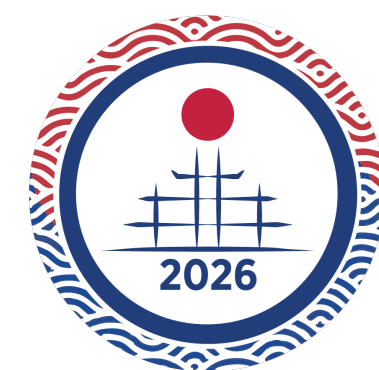




P2.144: Evolutionary Trajectories of EGFR in Early Lung Adenocarcinoma: Unmasking Indolent Atypical Drivers



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INTRODUCTION

- Background:**
 - Classic EGFR mutations (L858R/Ex19del) confer strong biological growth advantage, propelling aggressive expansion into advanced surgical stages.
 - Atypical mutations (e.g., EGFR exon 20 insertions) are traditionally considered "rare", yet targeted re-sequencing of early "wild-type" tumors reveals a high baseline prevalence.
- Specific Aim:**
To map stage-dependent EGFR trajectories (IA1–IA3) and test whether atypical drivers exhibit indolent oncogenic evolution (early growth stalling) rather than true baseline rarity.

METHODS

- A retrospective cohort study.**
- Patient Cohort & Study Period:**
 - Jan 2023– Dec 2024
 - All patients with *surgically resected lung cancer* who underwent **EGFR mutation testing** at the National Taiwan University Cancer Center (NTUCC).
 - Those with pathological stage from **IA1 to IIIA**.
- Key Variables Collected:**
 - ✓ Detailed EGFR mutation analysis results (e.g., specific mutation type).
 - ✓ Histologic subtype (e.g., adenocarcinoma, squamous cell).
 - ✓ Histologic grade (e.g., well, moderately, or poorly differentiated).
 - ✓ Complete pathological TNM staging (pT, pN).

DISCUSSION AND CONCLUSION

- Divergent Trajectories & "Illusion of Rarity":**
Classic mutations drive stage expansion; Ex20ins shows primary growth indolence (aOR=1.18, p=0.536). Late-stage scarcity reflects early growth stalling, not baseline rarity.
- Primary Indolence vs. Therapeutic Vulnerability:**
Ex20ins is intrinsically indolent pre-resection. Poor post-surgical DFS reflects lack of effective adjuvant TKIs rather than primary aggressiveness.
- Differential Role of Mutation Types:**
 - Ex20ins is an indolent, early-stalling driver in early lung adenocarcinoma.
 - Molecular subtyping stratifies aggressive expanders (Classic) from indolent drivers (Ex20ins).

REFERENCES



Key
Reference



All statistical data were independently analyzed, with AI tools utilized solely to assist in figure visualization and aesthetic formatting.

RESULTS

Table 1: Baseline Characteristics and Stage Distribution across EGFR Subtypes

EGFR Category	Stage IA1, n (%)	Stage IA2, n (%)	Stage IA3, n (%)	Total N (%)	p-value
Classic (Ex19del/L858R)	447 (52.1%)	348 (74.2%)	149 (81.0%)	944 (62.5%)	< 0.001
Wild Type	299 (34.9%)	83 (17.7%)	24 (13.0%)	406 (26.9%)	(Chi-Square)
Exon 20 insertion	66 (7.7%)	18 (3.8%)	4 (2.2%)	88 (5.8%)	
Other Rare	46 (5.4%)	20 (4.3%)	7 (3.8%)	73 (4.8%)	
Total Stage Cohort	858 (100.0%)	469 (100.0%)	184 (100.0%)	1,511 (100.0%)	

Table 2: Crosstabulation of Histologic Grade by EGFR Mutation Subtype

EGFR Subtype	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Total N	p-value
Classic (Ex19del/L858R)	200 (21.2%)	671 (71.1%)	73 (7.7%)	944 (62.5%)	< 0.001
Wild Type (WT)	163 (40.2%)	210 (51.7%)	33 (8.1%)	406 (26.9%)	(Monte Carlo)
Exon 20 insertion	33 (37.5%)	54 (61.4%)	1 (1.1%)	88 (5.8%)	
Other Rare	26 (35.6%)	39 (53.4%)	8 (11.0%)	73 (4.8%)	
Overall Total	422 (27.9%)	974 (64.5%)	115 (7.6%)	1,511 (100.0%)	

Table 3: Multivariable Logistic Regression Analysis for High Histologic Grade (Grade 2/3 vs. 1)

Variable	Beta Coefficient	Adjusted Odds Ratio	95% Confidence Interval	p-value
EGFR: Classic	0.4919	1.64	1.24 – 2.16	< 0.001 (***)
EGFR: Ex20ins	0.1616	1.18	0.70 – 1.96	0.536 (NS)
EGFR: Rare	-0.0118	0.99	0.55 – 1.76	0.968 (NS)
Stage: IA2 vs. IA1	2.3663	10.66	7.21 – 15.76	< 0.001 (***)
Stage: IA3 vs. IA1	3.4928	32.88	12.07 – 89.57	< 0.001 (***)

Fig. 1 Stage vs. EGFR Stacked Proportion Chart
Visualizes the divergent stage trajectories — rapid clonal expansion of Classic drivers versus early stalling of Ex20ins.

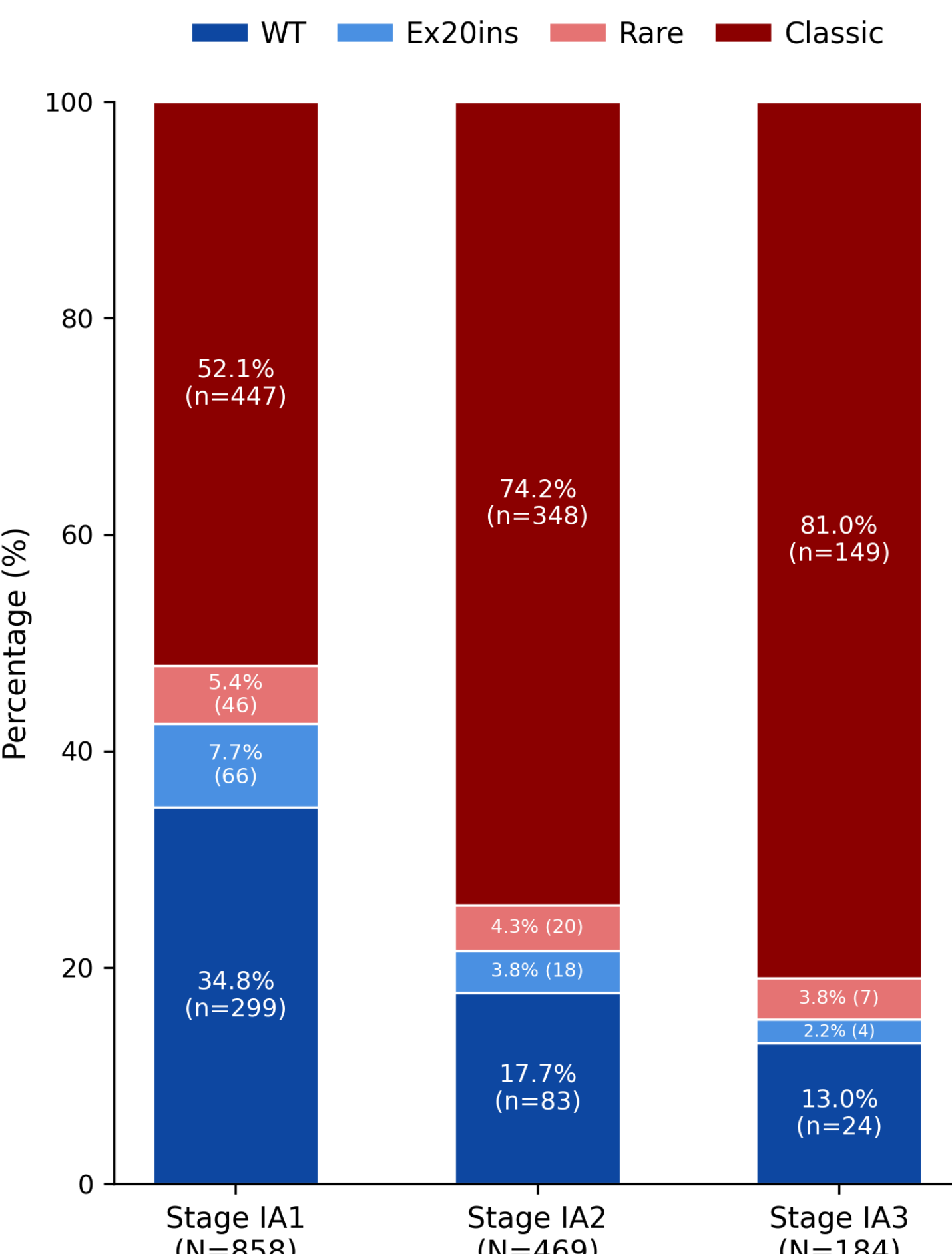
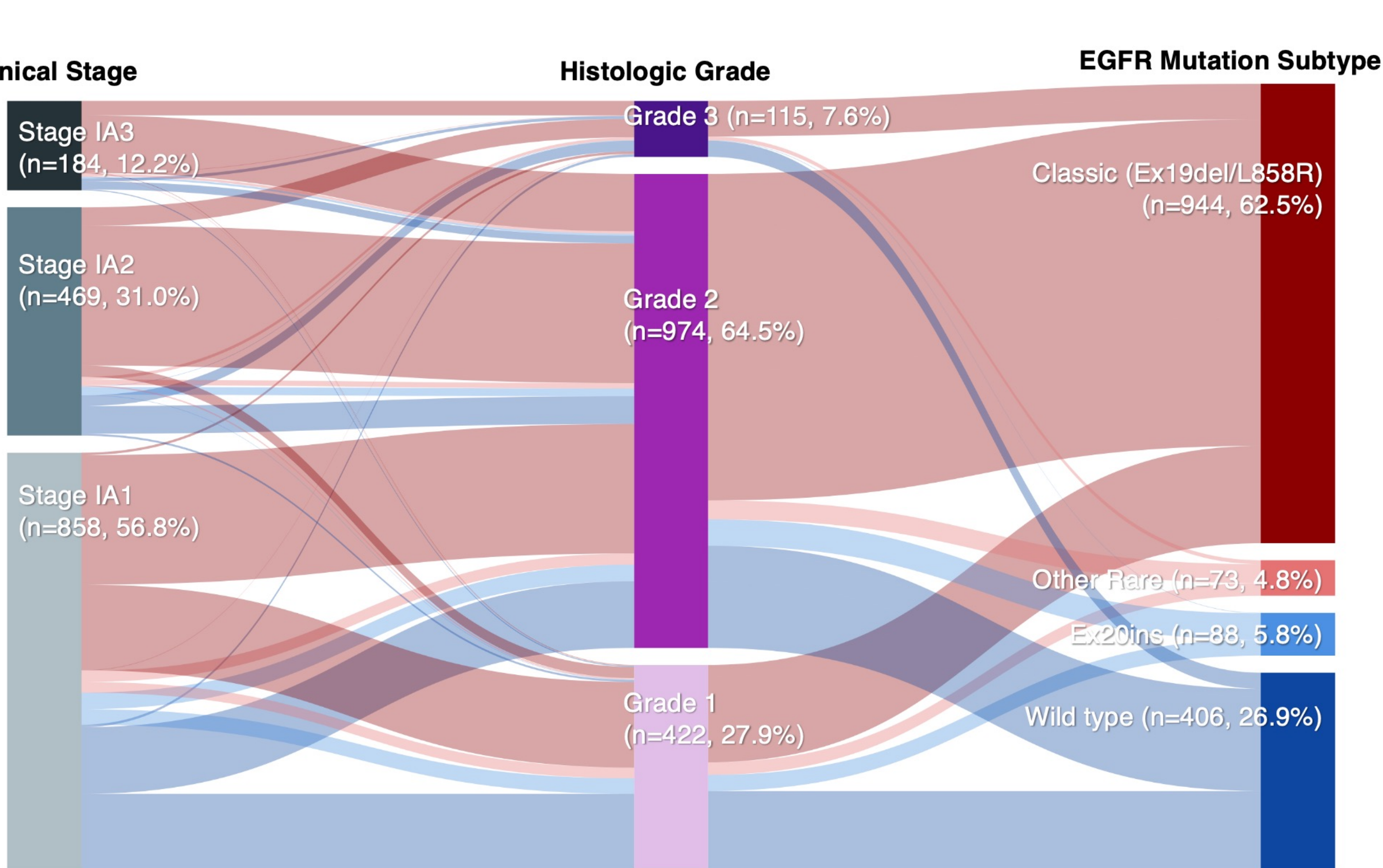


Fig. 2 Alluvial Flow Diagram
Traces individual patient evolution from Stage => Grade => EGFR type. Ex20ins and wild type tightly co-navigate the indolent Grade 1 pathway (blue/sky-blue flows), while Classic drivers fuel the aggressive Grade 2/3 route (dark red flows).



- Stage Shift**
Classic mutations progressively dominate higher surgical stages, whereas Ex20ins peaks sharply in stage IA1 (p < 0.001).
- Biological Indolence**
Multivariable model confirms Ex20ins is histologically indolent and statistically indistinguishable from wild type (p = 0.536).

In the multivariable logistic regression model adjusting for pathological stage, EGFR wild-type (WT) and Stage IA1 were designated as the baseline reference groups.