Management of Uncommon EGFR Mutations

- Prof Vijay Patil
- Department of Medical Oncology
- Tata Memorial Centre, Mumbai

Conflict of Interest

- None for this talk

Panelists

Dr. Deepak Shukla **Consultant, Medical Oncologist** **Manipal Hospital, Jaipur**
Dr. Anu Rajpurohit **Consultant Medical Oncologist** **NIIMS Medical College and Hospital, Jaipur**
Dr. Amit Verma **Founder and Director,** **Dr AV Institute of Personalized Cancer Treatment and Research** **Gurgaon**
Dr. Ankit Agarwal **Consultant - Medical Oncology** **Geetanjali Hospital, Udaipur**
Dr. Rakesh Pinninti **Consultant Medical Oncologist,** **Basavatarakam Hospital,** **Hyderabad**
Dr. Ashish Joshi **Consultant - Medical Oncology and Haematology** **Nanavati Super Speciality Hospital,** **Mumbai.**
Dr. Manoj Mahajan, **Director in the Department of Oncology and Hematology** **Pacific Medical College Hospital, Udaipur**

How do you define uncommon mutations & Complex mutations?

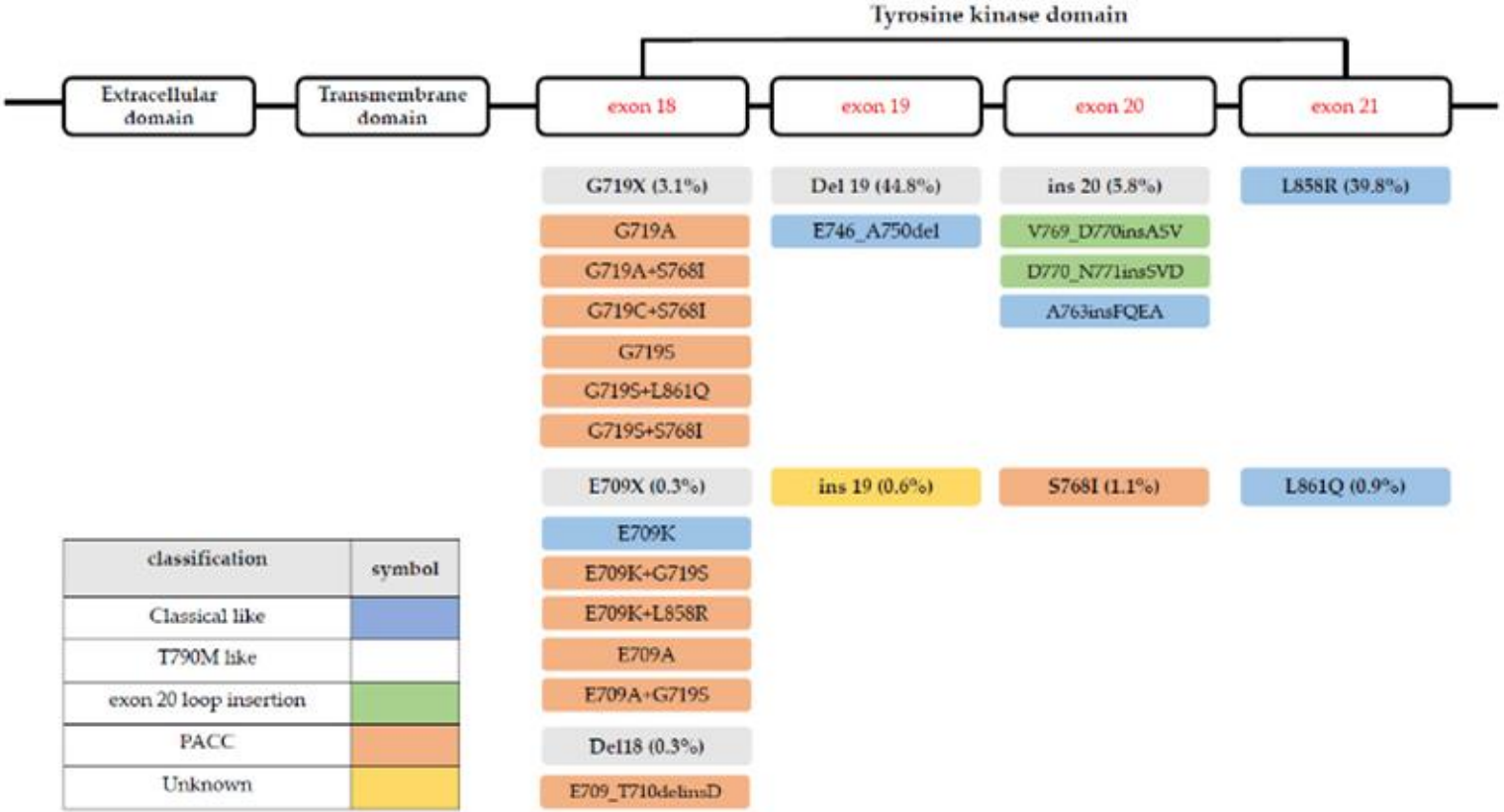


Figure 1. Structure of *EGFR* revealing common and uncommon mutations, compared with structural-based classification [18,19]. We have listed the mutations which are seen in more than 5% in each subgroup (*719X*, *E709X*, etc.), and assigned structural classifications.

Kitdai et al. Cancers (Basel)2022 May 20;14(10):2519. doi: 10.3390/cancers14102519.

What is the incidence?

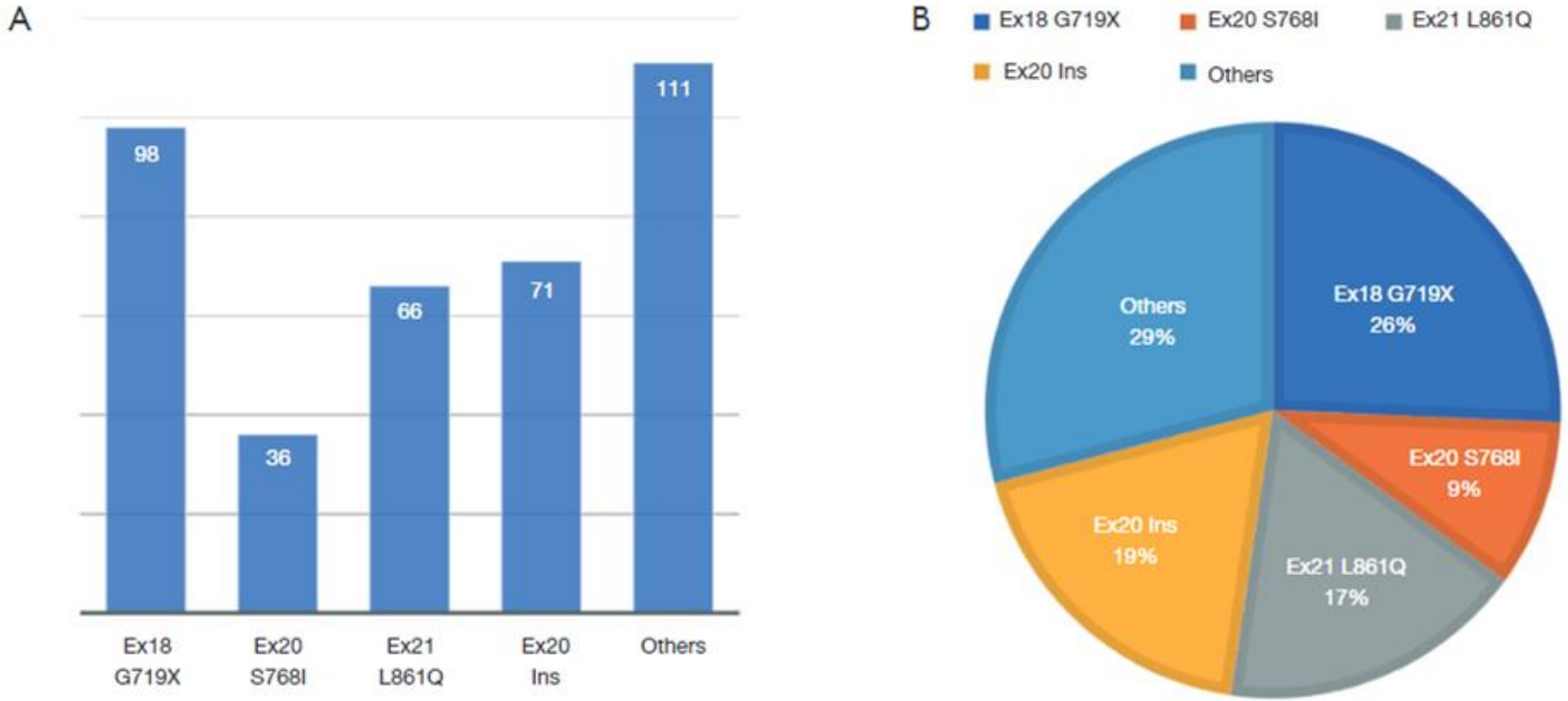


Figure 4 A comprehensive view of uncommon EGFR mutations from five studies: (A) a summary of frequency of G719X, S768I, L861Q, Exon 20 insertions and other mutations (complex mutations included); (B) a summary of these single point mutations and exon 20 insertions. EGFR, epidermal growth factor receptor.

Indian Data???

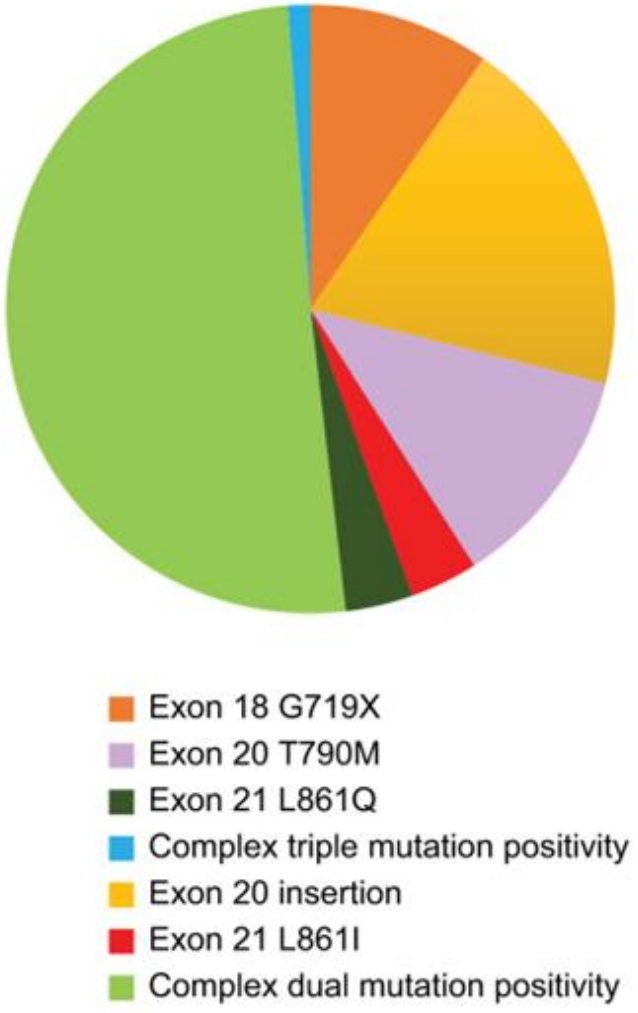
Lung Cancer (Auckl). 2019; 10: 1–10.
Published online 2019 Jan 29. doi: 10.2147/LCTT.S181406
PMCID: PMC6357894
PMID: 30774491

Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: a single center retrospective analysis

Shruti Kate,[1] Anuradha Chougule,[2] Amit Joshi,[1] Vanita Noronha,[1] Vijay Patil,[1] Rohit Dusane,[3] Leena Solanki,[1] Priyanka Tiwrekar,[2] Vaishakhi Trivedi,[1] and Kumar Prabhash[1]

▸ Author information ▸ Copyright and License information Disclaimer

1,260 EGFR mutation-positive patients, 83 (6.58%) had uncommon mutations in isolation or in various combinations



LUNG CANCER—NON-SMALL CELL METASTATIC

Treatment pattern and outcomes in patients with uncommon or compound EGFR mutations in India: CRSF 2020-03 study.

Manuprasad Avaronnan, Rushabh Kothari, Avinash Talele, Vikas Talreja, Gautam Goyal, Nirmal Vivek Raut, ...

Most common mutations were exon 20 insertion (n=34, 35%) and T790M (N=16,16%). Other frequent mutations observed were exon 18 G719X (n=7,7%) and exon 21 L861Q (n=3,3%).

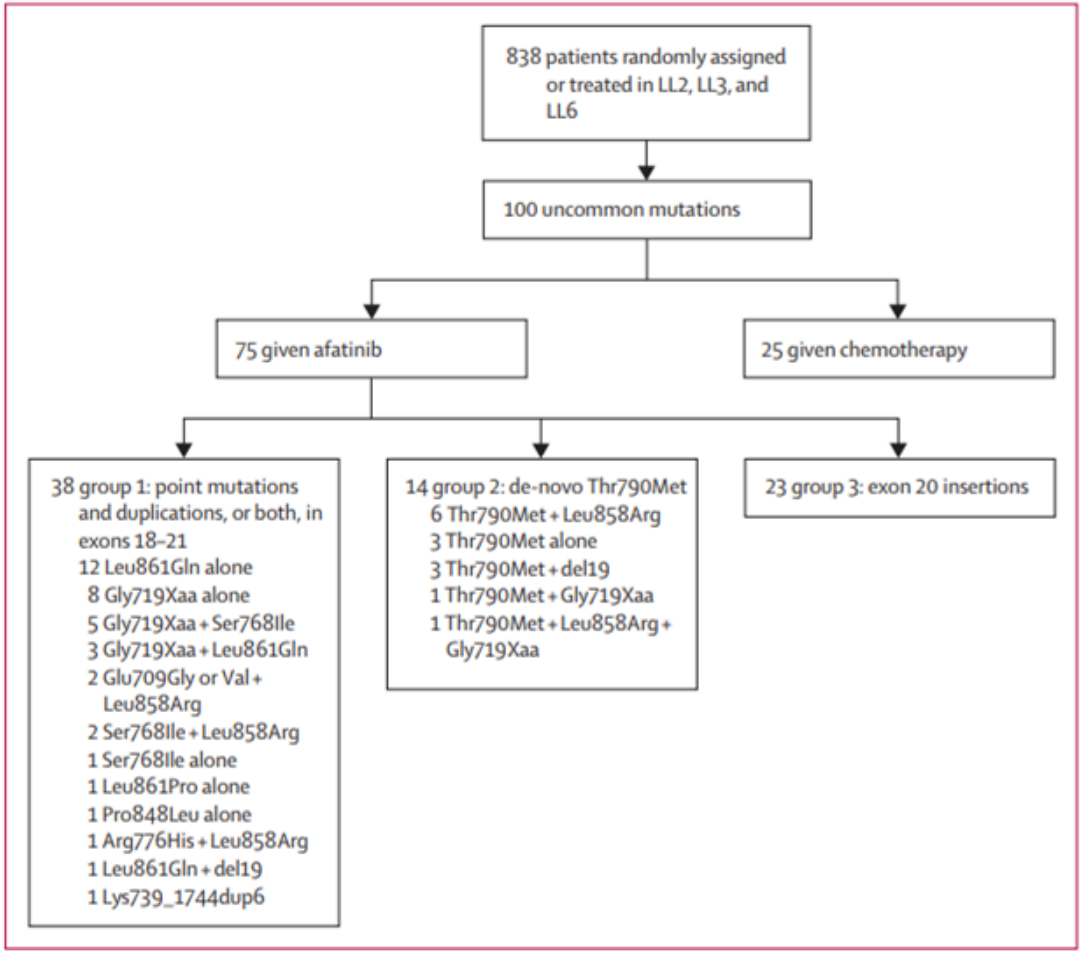


Figure 1: **Subgroups of uncommon mutations**

Exon 18 G719X- Treatment?

Which & why?

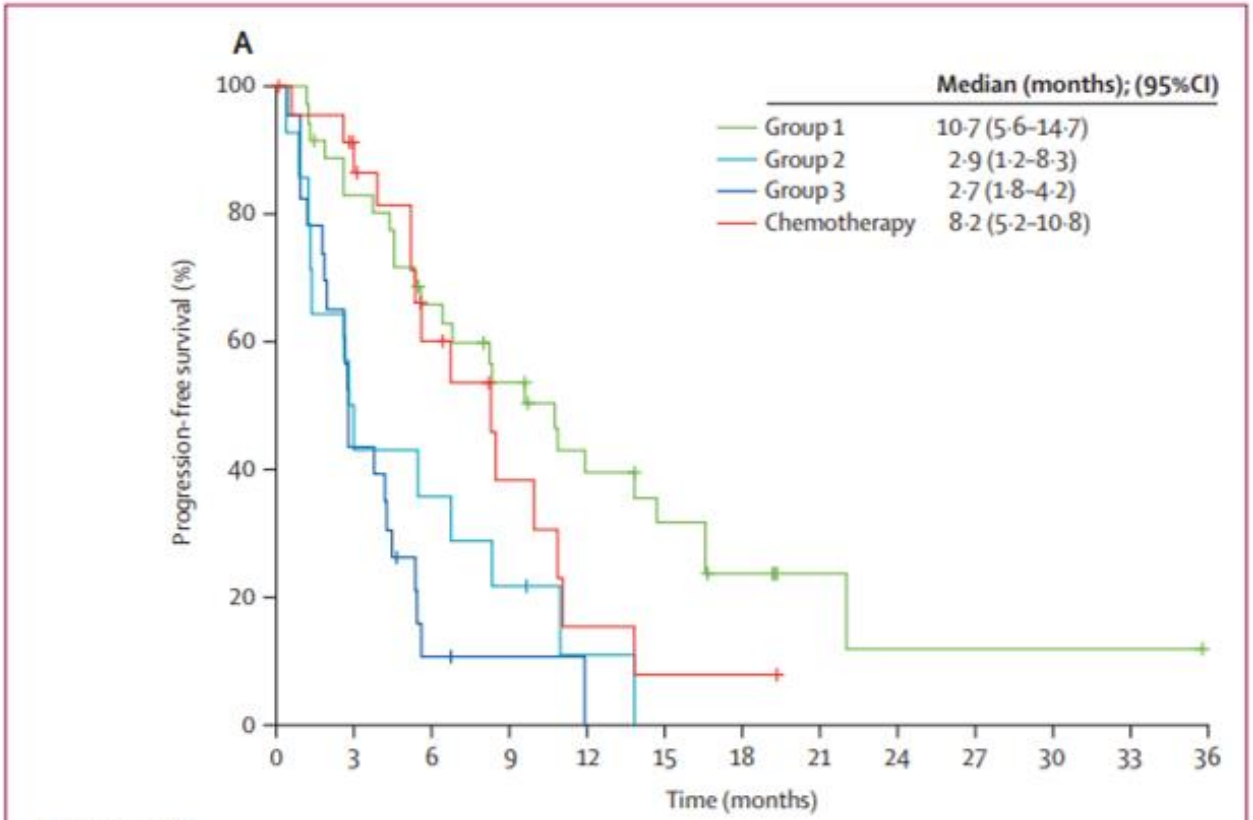
1. First generation TKI
2. Second generation TKI
3. Third generation TKI
4. Gefitinib + Chemotherapy
5. Chemotherapy
6. Immunotherapy

Single versus Complex is the response different

Table 1 Clinical outcomes in exon 18 G719X treated with TKI

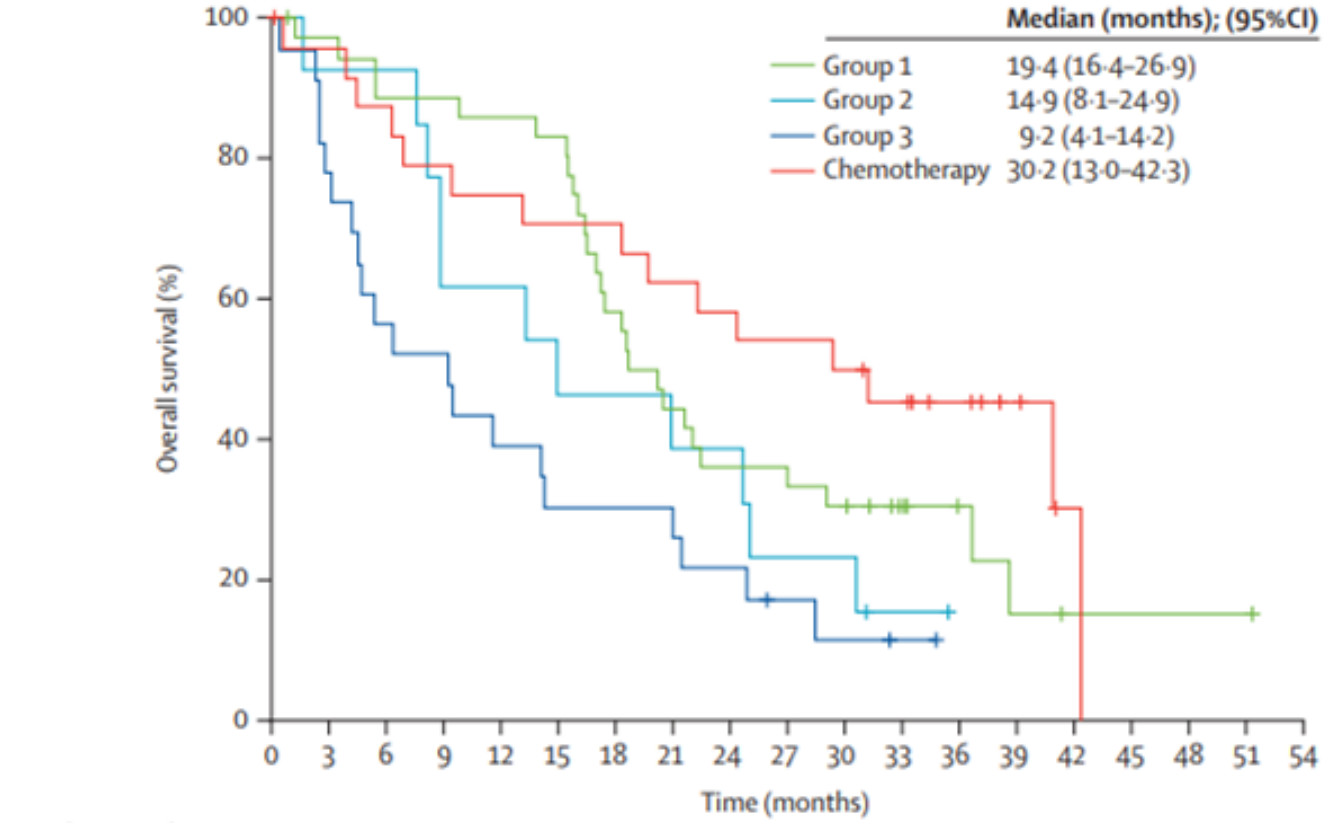
Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=18	18	77.80%	13.8 (6.8–NE)	26.9 (16.4–NE)
		G719X [8]	2nd			
		G719X + Others [10]*				
Zhang, 2017 (14)	Retrospective	N=22	22	22.70%	7.6 (4.9–10.4)	NR
		G719X [14]	1st			
		G719X + Others [8]				
Wu, 2011 (24)	Retrospective	N=15	15	53.30%	8.1	16.4
		G719X/G719X + Others [15]	1st			
Xu, 2016 (16)	Retrospective	N=14	14	42.90%	5.98 (1.53–10.42)	19.81 (16.8–22.81)
		G719X [14]	1st			
Chiu, 2015 (25)	Retrospective	N=97	78			NR
		G719X [78]	1st	36.80%	6.3	
		G719X + L861Q [9]		88.90%	11.9	
		G719X + S768I [10]		50%	6.5	
Shi, 2017 (15)	Retrospective	N=27	27	NR	8.2	NR
		G719X [27]	1st			

NR, not reported; NE, not estimable; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival. *, means complex mutation involves T790M.



Number at risk

Group 1	38	29	22	17	11	8	5	2	1	1	1	1	0
Group 2	14	6	5	3	1	0	0	0	0	0	0	0	0
Group 3	23	10	2	1	0	0	0	0	0	0	0	0	0
Chemotherapy	25	18	10	5	2	1	1	0	0	0	0	0	0



Number at risk

Group 1	38	35	32	32	31	30	21	16	13	12	11	7	4	2	1	1	1	1	0
Group 2	14	12	12	8	8	6	6	5	5	3	3	1	0	0	0	0	0	0	0
Group 3	23	18	13	12	9	7	7	6	5	3	2	1	0	0	0	0	0	0	0
Chemotherapy	25	23	21	19	18	17	17	15	14	13	12	10	7	4	1	0	0	0	0

Inspite of 59% receiving subsequent therapy in afatinib versus 48% in Chemotherapy

Chemotherapy- Lux data

1. Of the patients with the most frequent uncommon mutations treated with chemotherapy, four (30·8%, 95% CI 9·1–61·4) of 13 with with Gly719Xaa mutations
2. None (0·0%, 0·0–52·2) of five with Leu861Gln mutations
3. Two (33·3%,4·3–77·7) of six with Ser768Ile had objective responses.

France- Brindle et al ESMO 2018

- The majority of uncommon mutations included 47 (50%) exon 18 mutations, comprised of 15% E709X and 35% G719X alterations.
- Median OS was 27.7 months; 95% confidence interval [CI] 21.6 - 35 with chemotherapy compared to 16.9 months; 95% CI, 13.6 - 25.9 with a TKI (first line) ($p = 0.075$, all mutations included).
- Exon 18 and exon 20 associated with a better prognosis, whereas L861Q was linked to a poorer prognosis.
- The presence of a second rare EGFR mutation associated with better OS ($p = 0.002$).

RAPID COMMUNICATIONS | Lung Cancer

Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study

Yukio Hosomi, MD, PhD[1]; Satoshi Morita, PhD[2]; Shunichi Sugawara, MD, PhD[3]; Terufumi Kato, MD[4]; Tatsuro Fukuhara, MD, PhD[5]; Akihiko Gemma, MD, PhD[6]; ...

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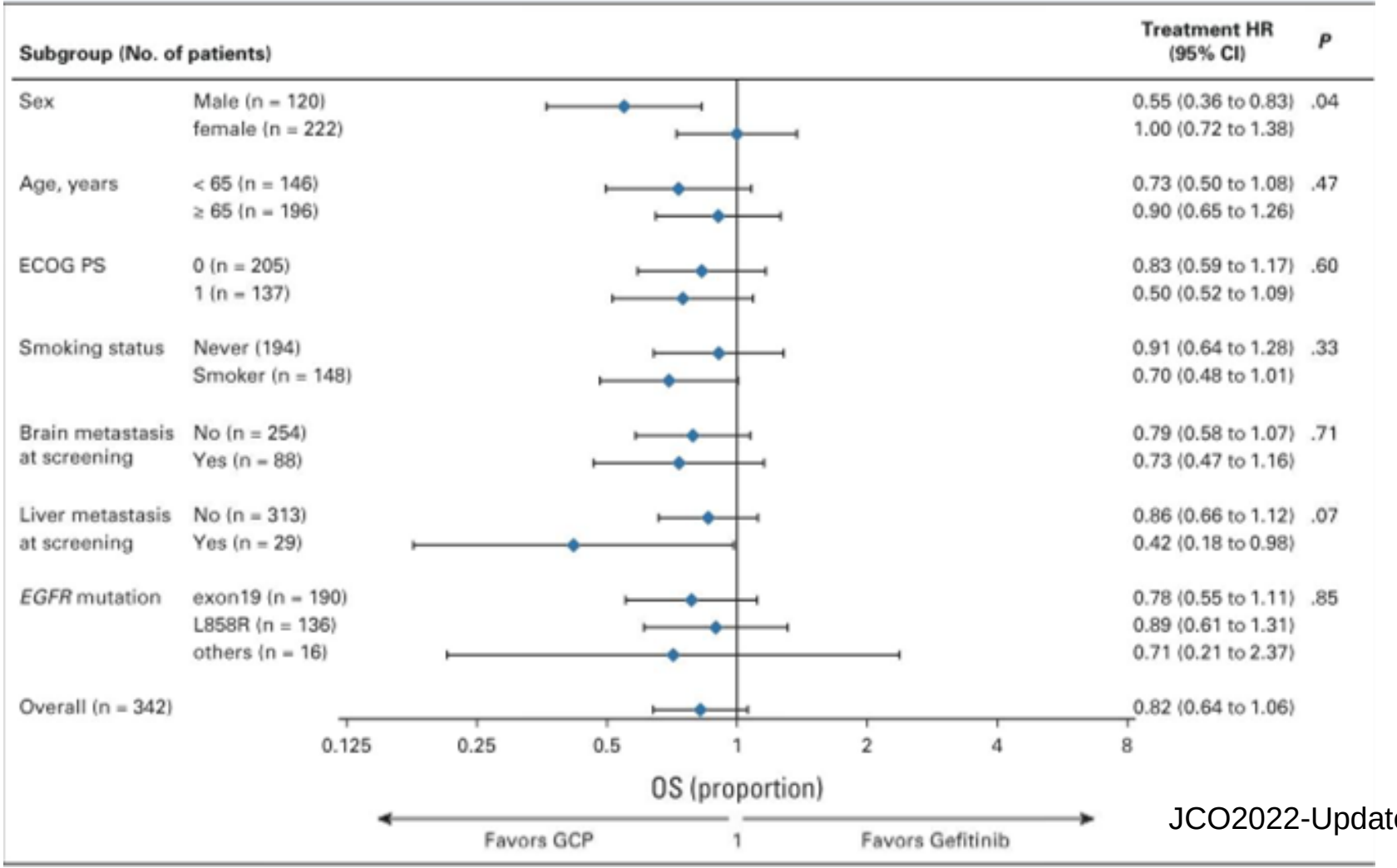
Patient Population

This study was conducted according to the Declaration of Helsinki and was approved by the ethics review boards of each participating institution. Each patient provided written informed consent. The main eligibility criteria were chemotherapy naïve, stage IIIB or IV or relapsed nonsquamous NSCLC with EGFR mutations (exon 19 deletion, L858R, G719A, G719C, G719S, and L861Q), age 20 to



JCO2022-Update

Osimertinib for Patients With Non–Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09)

Jang Ho Cho, MD[1,2]; Sung Hee Lim, MD[3]; Ho Jung An, MD, PhD[4]; Ki Hwan Kim, MD[5]; Yoon Hee Choi, MD[8]; Mi Sun Ahn, MD[9]; Myung Hee Lee, PhD[10]; Jong-Mu Sun, M Jin Seok Ahn, MD, PhD[1]; Keunchil Park, MD, PhD[1]; and Myung-Ju Ahn, MD, PhD

Line of therapy	
First line	22 (61)
Second line	11 (31)
Third line	3 (8)

Mutation	Objective Response		Median Progression-Free Survival, Months (95% CI)
	No. (%)	95% CI	
G719X (n = 19)	10 (53)	28 to 77	8.2 (6.2 to 10.2)
G719X (n = 15)			
G719X + S768I (n = 2)			
G719X + L861Q (n = 2)			
L861Q (n = 9)	7 (78)	44 to 100	15.2 (1.3 to 29.1)
L861Q (n = 7)			
L861Q + G719X (n = 2)			
S768I (n = 8)	3 (38)	0 to 81	12.3 (0 to 28.8)
S768I (n = 6)			
S768I + G719X (n = 2)			

Patient groups	Objective response, %, (95% CI)	Disease control, %, (95% CI)	DoR, months, (95% CI)
Overall (n=21)	47.6 (25.7, 70.2)	85.7 (63.7, 97.0)	7.9 (0, 17.0)
1st line cohort (n=11)	63.6 (30.8, 89.1)	100 (71.5, 100)	12.1 (0, 29.2)§
Pretreated cohort (n=10)	30.0 (6.7, 65.2)	70.0 (34.8, 93.3)	7.8 (4.2, 11.4)§
G719X compound mutations (n=8)	62.5 (24.5, 91.5)	100.0 (63.1, 100)	12.4 (11.9, 12.9)*
G719X + S768I (n=5)			
G719X + S768I + T790M (n=1)			
G719X + L861Q (n=1)			
G719X + L861Q + T790M (n=1)			
Other mutations (n=13)	38.5 (13.9, 68.4)	76.9 (46.2, 95.0)	3.8 (2.5, 4.1)*
G719X (n=4)			
G719X + T790M (n=1)			
L861Q (n=7)			
L861Q + ex20ins (n=1)			

Osimertinib

Edie et al. Transl Lung Cancer Res. 2022 Jun; 11(6): 953–963.

G719X- Conclusion

Exon 20 S768I

Table 2 Clinical outcomes in exon 20 S768I treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=8	8	100%	14.7 (2.6–NE)	NE (3.4–NE)
		S768I [1]	2nd			
		S768I + Others [7]				
Zhang, 2017 (14)	Retrospective	N=11	11	27.30%	8.0 (4.3–11.8)	NR
		S768I [4]	1st			
		S768I + Others [7]				
Shi, 2017 (15)	Retrospective	N=9	9		3.4	NR
		S768I [9]				
Chen, 2016 (44)	Retrospective	N=10	10	20%	2.7	14.5
		S768I [3]				
		S768I + Others [7]				

NR, not reported; NE, not estimable; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival.

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S768I (n = 6)			
S768I + G719X (n = 2)			

Exon 21 L861Q???

Table 3 Clinical outcomes in exon 21 L861Q treated with TKI

Article reference	Research type	N, cases in the study	TKI therapy	ORR (%)	Median PFS (month)	Median OS (month)
Yang, 2015 (2)	Prospective	N=16	16	56.30%	8.2 (4.5–16.6)	17.1 (15.3–21.6)
		L861Q [12]	2nd			
		L861Q + Others [4]				
Zhang, 2017 (14)	Retrospective	N=5	5	0.00%	5.7 (1.6–9.8)	NR
		L861Q [4]	1st			
		L861Q + Others [1]				
Wu, 2011 (24)	Retrospective	N=15	15	60.00%	6.0	15.2
		L861Q/L861Q + Others [15]	1st			
Xu, 2016 (16)	Retrospective	N=15	15	46.70%	8.9 (4.47–13.34)	21.98 (12.35–31.61)
		L861Q [15]	1st			
Chiu, 2015 (25)	Retrospective	N=66	66			NR
		L861Q [57]	1st	39.60%	8.1	
		L861Q + G719X [9]		88.90%	11.9	

NR, not reported; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival.

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Meeting Abstract | 2022 ASCO Annual Meeting I

LUNG CANCER—NON-SMALL CELL METASTATIC

Uncommon EGFR mutations on osimertinib, real-life data (UNICORN study): Updated results, brain efficacy, and resistance mechanisms.

Jair Bar, Nir Peled, Shiruyeh Schokrpur, Elizabeth Dudnik, Mira Wollner, Nicolas Girard, ...

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	N (% of 62)	ORR -% of patients with evaluable disease (95% C.I.)	mPFS Months (95% C.I.)	mOS Months (95% C.I.)	mDOR Months (95% C.I.)
G719X	18 (29)	47 (26-69)	8.8 (7.9-NA)	NA (17.4-NA)	9.1 (8.6-NA)
L861Q	12 (19)	80 (55-100)	16 (11-NA)	26.3 (22.1-NA)	16 (11-NA)
de novo T790M	10 (16)	40 (10-70)	12.7 (9.5-NA)	42.7(12-NA)	46.2 (3.8-NA)
Compound including L858R/del19* /de novo T790M	17 (27)	57 (31-83)	30 (12.7-NA)	34.5 (31.4-NA)	46.2 (30.7-NA)

*Common exon 19 deletion, without insertion. ORR: overall response rate.

LUNG CANCER—NON-SMALL CELL METASTATIC

Treatment pattern and outcomes in patients with uncommon or compound EGFR mutations in India: CRSF 2020-03 study.

Manuprasad Avaronnan, Rushabh Kothari, Avinash Talele, Vikas Talreja, Gautam Goyal, Nirmal Vivek Raut, ...

Twenty-three patients (n=23,23%) were eligible only for best supportive care.
Thirty-two patients (32%) received first-generation TKI, 30 patients (30%) received palliative chemotherapy and 11 patients (11 %) received Osimertinib.

Conclusion