Supplemental Table 7: Cases with two or more oncogenic driver alterations.

Driver 1	Driver 2	Driver 3	*MET*: CEP7 ratio	Full genotyping	Targeted therapy	Comments	Frequency (among all tested cases)**	Frequency (among driver 1 mutation class)***
EGFR p.E709A *EGFR* p.L858R	*MET* amp		15	Y	Erlotinib		0.4% (*EGFR*+*MET*) 0.14% (*EGFR*+*RET*r)	2.5% (*MET* amp) 0.86 % (*RET*r)
EGFR p.L858R	*MET* amp		4.43	N	Erlotinib			
EGFR p.L858R	*MET* amp	*RET*r*	2.7	N	Erlotinib	27% *RET*r nuclei by FISH		
EGFR p.L858R	*ALK* 5' deletion*		--	N	Erlotinib	*ALK* IHC negative, no fusion by NGS	0.1%	1.7%
*ALK*r*	*EGFR* p.I740_ K745dup		--	N	Crizotinib, ceritinib		0.1%	5.5%
EGFR ex19del	*KRAS* p.G12D		--	N	Erlotinib		0.1%	2.5%
EGFR p.G719S	*KRAS* p.G12V		--	N	none		0.1%	
EGFR ex19del	*KRAS* p.Q61R		--	Y	Erlotinib		0.1%	
KRAS p.G12C	*ROS1*r*		--	N	none		0.2%	0.74%
KRAS p.G13C	*ROS1*r*		--	N	none	52% ROS1r nuclei by FISH		
BRAF p.V600E	*KRAS* p.G12V		--	N	none		0.1%	3.7%
BRAF p.V600E	*MET* amp		2.5	Y	none		0.3%	7.4%
BRAF p.V600E	*MET* amp		2	Y	Dabrafenib			
KRAS p.G12V	NRAS p.Q61R		--	Y	none		0.1%	0.37%
KRAS p.G12V	*MET* amp		2	Y	none		1.0%	3.0%
KRAS p.G12V	*MET* amp		3.1	Y	none			
KRAS p.G12A	*MET* amp		2.77	N	none			
KRAS p.G12V	*MET* amp		3.26	N	NR			
KRAS p.G12V	*MET* amp		3.3	Y	none			
KRAS p.G12D	*MET* amp		2.1	Y	none			
KRAS p.G12V	*MET* amp		2.1	Y	none			
KRAS p.G12D	*MET* amp		2.24	N	none			

*ALK*r = *ALK* rearranged; ROS1r = ROS1 rearranged; *RET*r = *RET* rearranged; amp = Gene amplification; NR = not reported
*All rearrangement events here were detected by fluorescence in situ hybridization (FISH).
** Frequency indicates rate of duplicate events within both classes of events and is restricted to cases for which both were tested
***Total cases with complete testing for *EGFR* and *MET* FISH = 671, *EGFR* + *ALK* = 805, *EGFR* + *RET* = 767, *EGFR* + *KRAS* = 862, ROS1 + *KRAS* = 780 *KRAS* + *BRAF* = 860, *KRAS* + *NRAS* = 860, *BRAF* + *MET* FISH = 661, *KRAS* + *MET* FISH = 689

Supplemental Table 8. Comparison of LCMC I and LCMC II.

	LCMCI n=1007	**LCMCII n=904**	**P value**
Smoking history			
Never	341 (34%)	219 (25%)	<0.001
Former	589 (59%)	556 (62%)	
Current	73 (7%)	115 (13%)	
Genotype			
*EGFR**	225 (23%)	136 (16%)	<0.001
KRAS	250 (25%)	269 (31%)	0.006
*ALK*r	86 (9%)	36 (4%)	<0.001
ERBB2	24 (3%)	16 (2%)	0.867
BRAF p.V600E	17 (2%)	26 (3%)	0.086

*including both sensitizing and other EGFR variants.

**ALKr= ALK rearrangement