CLINICAL FLASHCARDS

Hacking the Lung Cancer Genetic Code

The Life Science Feed

QUESTION

What percentage of Western patients with NSCLC adenocarcinoma typically harbour EGFR mutations?

ANSWER

Roughly 10-15%.

QUESTION

EGFR mutations are found in up to _____% of East Asian patients with adenocarcinoma.

ANSWER

50%.

QUESTION

In which exons do targetable EGFR mutations primarily cluster?

ANSWER

Exons 18-21.

QUESTION

Which two specific EGFR mutations account for approximately 85% of all cases?

ANSWER

Exon 19 deletions and exon 21 L858R substitutions.

QUESTION

What was the primary mechanism of resistance that emerged in 60% of patients treated with first-generation EGFR TKIs?

ANSWER

The T790M mutation.

QUESTION

Which third-generation EGFR TKI was specifically designed to inhibit the T790M resistance mutation?

ANSWER

Osimertinib.

QUESTION

The _____ trial established osimertinib as the global standard of care for treatment-naïve EGFR-mutant advanced NSCLC.

ANSWER

FLAURA.

QUESTION

What was the median progression-free survival (PFS) for osimertinib in the FLAURA trial?

ANSWER

18.9 months.

QUESTION

What was the median overall survival (OS) for patients receiving osimertinib in the FLAURA trial?

ANSWER

38.6 months.

QUESTION

The FLAURA2 trial investigated the combination of osimertinib and _____ in the first-line setting.

ANSWER

Platinum-pemetrexed chemotherapy.

QUESTION

In FLAURA2, what was the median PFS for the osimertinib plus chemotherapy arm?

ANSWER

25.5 months.

QUESTION

According to the MARIPOSA trial, what is the target of the bispecific antibody amivantamab?

ANSWER

EGFR and MET.

QUESTION

Which EGFR TKI was combined with amivantamab in the MARIPOSA trial?

ANSWER

Lazertinib.

QUESTION

What was the median PFS for the amivantamab plus lazertinib arm in the MARIPOSA trial?

ANSWER

23.7 months.

QUESTION

List two common toxicities associated with the amivantamab component in the MARIPOSA trial.

ANSWER

Infusion-related reactions and paronychia (or hypoalbuminaemia).

QUESTION

The PAPILLON trial established a new standard of care for which specific EGFR mutation?

ANSWER

EGFR exon 20 insertions.

QUESTION

What treatment combination did the PAPILLON trial validate for EGFR exon 20 insertions?

ANSWER

Amivantamab plus carboplatin-pemetrexed chemotherapy.

QUESTION

What is the typical prevalence of ALK rearrangements in NSCLC?

ANSWER

3-5%.

QUESTION

Patients with ALK-positive NSCLC are disproportionately likely to have what smoking history?

ANSWER

Never-smokers.

QUESTION

What was the primary clinical limitation of the first-generation ALK inhibitor crizotinib?

ANSWER

Poor CNS (central nervous system) penetration.

QUESTION

The _____ trial compared alectinib to crizotinib in untreated ALK-positive NSCLC.

ANSWER

ALEX.

QUESTION

Which third-generation ALK inhibitor was evaluated in the CROWN trial?

ANSWER

Lorlatinib.

QUESTION

According to five-year CROWN trial data, what percentage of patients on lorlatinib remain progression-free?

ANSWER

60%.

QUESTION

What was the intracranial objective response rate for lorlatinib in patients with baseline brain metastases in the CROWN trial?

ANSWER

Approximately 82%.

QUESTION

Which diagnostic tool is commonly used as a screening tool for ALK rearrangements?

ANSWER

Immunohistochemistry (IHC).

QUESTION

Which two methods are typically used to confirm an ALK rearrangement after a positive IHC screen?

ANSWER

FISH or Next-Generation Sequencing (NGS).

QUESTION

What is the primary rationale for using alectinib before lorlatinib in the first-line setting?

ANSWER

It preserves lorlatinib as an effective second-line option after progression.

QUESTION

What is the most common oncogene mutated in NSCLC overall?

ANSWER

KRAS.

QUESTION

KRAS mutations are present in approximately _____% of NSCLC adenocarcinomas.

ANSWER

25-30%.

QUESTION

Why was KRAS historically considered 'undruggable'?

ANSWER

It has a smooth surface without obvious binding pockets and very high affinity for GDP and GTP.

QUESTION

Which specific KRAS mutation is targeted by sotorasib and adagrasib?

ANSWER

KRAS^{G12C}.

QUESTION

What percentage of NSCLC adenocarcinomas harbour the KRAS^{G12C} mutation?

ANSWER

Approximately 13%.

QUESTION

In which state does sotorasib covalently lock the KRAS^{G12C} protein?

ANSWER

The GDP-bound (inactive) state.

QUESTION

What is the name of the cryptic binding pocket exploited by KRAS^{G12C} inhibitors?

ANSWER

The switch II pocket.

QUESTION

The CodeBreaK 200 trial compared sotorasib against which chemotherapy agent?

ANSWER

Docetaxel.

QUESTION

What was the median PFS for sotorasib in the CodeBreaK 200 trial?

ANSWER

5.6 months.

QUESTION

Which KRAS^{G12C} inhibitor has demonstrated documented CNS responses in patients with active brain metastases?

ANSWER

Adagrasib.

QUESTION

What was the median PFS for adagrasib in the KRYSTAL-1 phase 2 cohort?

ANSWER

6.5 months.

QUESTION

Presence of STK11 and _____ co-mutations is known to blunt the clinical benefit of KRAS^{G12C} inhibitors.

ANSWER

KEAP1.

QUESTION

What was the primary safety concern identified in the KRYSTAL-7 trial (adagrasib plus pembrolizumab)?

ANSWER

Liver toxicity.

QUESTION

Which investigational KRAS inhibitor targets the G12D mutation?

ANSWER

MRTX1133.

QUESTION

What is the global standard of care for first-line EGFR-mutant NSCLC monotherapy?

ANSWER

Osimertinib.

QUESTION

Why is comprehensive molecular testing at diagnosis preferred over sequential single-gene testing?

ANSWER

It is faster and less likely to miss fusions or rare targetable alterations.

QUESTION

Status of which gene, along with STK11 and KEAP1, significantly influences prognosis and treatment selection in NSCLC?

ANSWER

TP53.

QUESTION

What was the median PFS for the osimertinib monotherapy arm in the FLAURA2 trial?

ANSWER

16.7 months.

QUESTION

The hazard ratio for PFS in the MARIPOSA trial (amivantamab plus lazertinib vs osimertinib) was _____.

ANSWER

0.70.

QUESTION

What is the recommended first-line ALK inhibitor for patients with high-volume CNS involvement?

ANSWER

Lorlatinib.

QUESTION

Which trial established amivantamab plus chemotherapy as the standard for EGFR exon 20 insertions?

ANSWER

PAPILLON.

QUESTION

In the ALEX trial, what was the median PFS for the crizotinib control arm?

ANSWER

11.1 months.

QUESTION

What was the hazard ratio for PFS in the FLAURA2 trial comparing combination therapy to osimertinib alone?

ANSWER

0.62.

QUESTION

What was the median PFS for the chemotherapy arm in the PAPILLON trial?

ANSWER

6.7 months.

QUESTION

Which EGFR mutations are considered 'classical' or 'sensitising' mutations?

ANSWER

Exon 19 deletions and L858R.

QUESTION

True or False: KRAS^{G12C} inhibitors are typically used as first-line therapy in NSCLC.

ANSWER

False (they are currently approved for second-line or previously treated patients).

QUESTION

Which ALK inhibitor is considered a standard first-line option for patients without CNS disease prioritising tolerability?

ANSWER

Alectinib.

QUESTION

What approach is being investigated to overcome adaptive reactivation pathways in KRAS resistance?

ANSWER

Combination strategies (e.g., adding SHP2, MEK, or EGFR inhibitors).

QUESTION

In EGFR-mutant NSCLC, which patient population is most likely to be considered for osimertinib plus chemotherapy?

ANSWER

Those with high disease burden or rapid progression.

QUESTION

Which trial results at ASCO 2026 are expected to clarify the use of combination therapy in first-line EGFR disease?

ANSWER

Updated Overall Survival (OS) data from FLAURA2.

QUESTION

What is the primary diagnostic platform used to catch ALK rearrangements as part of a broader panel?

ANSWER

Next-Generation Sequencing (NGS).