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**IMPACT OF EGFR CNGs, SITE OF INSERTION AND FIRST LINE TREATMENT IN THE OUTCOME OF
NSCLC PATIENTS WITH EGFR EXON 20 INSERTIONS**

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Disclosure

Artificial Intelligence (AI) Use Disclaimer

Claude (Anthropic) was used for slide layout and language editing. All data, analyses and scientific content were generated and verified by the authors.

Background and study design

EGFR ex20ins: a heterogeneous subgroup with primary TKI resistance and poor outcome

Patients included **n = 124** · Overall survival **n = 100** · First-line PFS **n = 60** · EGFR copy number evaluable **n = 63** · Multivariate model **n = 47**

COHORT · retrospective multicentre

124 patients with EGFR ex20ins

16 institutions in 4 countries (Spain, Brazil, Argentina and Italy)

46 distinct variants

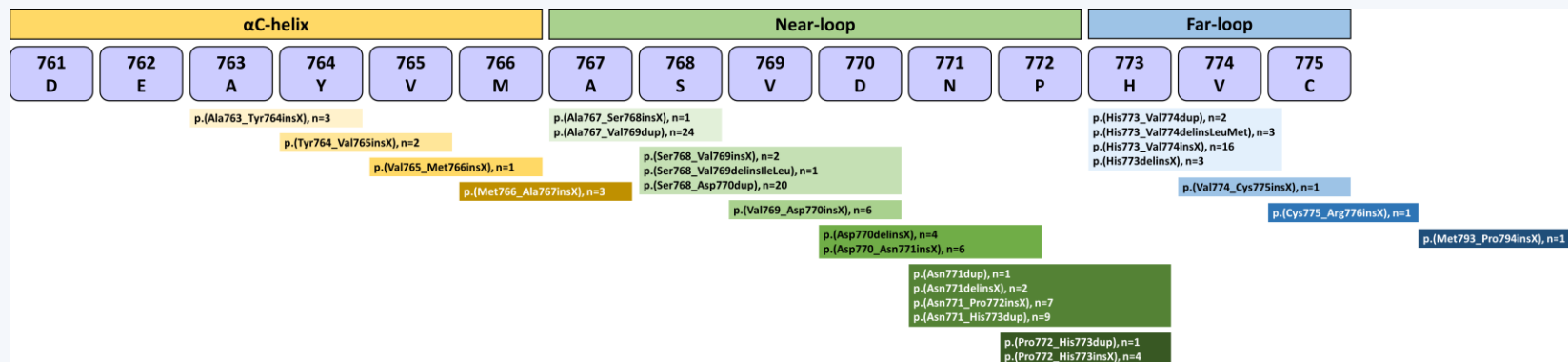
CLINICAL CHARACTERISTICS · n = 124

Median age, years	63 (36–88)
Female	78 (62.9%)
Never-smoker	58 (46.8%)
Adenocarcinoma	110 (88.7%)
Stage IIIB–IVB	98 (79.0%)

FIRST-LINE TREATMENT · % of full cohort

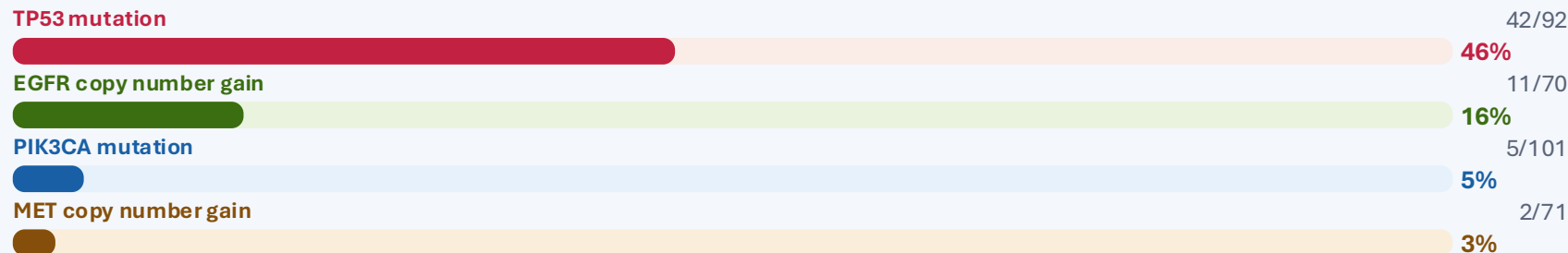
Chemotherapy	37 (29.8%)
Immune checkpoint inhibitors	17 (13.7%)
EGFR TKIs	14 (11.3%)
Monoclonal antibodies	6 (4.8%)
Not treated	10 (8.1%)

VARIANT DISTRIBUTION · position within exon 20



Near-loop 71.0% · **Far-loop 21.8%** · **αC-helix 7.2%** Three variants account for 43% of all cases, all near-loop

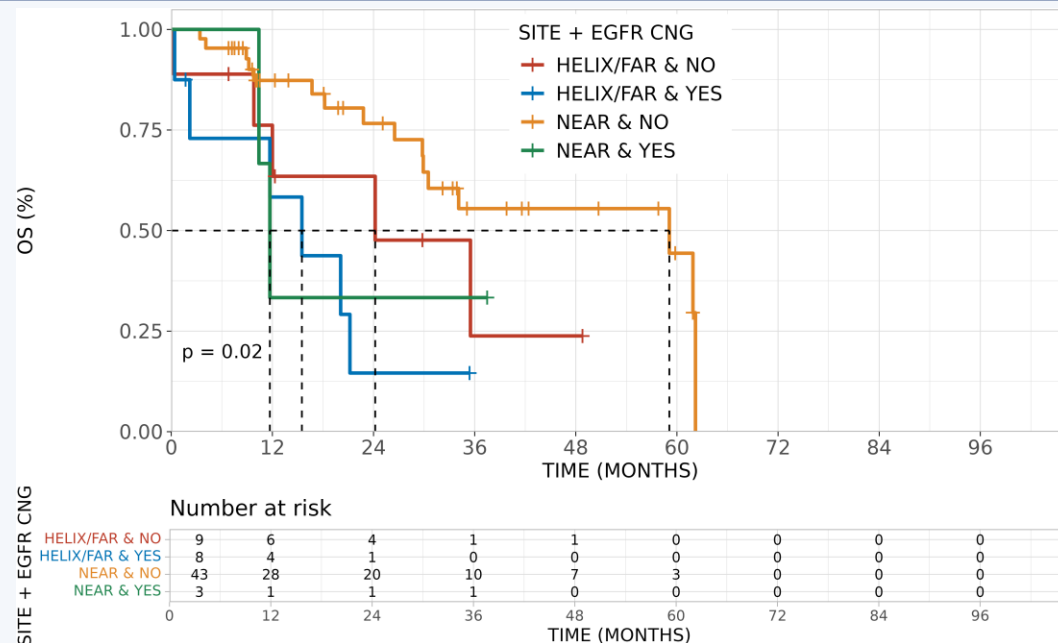
CO-OCCURRING ALTERATIONS



Retrospective multicentre cohort, 2015–2024 · NGS on tumour tissue (n=108) or plasma (n=16), 17 panels covering 6–523 genes · Variants grouped as near-loop vs αC-helix/far-loop · Only genes sequenced in >50% of samples were included in the co-alteration analysis

Site of insertion and EGFR copy number define four prognostic subgroups

OVERALL SURVIVAL · site of insertion × EGFR copy number gain



median OS **Best**

59.1 months

Near-loop · no CNG
n = 43

median OS

24.2 months

αC-helix/far · no CNG
n = 9

median OS

15.5 months

αC-helix/far · CNG
n = 8

median OS **Worst**

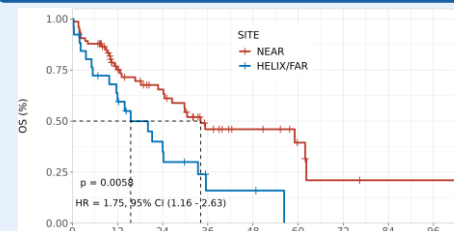
11.7 months

Near-loop · CNG
n = 3

Log-rank $p = 0.02$ · five-fold difference in median OS between the best and the worst subgroup

Subgroup analyses are exploratory and limited by sample size (n=3–43 per subgroup)

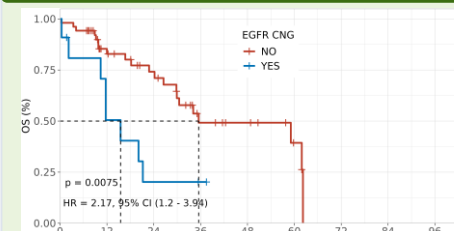
OS · SITE



34.1 vs 15.5 months

HR 1.75 (1.16–2.63) · $p = 0.006$

OS · EGFR CNG



35.5 vs 15.5 months

HR 2.17 (1.20–3.94) · $p = 0.008$

MULTIVARIATE COX MODEL · n = 47

Independent predictor

HR (95% CI)

Advanced stage

15.5 (2.4–101.6)

αC-helix/far-loop site

2.8 (1.2–6.5)

EGFR copy number gain

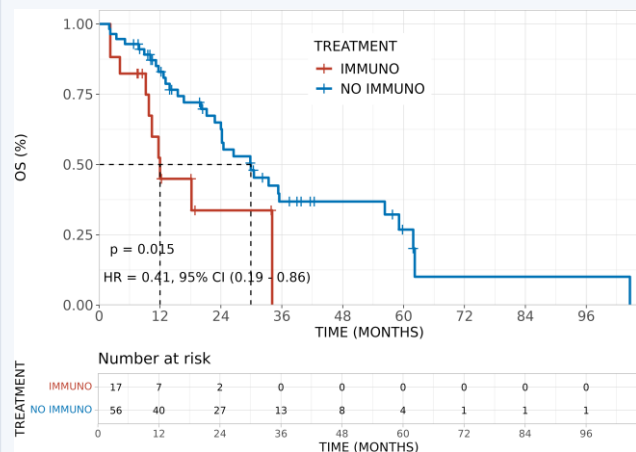
3.4 (1.3–9.1)

KEY FINDING

Neither the site of insertion nor EGFR CNG affected PFS to first-line treatment. The prognostic effect operates on overall survival, suggesting biology beyond initial treatment response.

First-line immunotherapy and conclusions

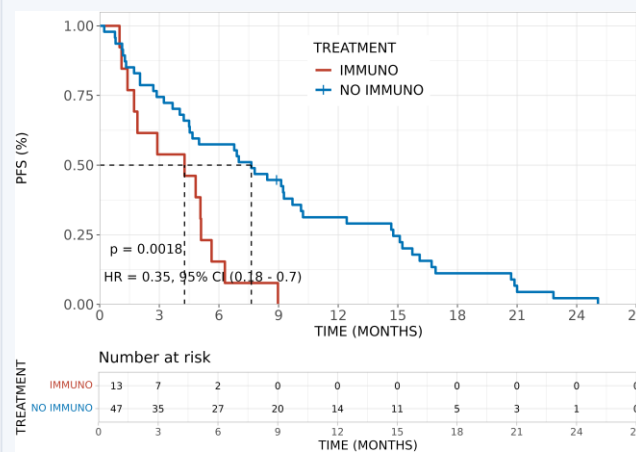
OVERALL SURVIVAL · ICI vs other strategies



12.0 vs 29.9 months

$HR 0.41 (0.19-0.86) \text{ for non-ICI} \cdot p = 0.015$

PROGRESSION-FREE SURVIVAL · first line



4.3 vs 7.6 months

$HR 0.35 (0.18-0.70) \text{ for non-ICI} \cdot p = 0.002$

FIRST-LINE IMMUNOTHERAPY

Consistent with previous reports, immune checkpoint inhibitors show limited efficacy as a first-line strategy in EGFR ex20ins NSCLC, with significantly inferior OS and PFS compared with chemotherapy, EGFR TKIs and anti-EGFR bispecific antibodies.

Only 17 patients received an ICI in first line, so the estimate is imprecise; the direction of effect nevertheless matches the published evidence.

Retrospective design and limited subgroup size warrant confirmation in larger, prospective cohorts

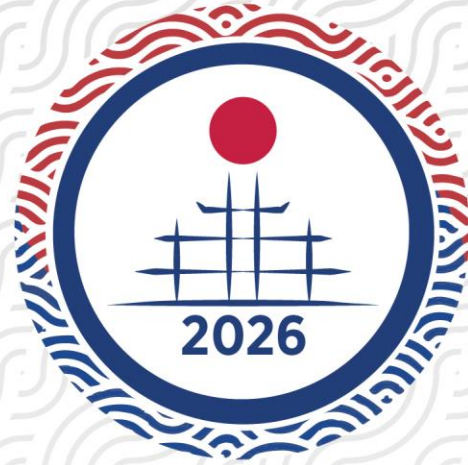
CONCLUSIONS

- EGFR ex20ins is not one disease**
46 variants; the near-loop region accounts for 71% of insertions.
- Two independent prognostic factors**
αC-helix/far-loop site (HR 2.8) and EGFR copy number gain (HR 3.4) both shorten OS but not first-line PFS.
- Four subgroups with distinct outcome**
Median OS ranges from 59.1 to 11.7 months — a five-fold difference.

TAKE-HOME MESSAGE

Comprehensive NGS reporting both the exact insertion site and EGFR copy number identifies patients at high risk of early death.

Both variables are already available in routine broad NGS panels, at no additional cost, and should be considered for stratification in prospective trials.



Thank You.●