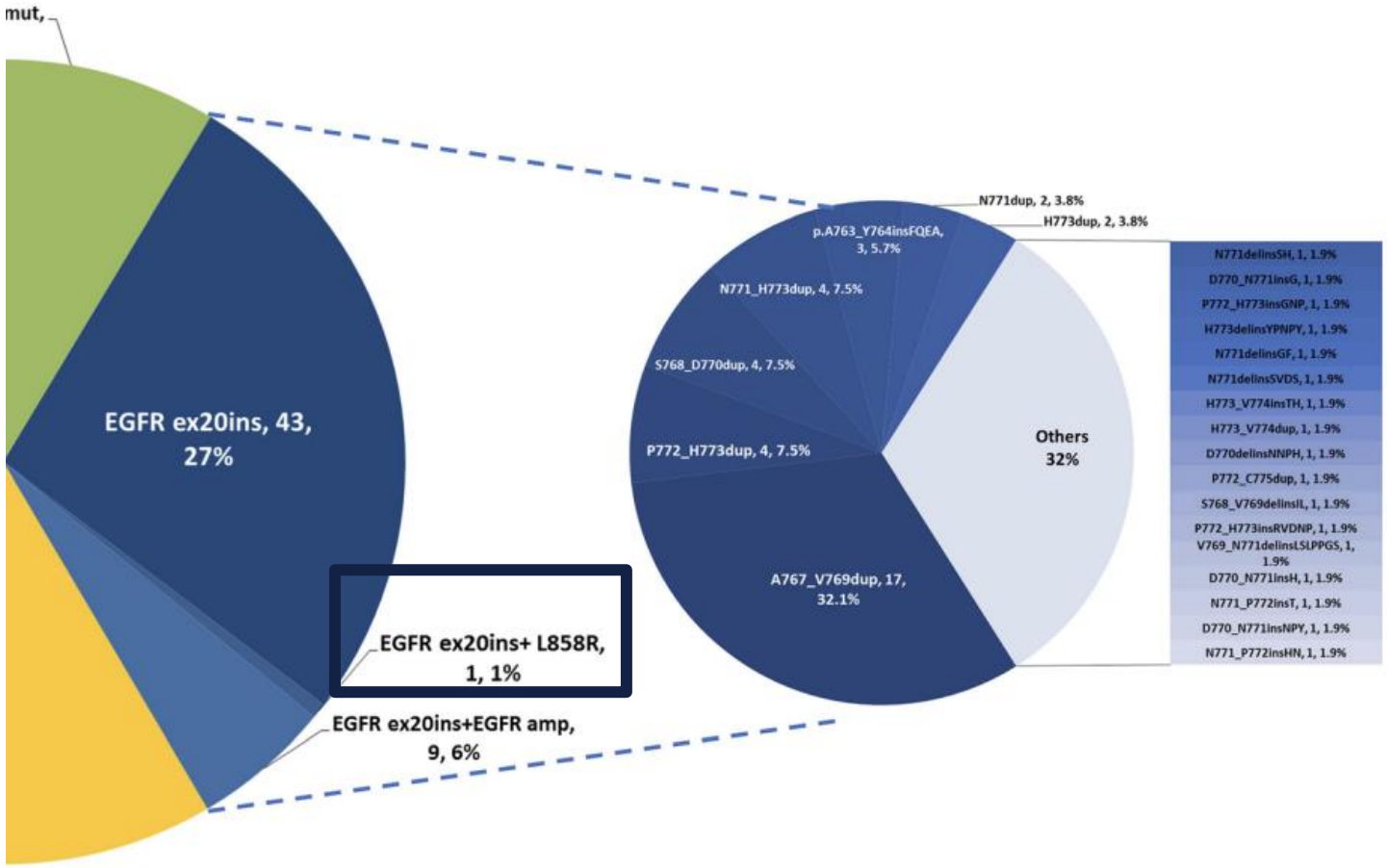
Diagnostic Name (Manufacturer)	Indication(s) - Sample Type	PMA (Approval Date)	Device Indication for a Specific Group of Oncology Therapeutic Products and Trade Name (Generic) – NDA/BLA
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	P120019/S031 (10/27/2020)	Non-small cell lung cancer (tissue): "Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: Tarceva (erlotinib) - NDA 021743 Tagrisso (osimertinib) - NDA 208065 Iressa (gefitinib) - NDA 206995 Gilotrif (afatinib) - NDA 201292 Vizimpro (dacomitinib) - NDA 211288
			Non-small cell lung cancer (plasma) "Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution

cobas® EGFR Mutation Test v2 – Potential for False "Mutation Detected" Results for Exon 20 Insertion

This Urgent Medical Device Correction (UMDC) only affects customers using:

Product	Analyzer	Catalog Number
cobas EGFR Mutation Test v2	**cobas z** 480	07248563190

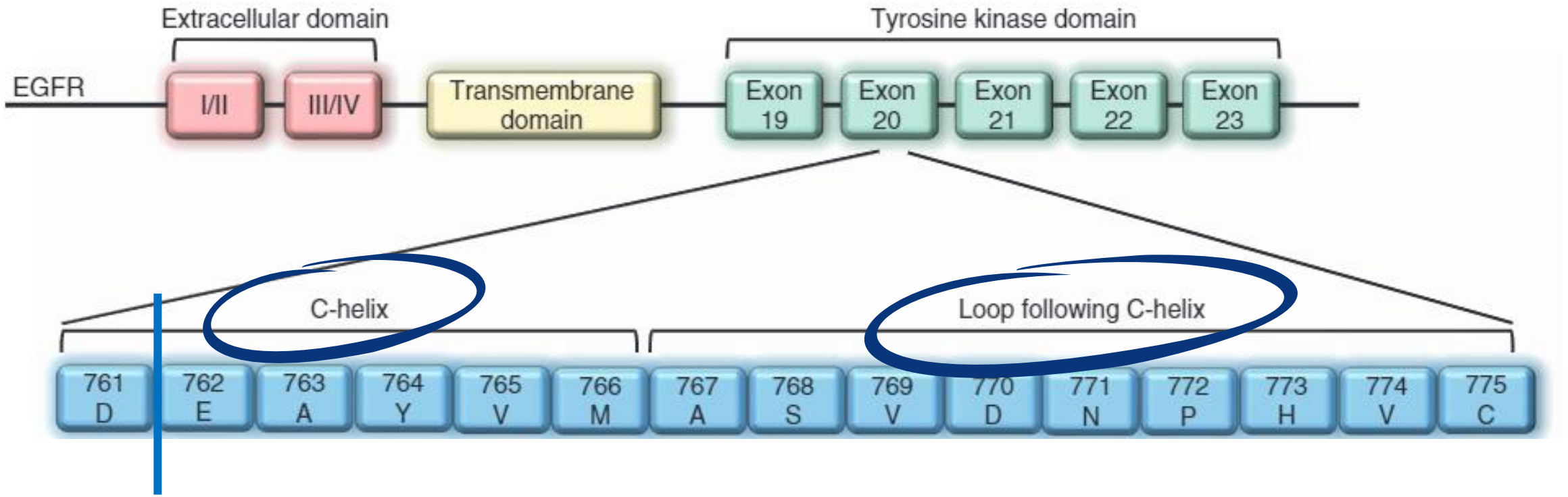
SMC (2022)	Cobas	ddEGFR/Sanger
E20ins only	**50**	**33**
E20ins + L858R E20ins + E19del	**36**	**0**



Speaker's data

Fang *et al. BMC Cancer* (2019) 19:595
https://doi.org/10.1186/s12885-019-5820-0

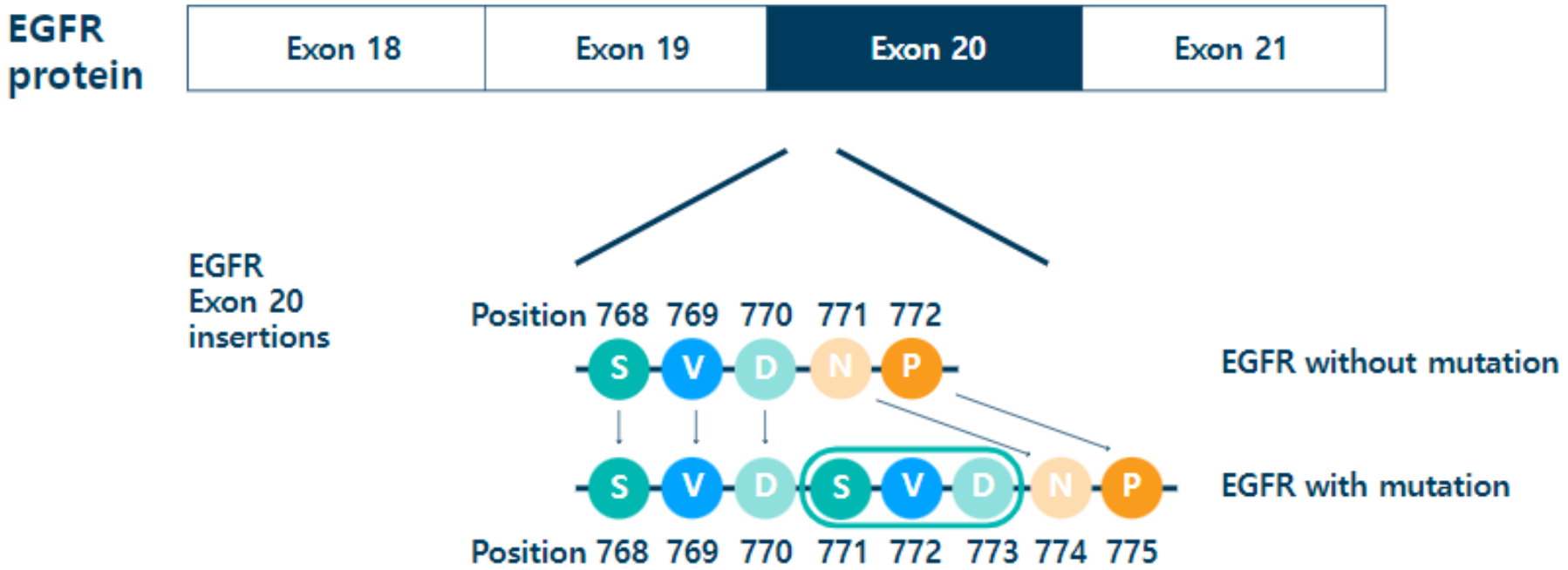
HETEROGENEITY OF EGFR EXON 20 INSERTION MUTATIONS IN NSCLC



Over 100 different *EGFR* exon 20 insertion muts have been reported in NSCLC and the majority are composed of 1 to 4 AA insertions located in the loop following the C-helix

Meador CB, et al. Cancer Discovery 2021

EGFR EXON20 INSERTION NOMENCLATURE

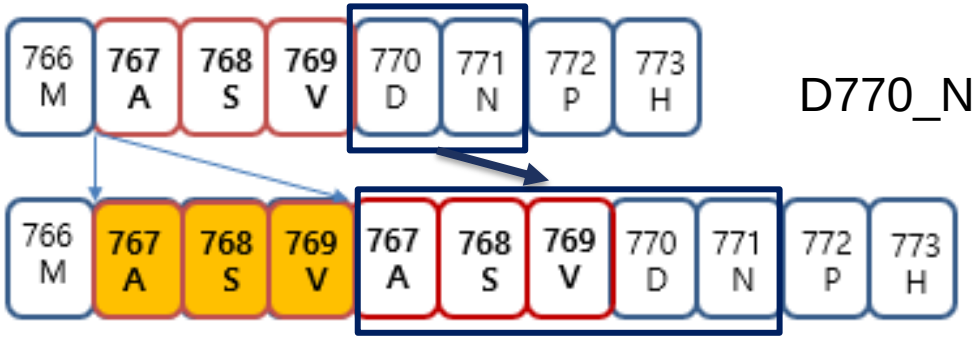


When SVD is newly inserted, how should it be named?

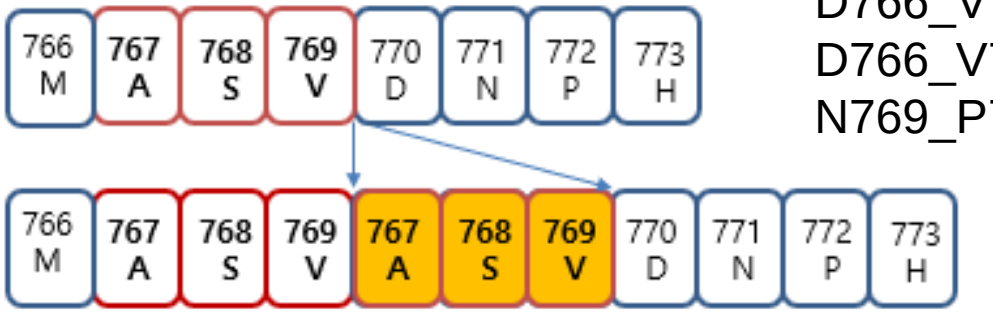
D770_S771 ins SVD
S767_S768 ins SVD
S768_D770 dup

HGVS nomenclature : 3' RULE

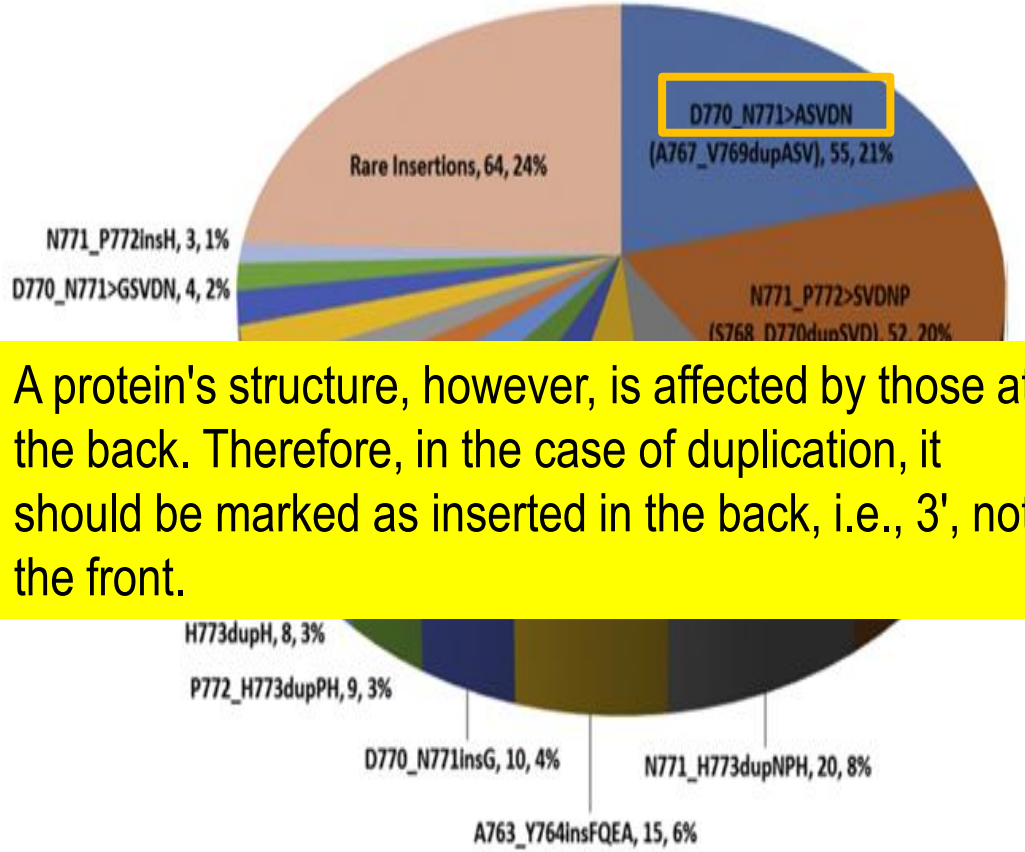
For all descriptions, the **most C-terminal position** possible of the reference sequence is arbitrarily assigned to have been changed



D770_N771>ASVDN



D766_V767insASV
D766_V767>MASVA
N769_P770insASV



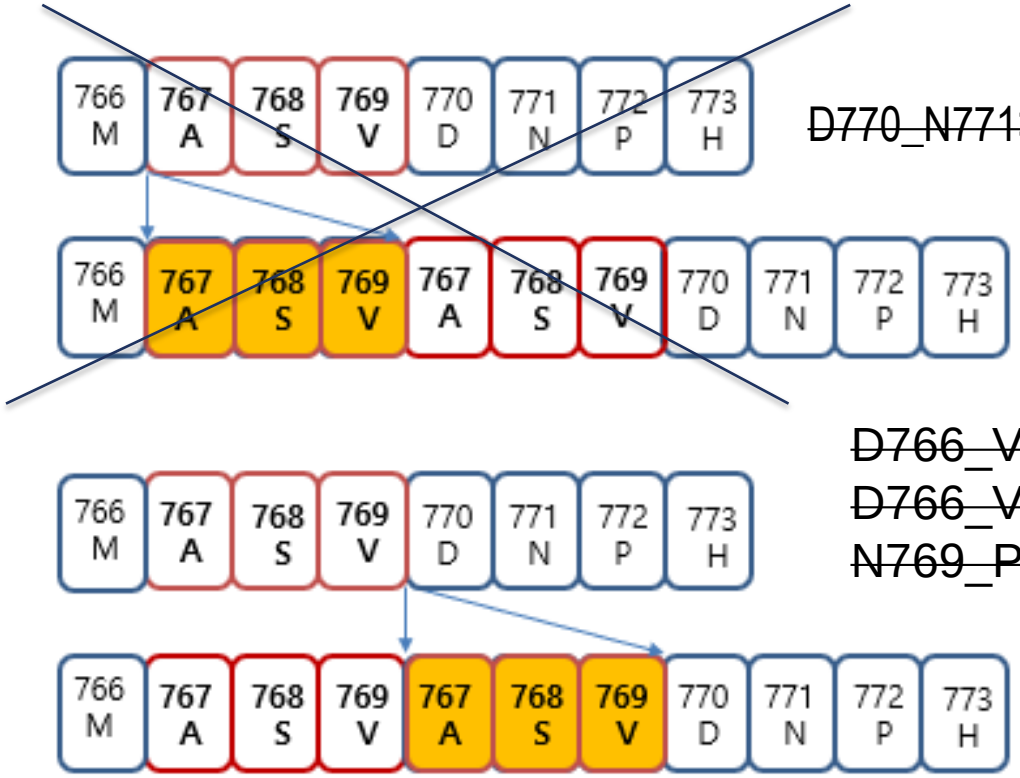
A protein's structure, however, is affected by those at the back. Therefore, in the case of duplication, it should be marked as inserted in the back, i.e., 3', not the front.

J Thorac Oncol. 2018 Oct;13(10):1560-1568

https://varnomen.hgvs.org/recommendations/protein/variant/duplication/

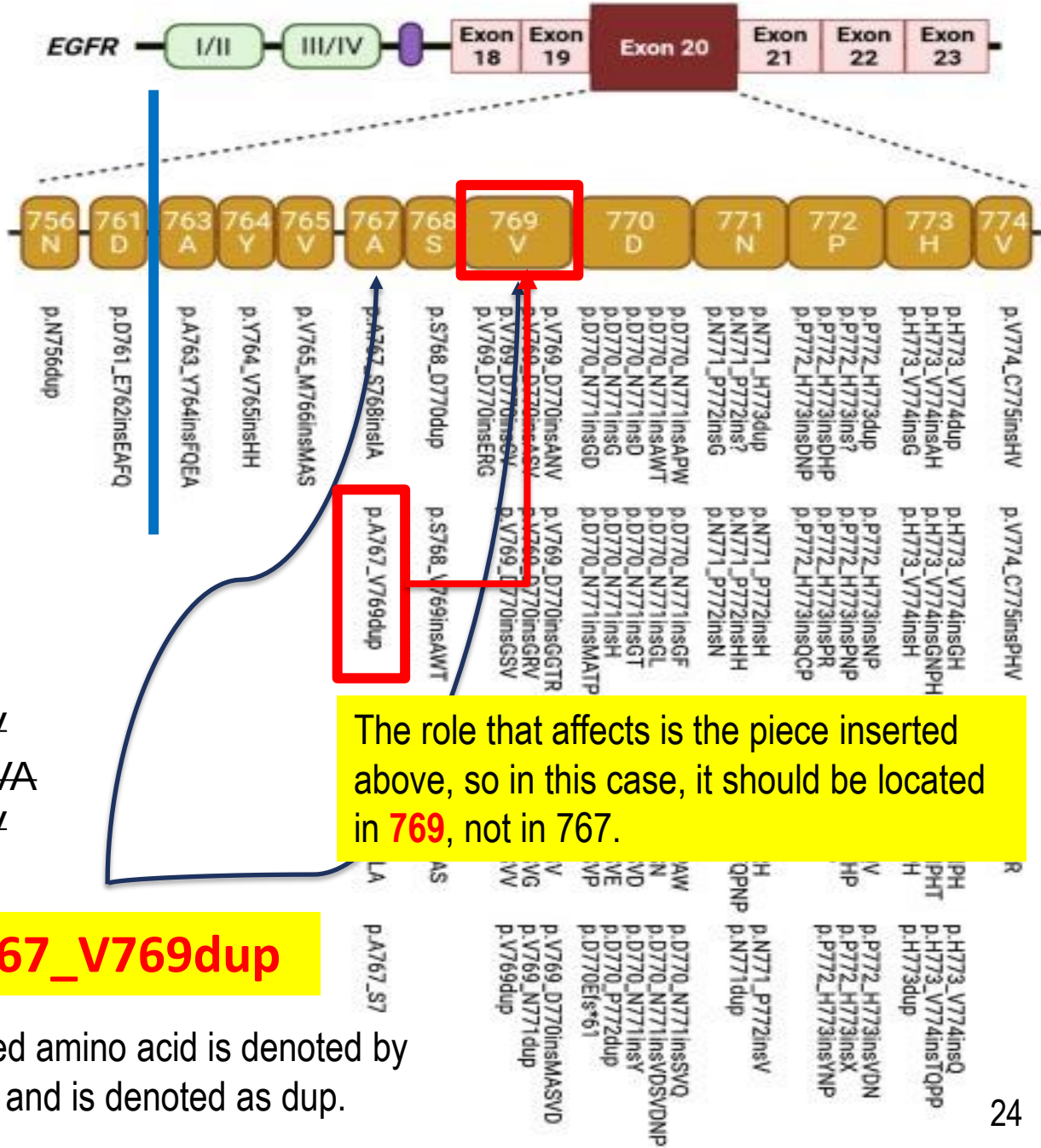
3’ RULE

For all descriptions, the **most C-terminal position** possible of the reference sequence is arbitrarily assigned to have been changed



~~D770_N771>ASVDN~~

~~D766_V767insASV~~
~~D766_V767>MASVA~~
~~N769_P770insASV~~



The role that affects is the piece inserted above, so in this case, it should be located in **769**, not in 767.

p.A767_V769dup

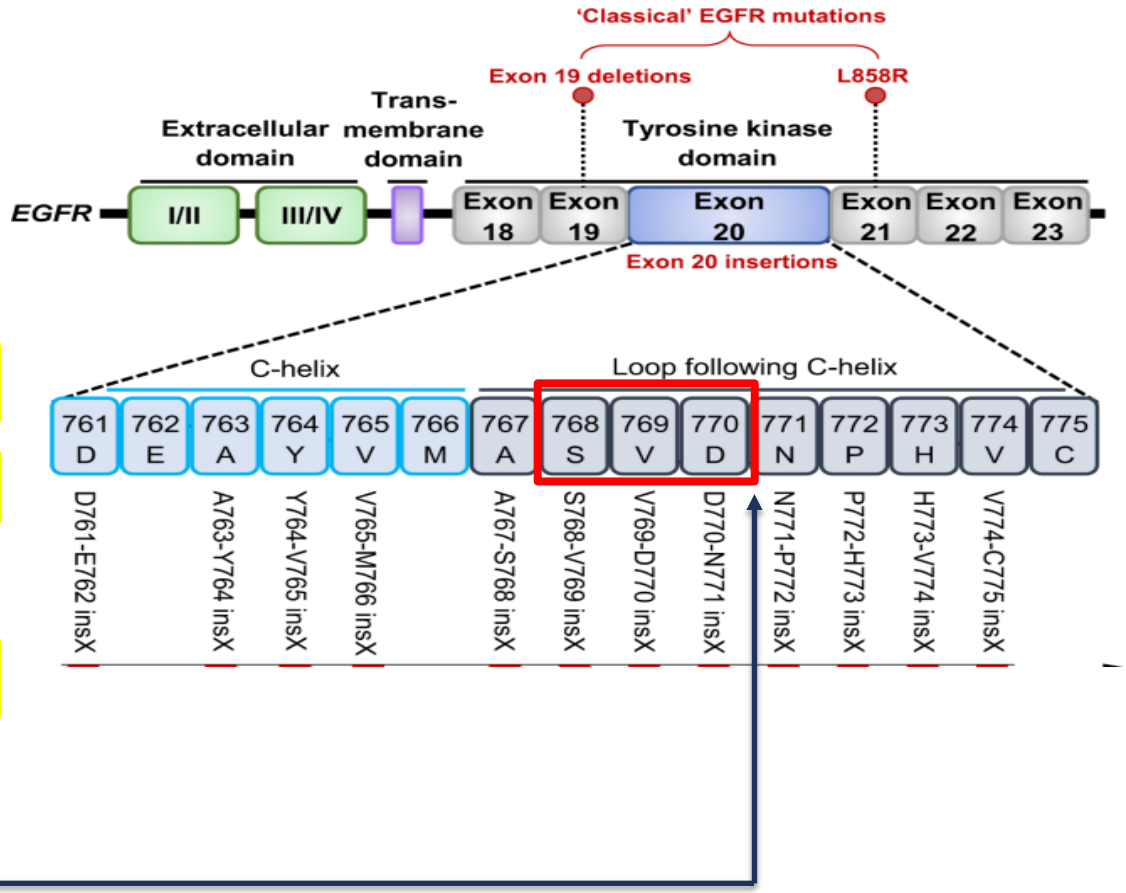
The repeated amino acid is denoted by the number and is denoted as dup.

https://varnomen.hgvs.org/recommendations/protein/variant/duplication/

EGFR EXON20INS

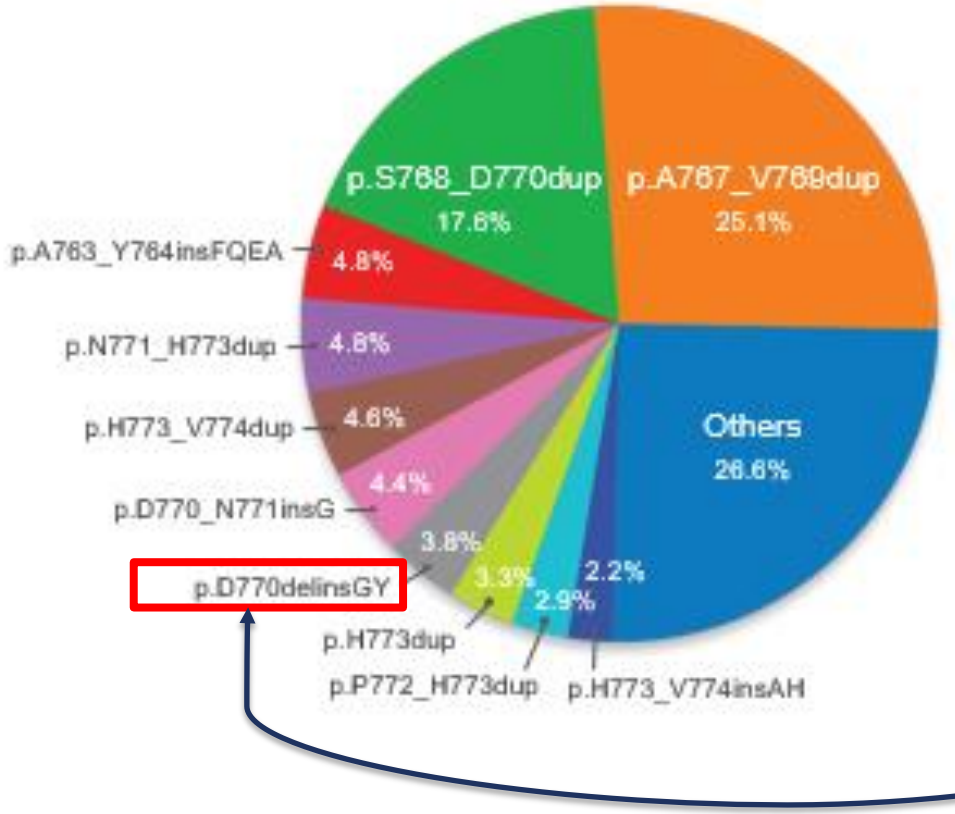
cobas® EGFR Mutation Test v2

p.V769_D770insASV	p.A767_V769dup
p.D770_N771insSVD	p.S768_D770 dup
p.D770_N771insG	
p.H773_V774insH	p.H773dup



EGFR exon20 insertion mutations are highly diverse

Frequencies of different EGFR ex20ins



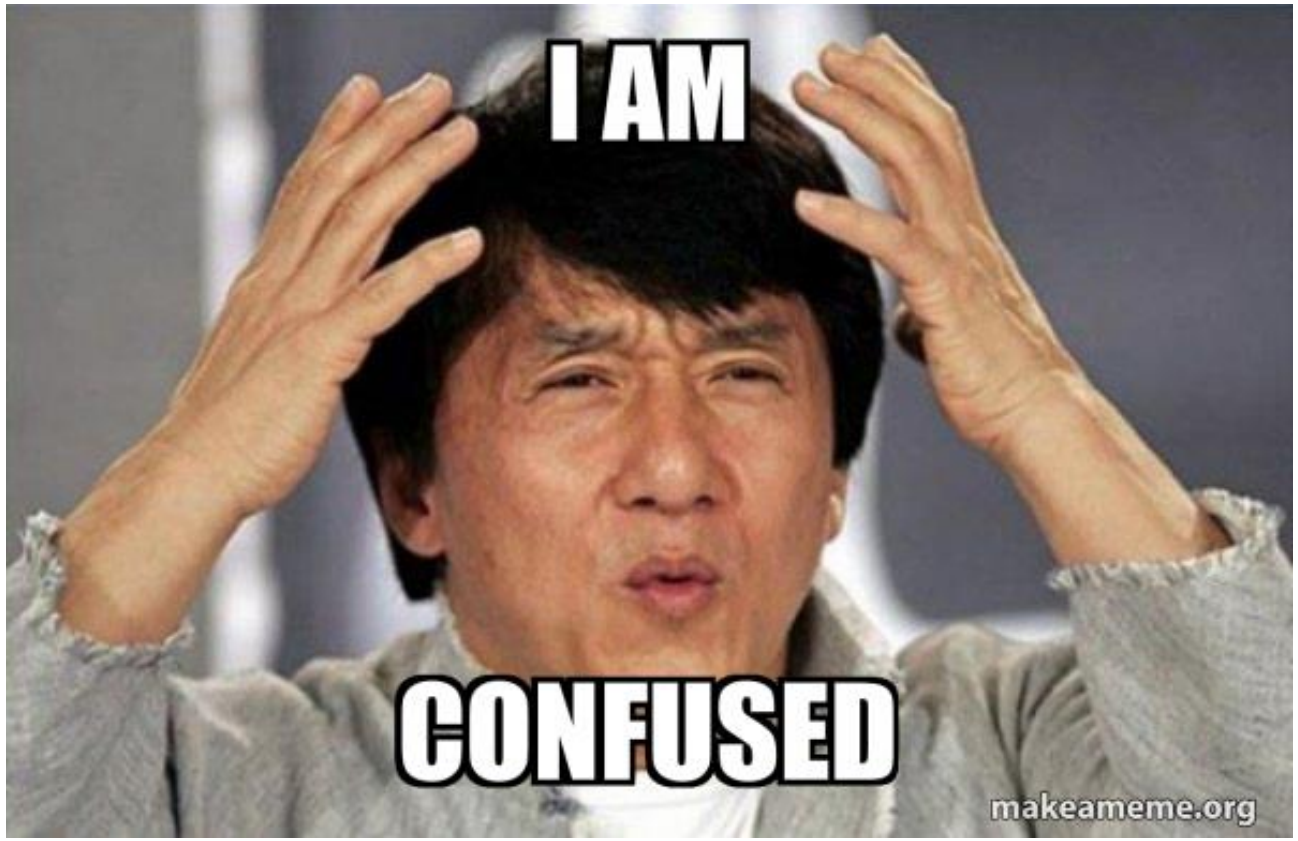
p.A767_V760dup
p.S768_D770dup

~~p.D770>GY~~

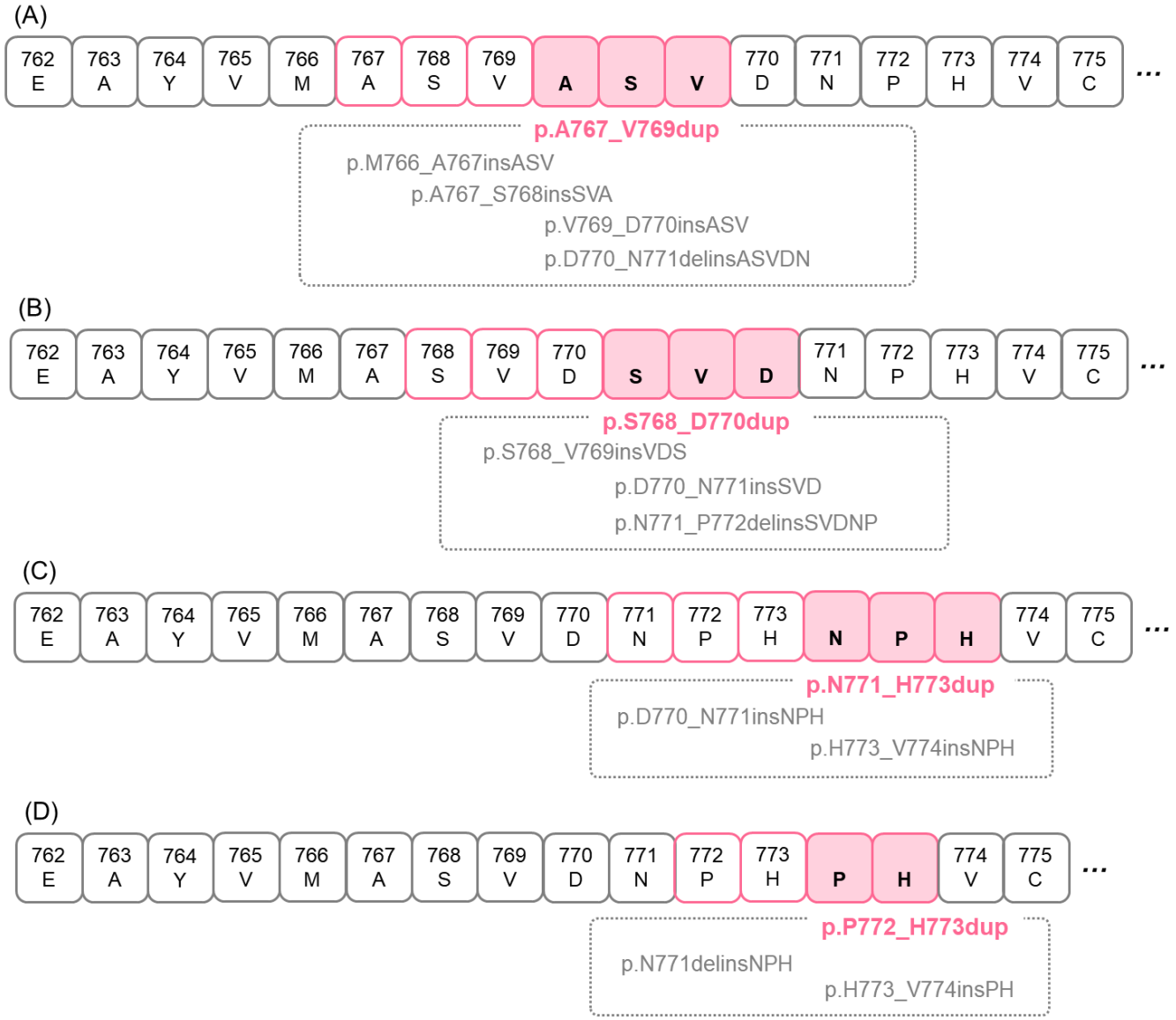
p.D770delinsGY

Out of 547 Chinese patients with NSCLC, a total **of 85 unique EGFR exon20ins variants** were identified

Qin Y, et al. *Mol Oncol.* 2020;14(8):1695-1704.


I AM
CONFUSED
makeameme.org

HGVS nomenclature : 3’ RULE

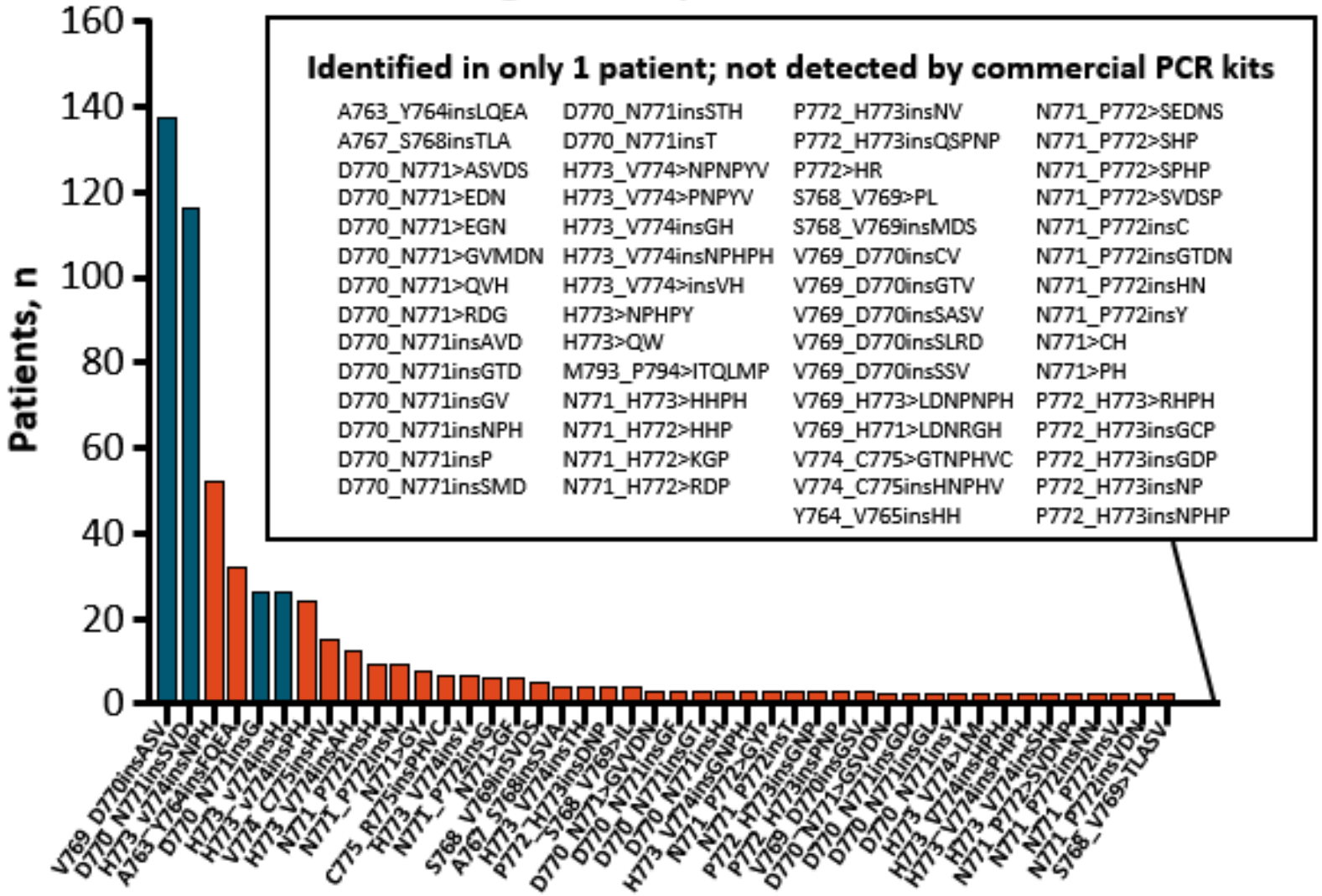


- Gray texts in a dotted box are mutations confusingly used in the literature, which should be reported according to the HGVS nomenclature (pink text) to avoid confusion.

- Most annotations that require correction according to the HGVS nomenclature were “duplications (dup)”, which were incorrectly expressed as “insertion (ins)” or “deletion-insertion (delins)”.

Under review

FoundationInsights®: Expected PCR Detection Results



Expected to be detected by

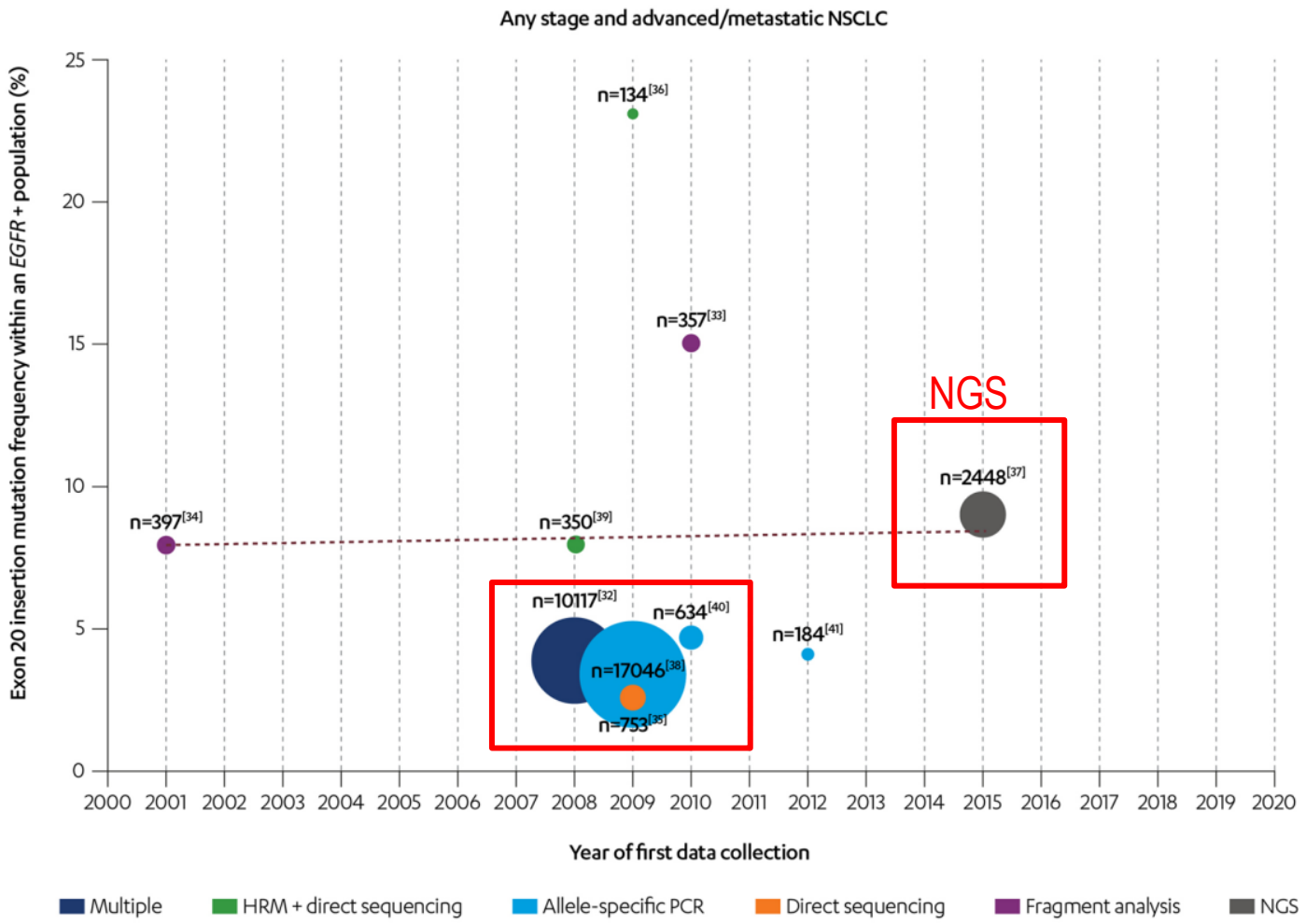
- Cobas®, therascreen
- Not detected by above kit

Method	Kit
qRT-PCR	Cobas® EGFR Mutation Test v2
	therascreen EGFR RGQ PCR

Bauml. WCLC 2020. Abstr FP07.12.

EGFR exon20 insertion : Frequency

Frequency of exon 20 insertion mutations in any stage of EGFR-mutated NSCLC

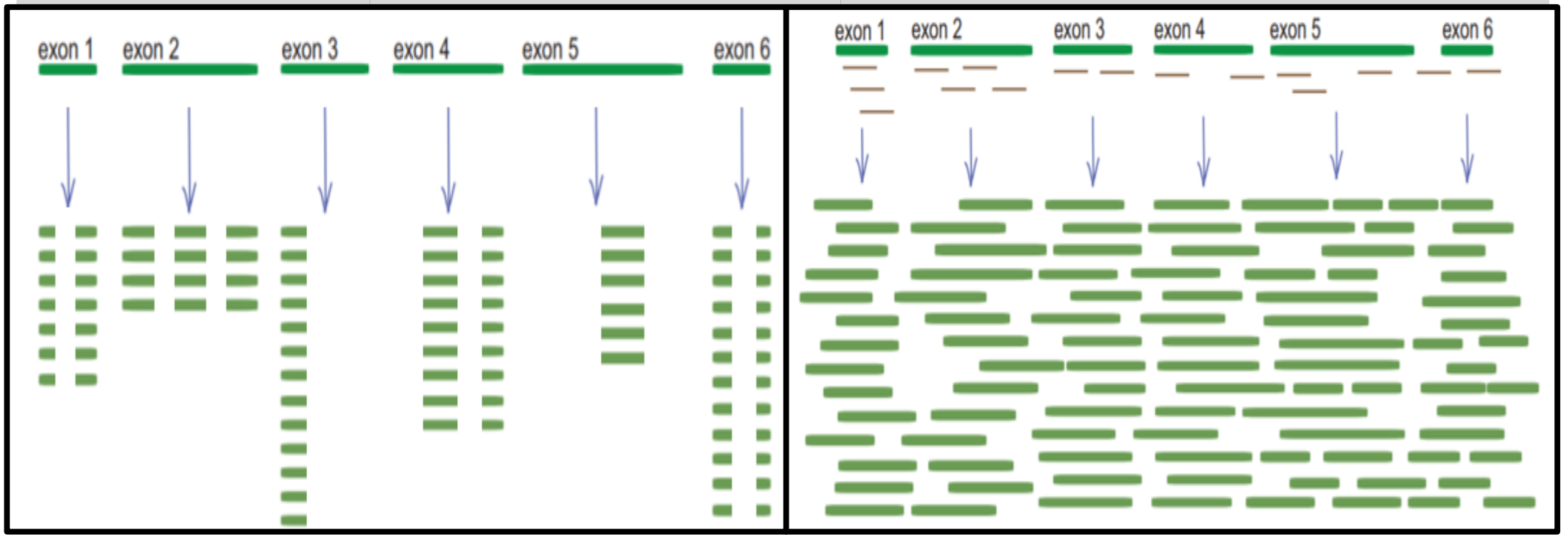


- 1.6% in the overall NSCLC population
- 9.0% in an EGFR-positive population
- 2-fold increase in frequency when NGS is applied.

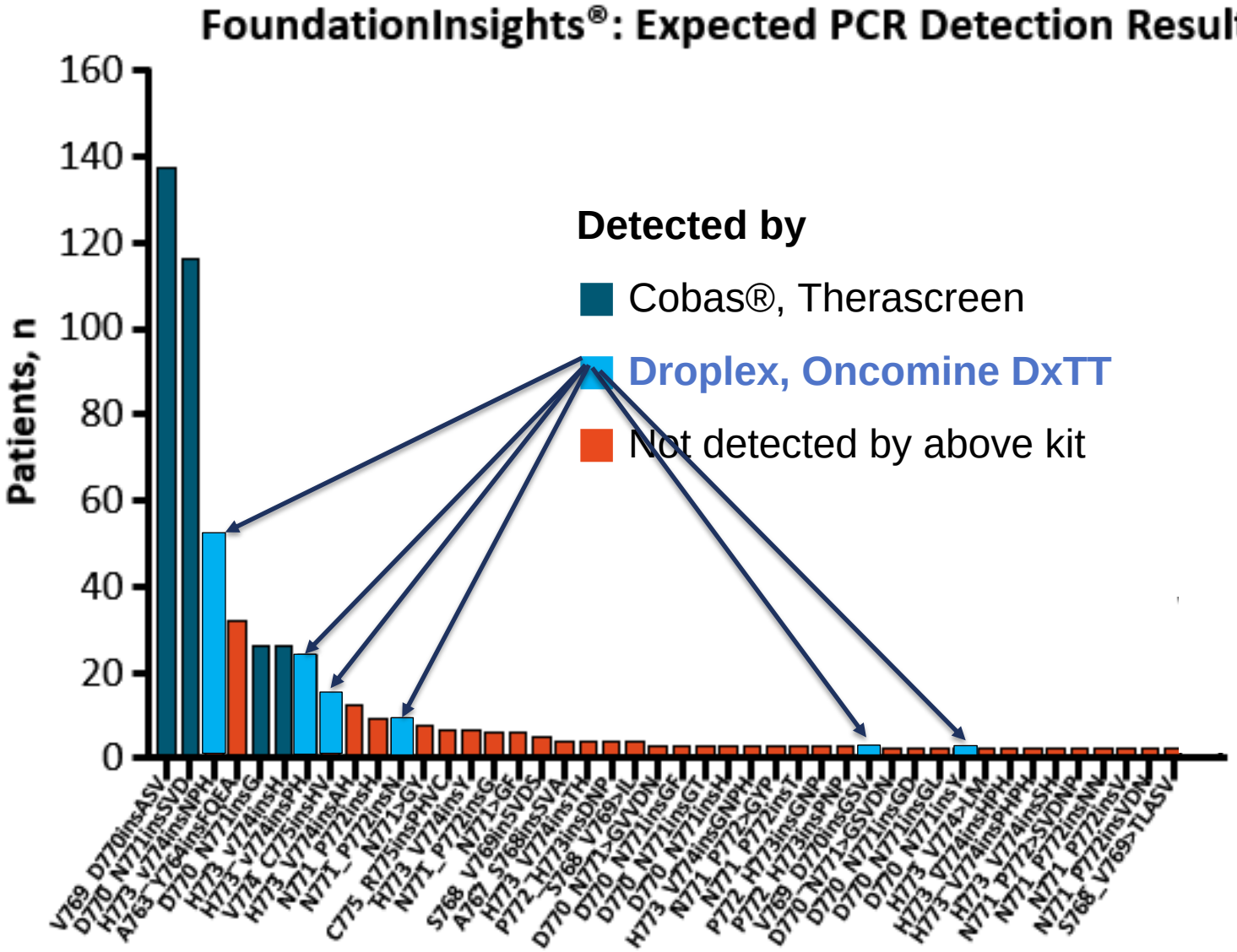
Target Oncol. 2022 Mar;17(2):153-166.

Amplicon vs. Capture Sequencing

Features	Amplicon method	Hybridization method
Representative panel	Oncomine DxTT	F1CDx, TSO500



Yatabe Y, Sunami K, Goto K et al. Multiplex gene-panel testing for lung cancer patients. Pathol Int 2020;70;921-931.



48.6%

Method	Kit
qRT-PCR	Cobas® EGFR Mutation Test v2
	therascreen EGFR RGQ PCR

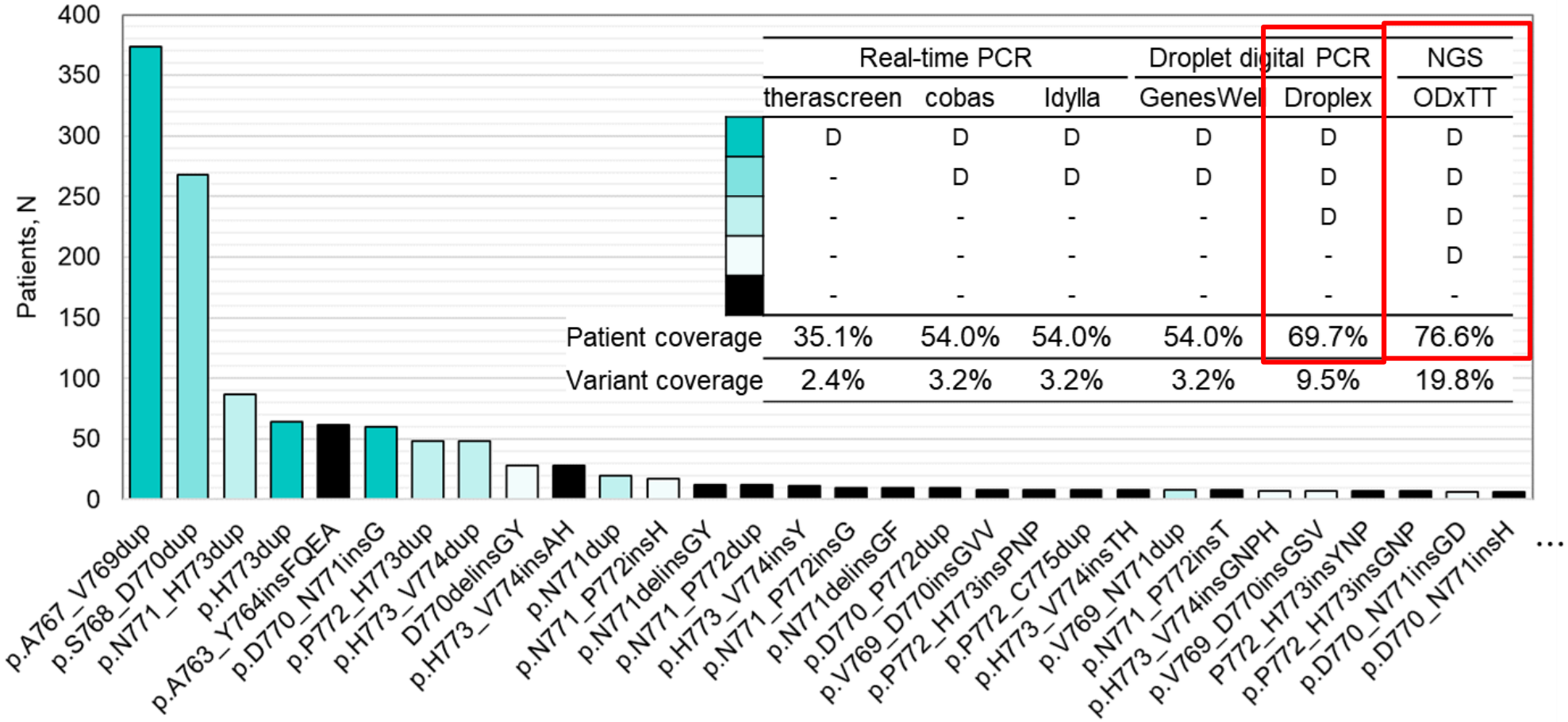
69.7~ 76.6%

Method	Kit
ddPCR	Droplex EGFR Mutation Test V2
NGS	Oncomine DxTT

Modified Bauml. WCLC 2020. Abstr FP07.12.

Detection coverages of EGFR exon20 insertion mutations

Total 1,418 EGFR exon20 insertion patients



- Oncomine Dx Target Test : 76.6%
- Droplex *EGFR* Mutation Test v2 : 69.7%

- Data from FoundationInsights database (n=625), Geneseeq Technology Inc. (n=517), Phase I/II trial of mobocertinib (n=95), Phase II study of poziotinib (n=47), phase I study of sunvozertinib (n=51), SMC (n=83)

Under review

Summary

- Testing for *EGFR* is **widely available** throughout the world.
- More than **half are PCR-based** single gene tests, and **NGS tests are growing**.
- A PCR-based single gene test **may miss 30 to 50%** of EGFR exon20 insertions compared with other activating mutations.
- It is possible to have **different levels of coverage of mutation variants** on the same platform (including NGS).
- In some cases, the **numbering and variable notation** **for EGFR exon20 insertion** mutations do not comply with the guidelines, which can be confusing.


KSP 2024
The 76th Annual Fall Meeting of
the Korean Society of Pathologists
I The 1st International Conference of KSP I
SAVE THE DATE
–
Oct. 30 ~ Nov. 1, 2024
Lotte Hotel Seoul, Korea
www.pathology.or.kr/english

Thank you


South Korea
First Time in Korea!
Welcome to Korea!
BLACKPINK가 여러분의 대한민국 방문을 환영합니다!
BLACKPINK

Q&A