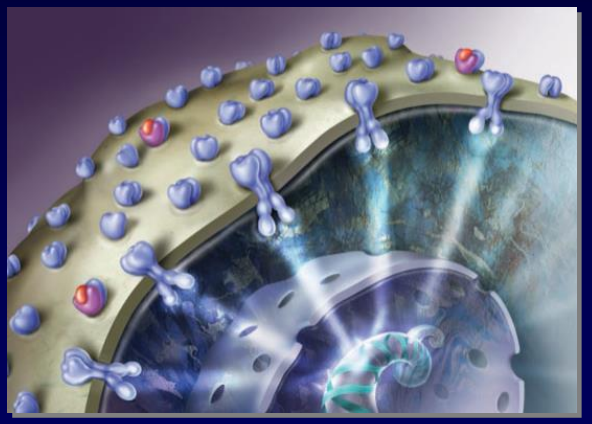
Personalization of Cancer Care:

The RIGHT Treatment for the RIGHT Patient



DR VOON Pei Jye
Medical Oncologist
Hospital Umum Sarawak

Personalized Medicine

With the Right Cancer

Finding the Right Drug for the Right Patient

Personalized Medicine
Using Tumor Genetics & Genomics

- Not a new concept at all
- It's just that we now have better (more efficient) tools to achieve treatment specificity

Personalized Medicine
Using Tumor Genetics & Genomics As Predictive Markers

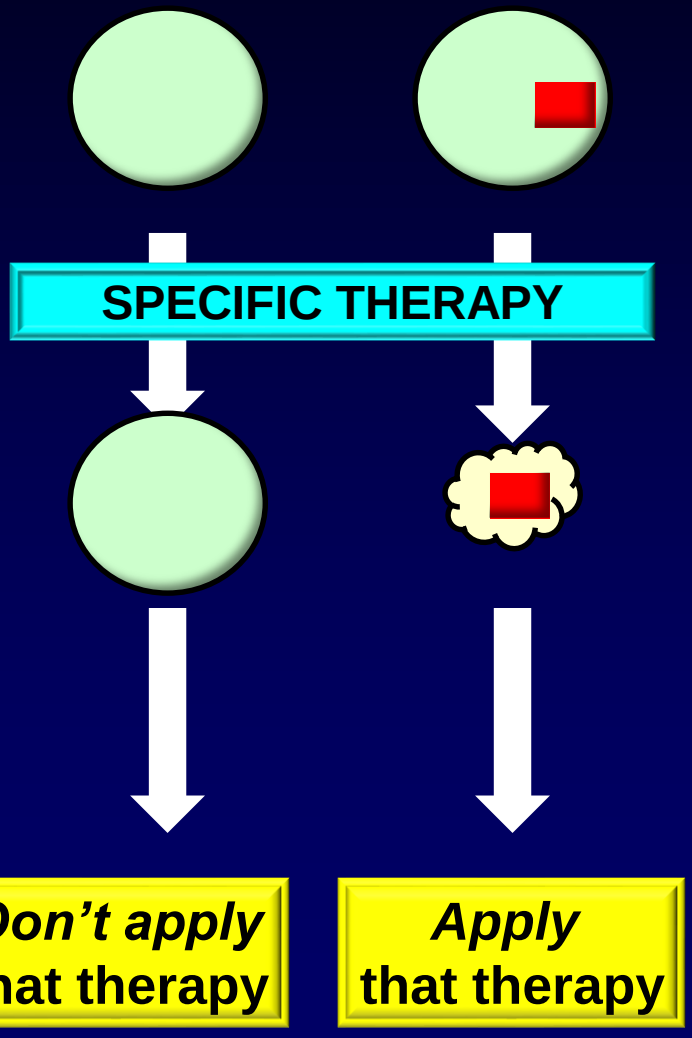
- Predictive markers are molecules that provide upfront (*de novo*) information as to whether or not a patient whose tumour bears this marker is statistically likely to benefit from a specific therapy

Personalized Medicine
Using Tumor Genetics & Genomics As Prognostic Markers

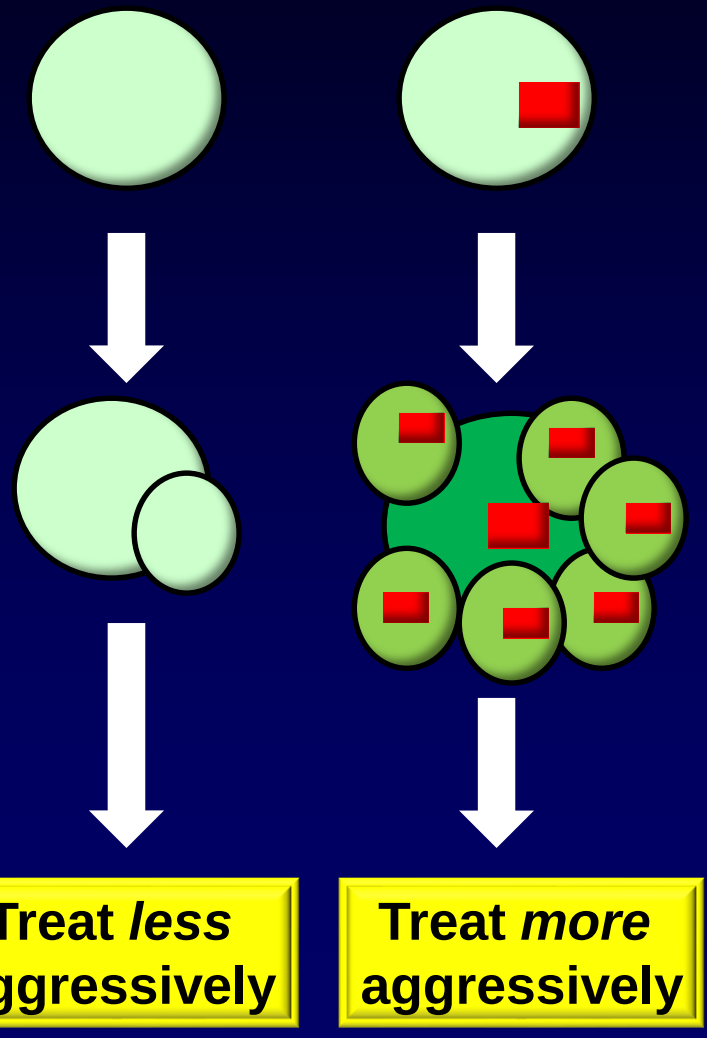
- Prognostic markers are molecules that allow the natural course of a specific disease (cancer) to be predicted
- Prognostic markers may also be predictive markers if drugs are developed against them

Predictive *vs* Prognostic Markers

Predictive Markers:



Prognostic Markers:



Personalized Medicine
Using Specific Molecular Traits of Tumors
The Old ER, PR Story

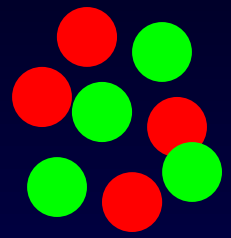
- Probably one of the best therapy predictive markers
- *1970s*: 50% of ER+ pts with ABC achieved ORR with endocrine ablative therapies; ER- pts rarely did
- *1990s*: EBCTCG: Tam x 5Y (vs placebo) confers DFS (50%↓) & OS (28%↓) benefits in ER+ EBC pts. Tam generally ineffective in ER- EBC pts.
- Note: ER has *high negative predictive value*; but only moderate positive predictive value

Personalized Medicine
Using Tumor Genetics & Genomics
Rationale

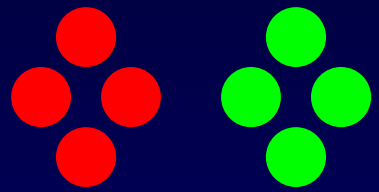
- Tumour heterogeneity - even within the ‘same tumour type’
- But what exactly is ‘same tumour type’ ?
- Anatomical diagnoses such as ‘*breast cancers*’, ‘*colorectal cancers*’ and ‘*lung cancers*’ are rapidly becoming meaningless in cancer treatment

Achieving Greater Treatment Specificity Strategy

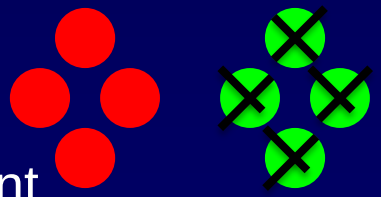
Subdividing tumors into smaller subgroups



Greater homogeneity within each subgroup



Presumably more predictable treatment responses



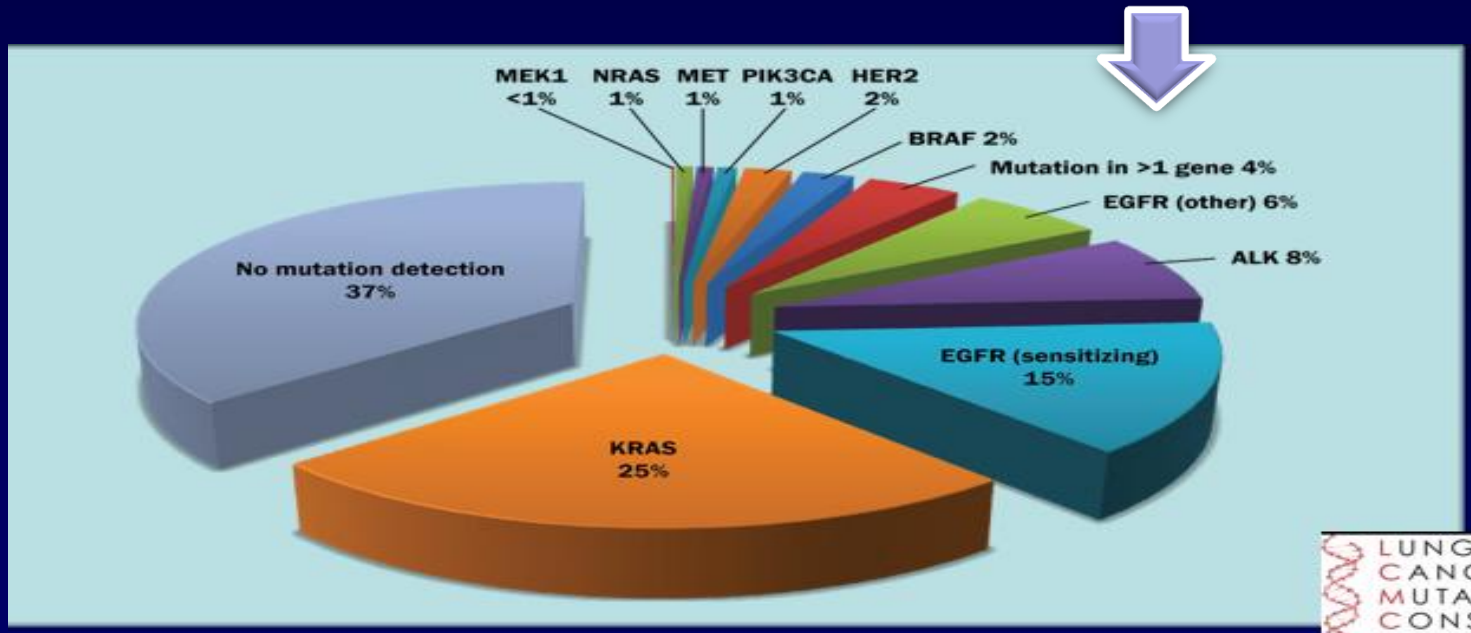
Minimize needless treatment / Lower cost of cancer treatment

Achieving Greater Subgroup Homogeneity

Lung Cancer

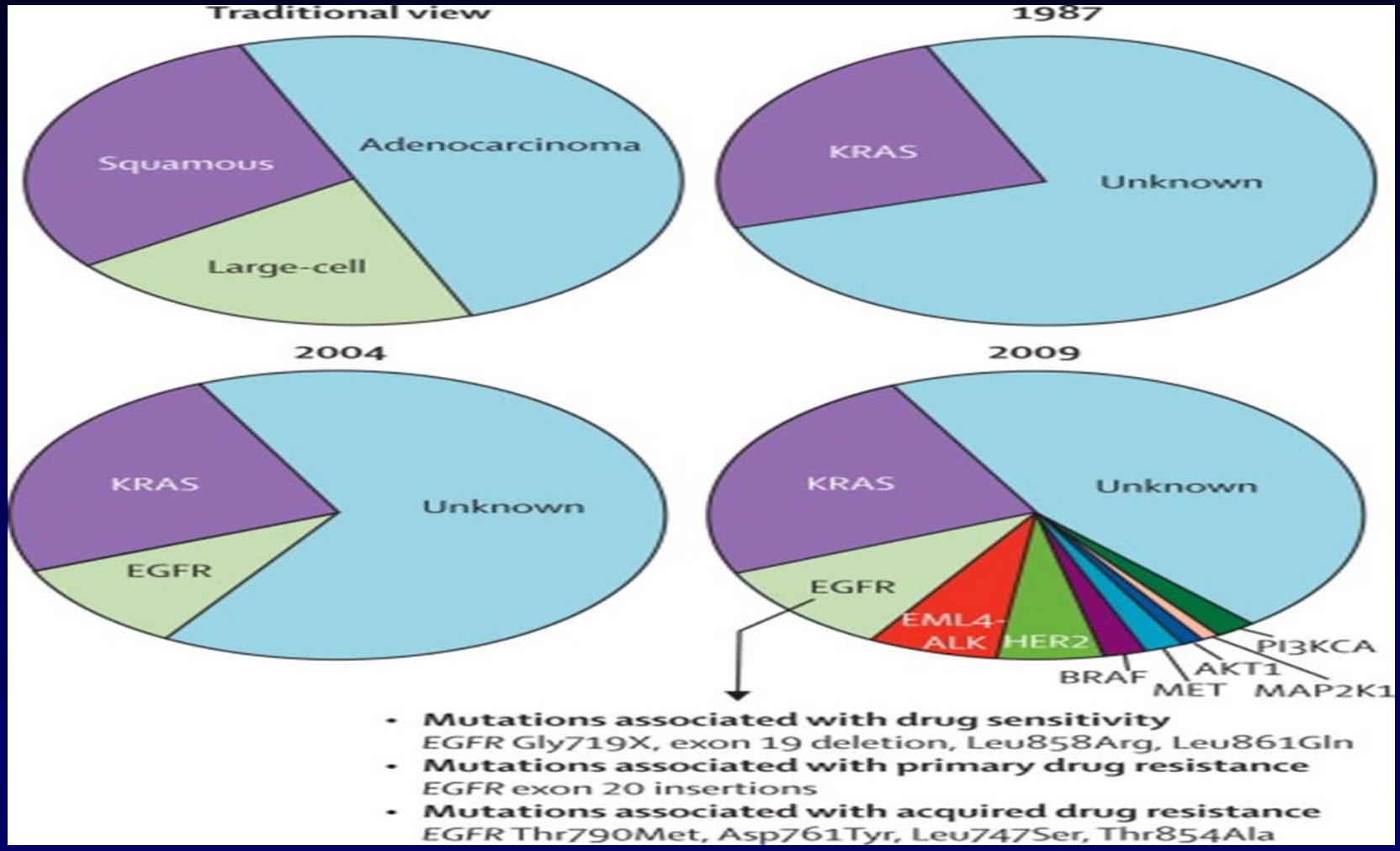
Small Cell Lung Cancer

Non-Small Cell Lung Cancer



LUNG CANCER MUTATION CONSORTIUM

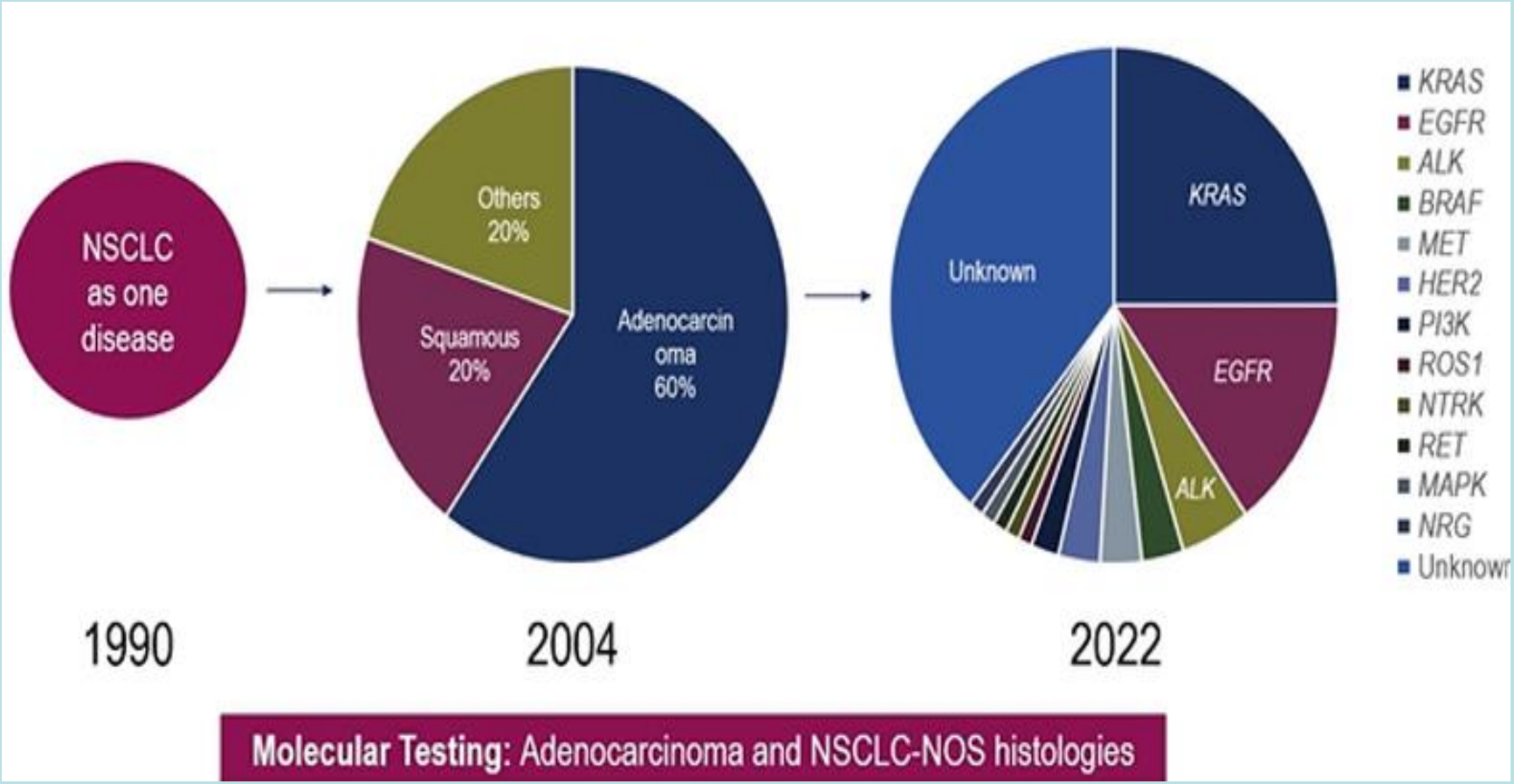
Once upon a time……



Molecular characterization

NSCLC MOLECULAR CLASSIFICATION

NSCLC classification has moved from histologic to molecular subtyping



NSCLC with Targetable Mutation

Driver Mutations

- Initiate the evolution of a non-cancerous cell to malignancy.
- Driver mutations often impart an oncogene-addicted biology to the transformed cell
- Serves as an Achilles' heel, making the cancer uniquely susceptible to down-regulation of signal originating from the driver

Driver Mutation in Lung Cancer by Ethnicity

	USA/Europe	East Asia
EGFR	5-19.4%	40-59%
KRAS	20-30%	7.4-11%
ALK	3-6%	3-7%
ROS1	1-2%	1-3%
BRAF	2-3%	0.5-1%
RET	1-2%	1-2%
MET	3%	2%
HER2	2-3%	2-3%
NTRK	0.23%	<1%

More than 50% of all lung adenocarcinomas harbour driver oncogenes
Incidence of genomic driver is variable among ethnic populations

WHO 5th ed. Lyon, France: IARC Press; 2021

METASTATIC NSCLC: ESMO CLINICAL PRACTICE

Molecular Pathology/Biology ESMO Testing Guideline Recommendations

2019 NSCLC Recommendations

1 'Must-test' Predictive Biomarkers

- *EGFR*
- *ALK*
- *ROS1*
- *BRAF*
- PD-L1

2 'Should-test' Emerging Biomarkers

- *KRAS*
- *RET*
- *NTRK*
- *MET*
- *HER2*

2021 NSCLC Recommendations

1 'Must-test' Predictive Biomarkers

- *EGFR*
- *ALK*
- *ROS1*
- *BRAF*
- *NTRK*
- PD-L1

2 'Should-test' Emerging Biomarkers

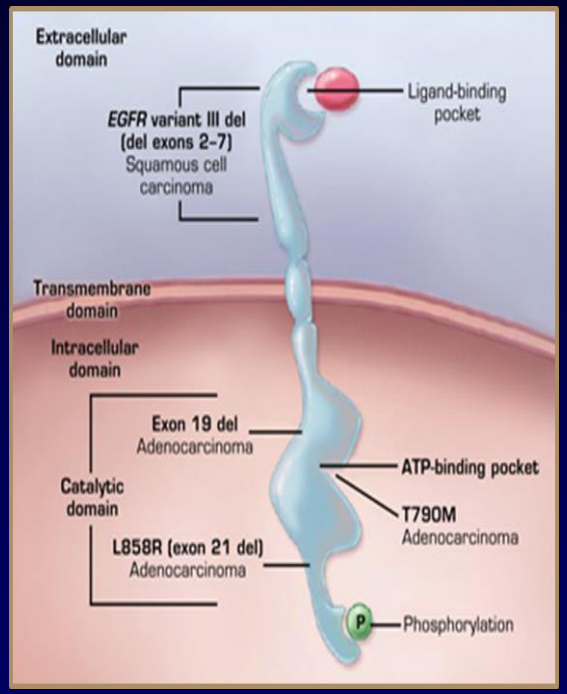
- *KRAS*
- *RET*
- *HER2*
- *MET*

Exp, expression; mut, mutation; NSCLC, non-small cell lung cancer; rearr, rearrangement

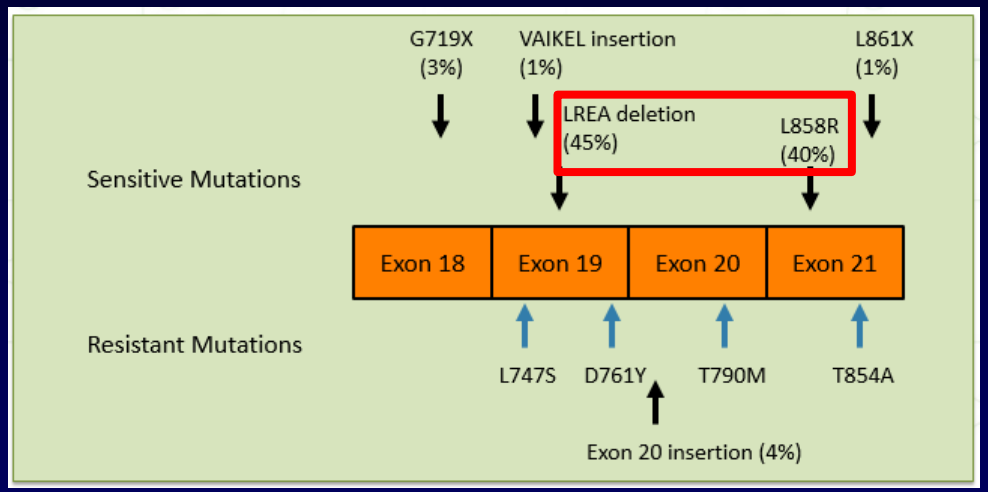
Planchard D, *et al*. Ann Oncol 2018 1;29(Supplement_4):iv192-iv237,
.Updated version published 15 September 2020 by the ESMO Guidelines Committee.

Which Target?

The EGFR receptor



Distribution of EGFR mutations in lung cancer.



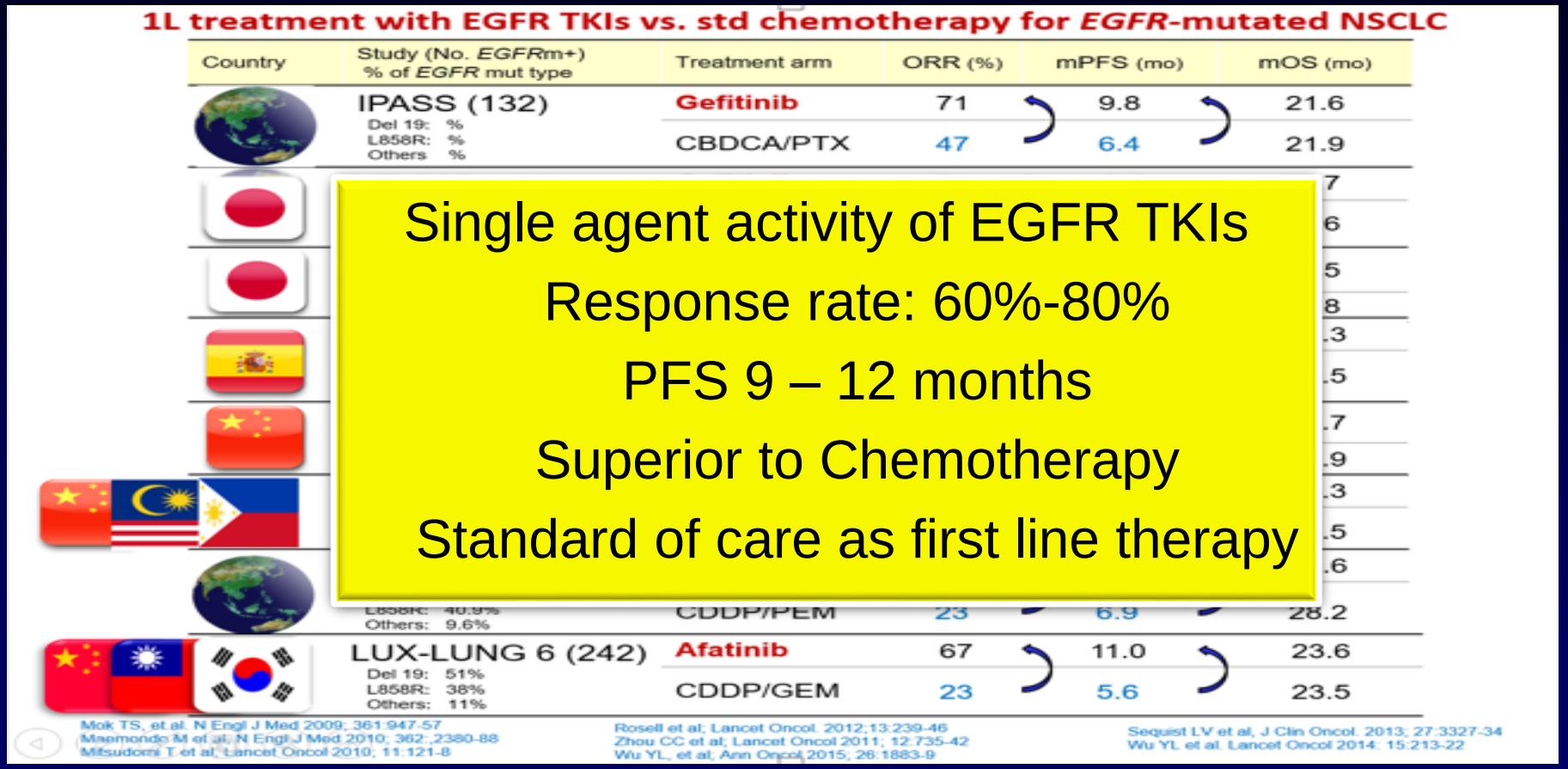
Ohashi K et al. JCO 2013;31:1070-1080

Why is EGFR mutation important in Asian?

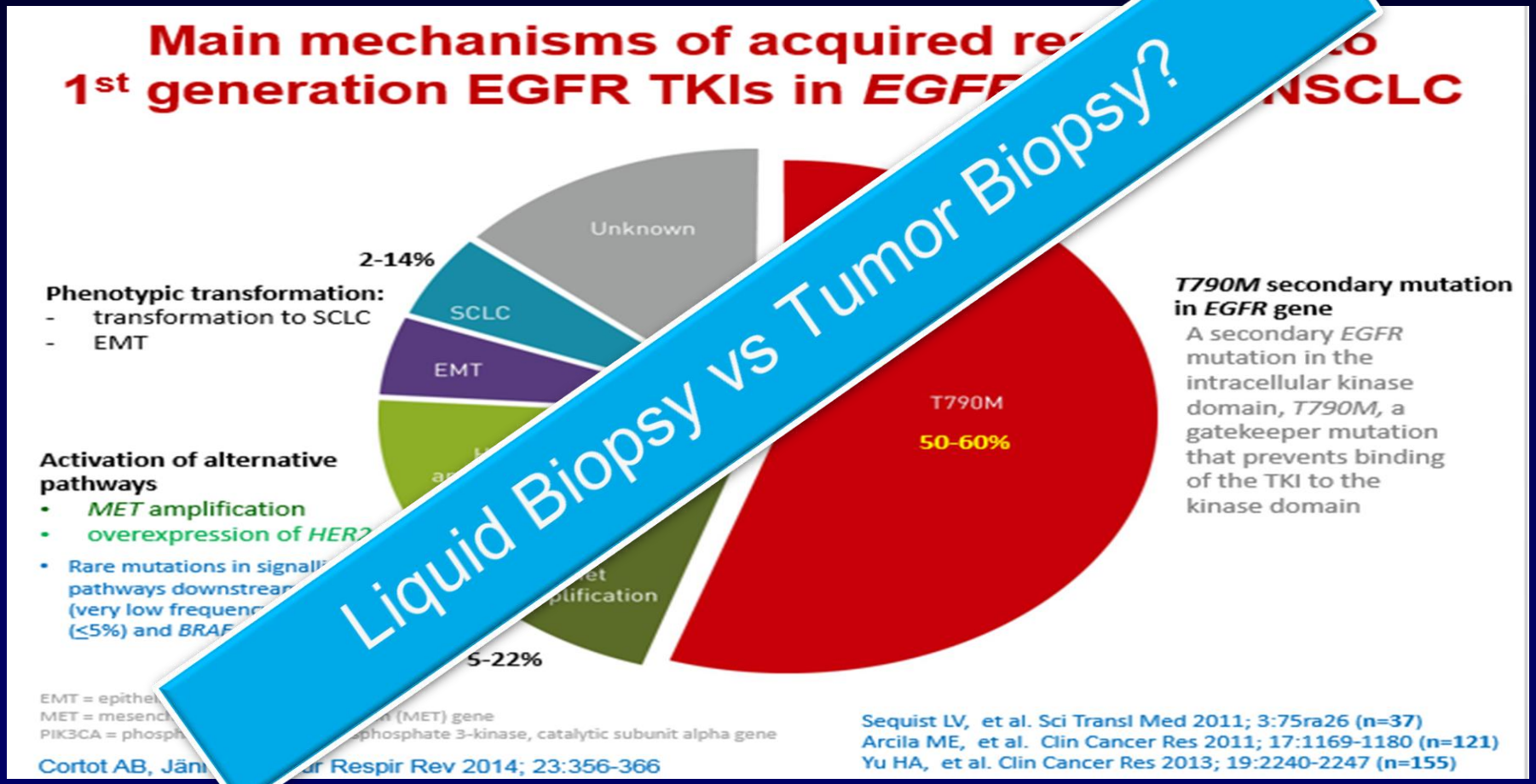
- Asians have a higher prevalence of EGFR mutation in lung tumors than whites
- The proportion of patients with EGFR mutations is higher among Asian patients (~30–40%) than non-Asian (~10–15%)
- The overall prevalence of EGFR mutations (i.e. exons 18~22) among Asians was approximately:
  - 30%- overall
  - 47% - patients with adenocarcinoma
  - 56%- never smokers.

Zhou W, Chin J Cancer 2011

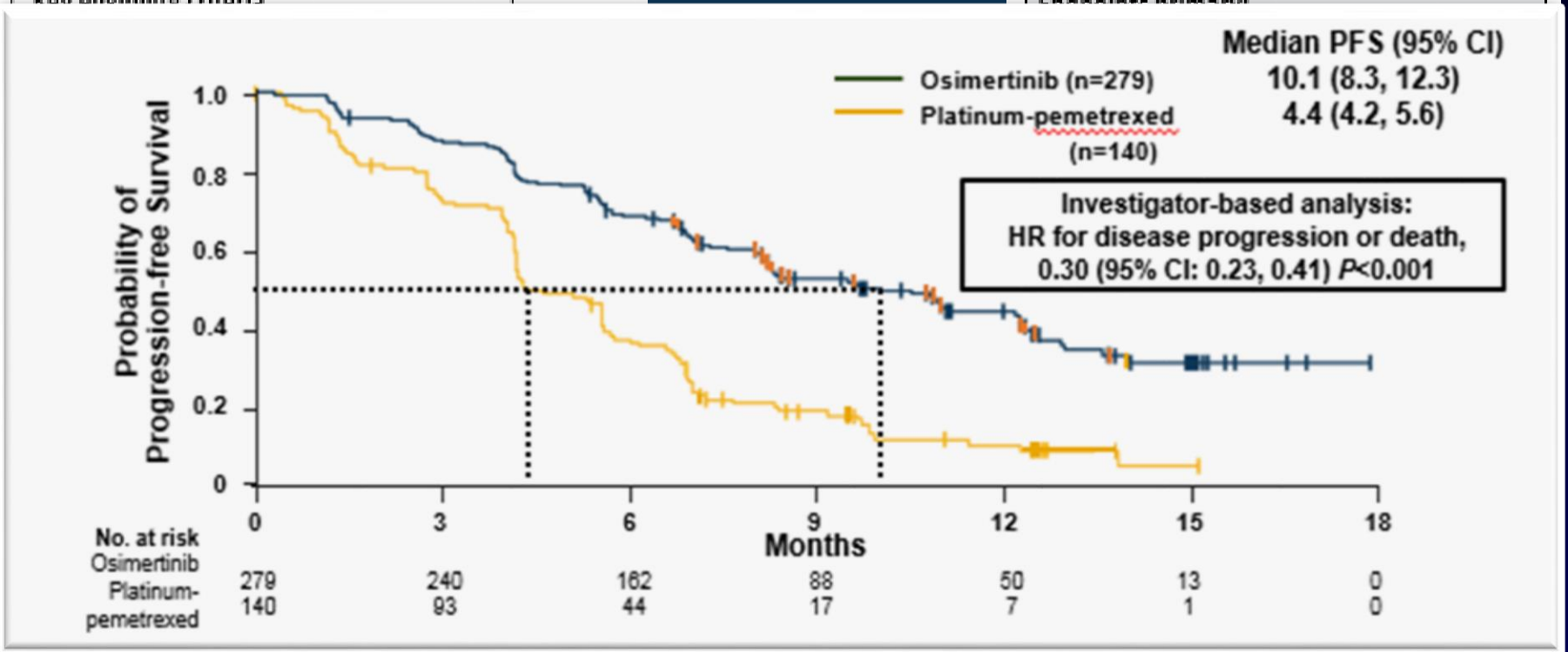
1L TKIs vs Chemo Data



Eventually, all patients will progress…



AURA3 study design

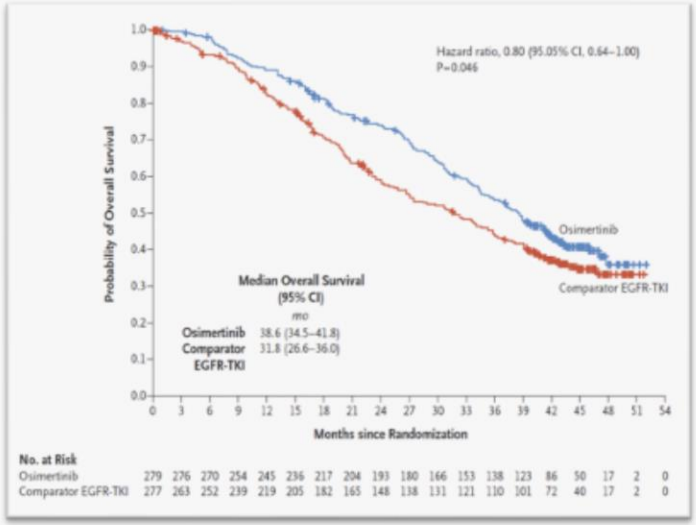


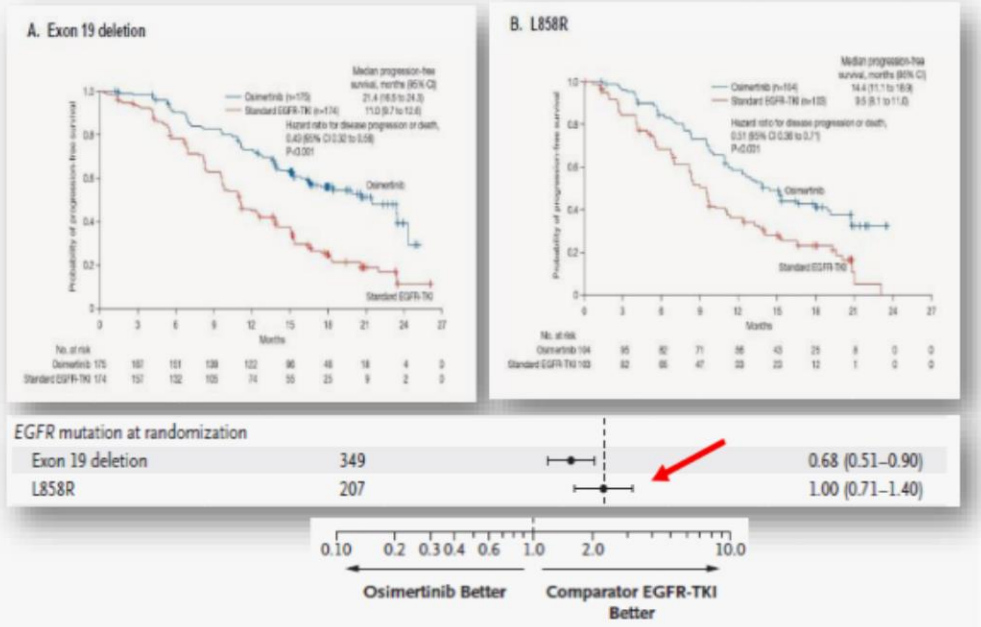
Mok TS, et al. N Engl J Med. 2017; 376:629-640

Any data for first line setting?

Advanced NSCLC with EGFR del19 or L858R

According to FLAURA





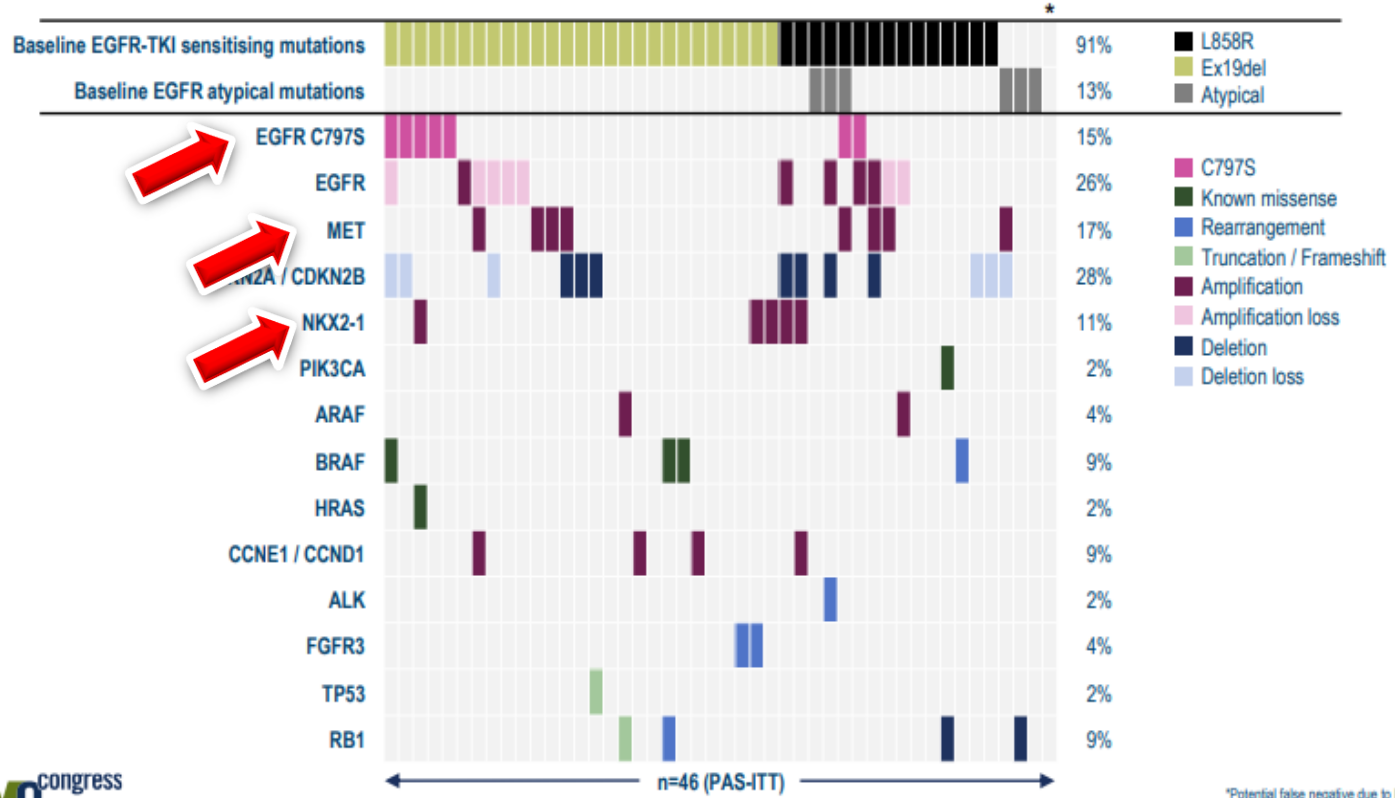
Soria JC. et al. N engl J Med 2017; Ramalingam SS. et al. N Engl J Med 2019

PARIS 2022 ESMO congress

ELIOS: a multicentre, molecular profiling study of patients with EGFRm advanced NSCLC treated with first-line osimertinib

Zofia Piotrowska[1], Myung-Ju Ahn[2], Yong Kek Pang[3], Soon Hin How[4], Sang-We Kim[5], Pei Jye Voon[6], Diego Cortinovis[7], Javier de Castro Carpeno[8], Marcello Tiseo[9], Delvys Rodriguez Abreu[10], Suresh S. Ramalingam[11], Jingyi Li[12], Leslie Servidio[12], Samuel Sadow[13], Ryan Hartmaier[14], Byoung Chul Cho[15]

CANDIDATE ACQUIRED ALTERATIONS WITH OSIMERTINIB



*Potential false negative due to low tumour content.

Zofia Piotrowska, MD

EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; TKI, tyrosine kinase inhibitor.

Advanced NSCLC with EGFR exon 20 ins.

	Mobocertinib	Amivantamab CRYSALIS	Osimertinib 160 mg/j	Osimertinib 160 mg/j	CLN-081 Phase I	DZD9008 Phase 1	Poziotinib ZENITH 20
Drug	EGFR/HER 2 TKI	EGFR/MET Ac	EGFR-TKI	EGFR-TKI	EGFR-TKI	**EGFR/HER2-TKI**	EGFR/HER2-TKI
n	PPP (n=114)	n=81	n=25	n=17	n=42	n=56	n=115
ORR	28 % (PPP)	40 %	28 %	24 %	50 % 54 % à 100 mg BID	**38 %**	14.8 %
Efficacy	DoR 17.5 months PFS 7.3 months OS 24 months	DoR 11.1 months PFS 8.3 months OS 22.8 months	PFS 6.8 months DoR : 4.2 months	PFS 9.6 months DoR NR	-		DoR 7.4 mois PFS 4.2 mois

Zhou C. et al. JAMA Oncol. 2021 ; Park J. et al. J Clin Oncol 2021 ; Zwierenga F. et al. ESMO 2021 ; Piotrowska Z. et al. ASCO 2020 ; Piotrowska Z. et al. ASCO 2021. Abstr 9077 ; Janne P. et al. WCLC 2021 ; Socinski. ESMO 2020

Personalized Medicine
Using Tumor Genetics & Genomics
Unanswered Questions

- Primary tumor *vs* metastatic lesions
- Evolution of genetic aberrations over time
- Evolution of genetic aberrations after initial therapies
- Multiple samplings?

Personalized Medicine Using Tumor Genetics & Genomics *Imperfections*

- Even molecularly-defined subgroups are not totally homogeneous → hence less than 100% ORR
- Presence of a particular tumor genetic mutation does not necessarily predict treatment response
- Taken together, prediction of treatment response in each 'subgroup' is still a matter of statistical probability: Good, but not good enough

Personalized Medicine Using Tumor Genetics & Genomics *Reality & Challenges*

- Danger of over-simplification
- Each tumor in a particular patient is unique, defined by the complex repertoire of upregulated and downregulated genes, whose status may vary dynamically over time.
- Real-time, real-tumor sensitivity testing against a panel of anti-cancer drugs is the holy grail → akin to bacterial sensitivity in each infected patient

Personalized Medicine
Tumor Genetics and Genomics

- Anatomical, clinical and conventional pathological descriptors are no longer sufficient to guide the practicing oncologists in the choice of therapies
- Tumor genetics and multi-gene tumor profiling offer useful identifiers that :
  - Provide better insights into the natural behavior of the tumors, and / or
  - Provide filters that predict who will benefit from a particular therapy
- ***Every patient is unique So is every tumor***

Thank you