

Management of EGFR TKI Failures, in the Salvage Setting

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Case Report



Day 0



4 months



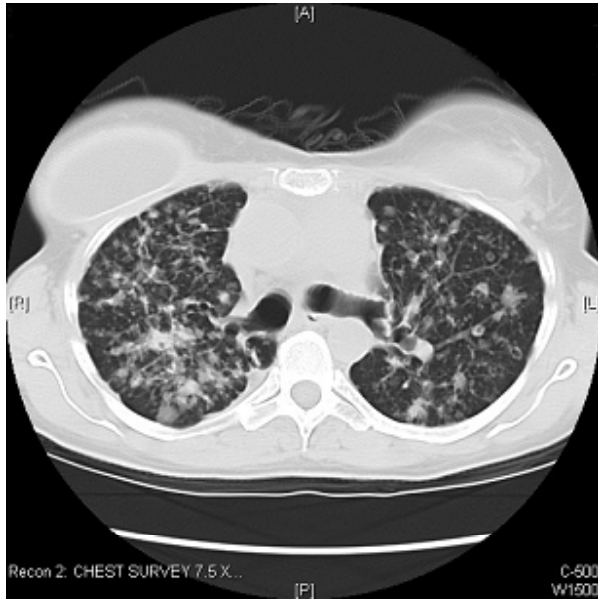
25 months

- 55 yo Caucasian woman
- 9 pk-yr smoking history
- s/p RLL and LUL lobectomies for bronchioloalveolar carcinoma with focal invasion (NSCLC)
- 2 years later, recurrence with bilateral pulm nodules
- Progression on systemic chemotherapy
- Response to erlotinib
- Then, acquired resistance

Working Definition of “Acquired Resistance”

- Previously received treatment with small molecule kinase inhibitors (e.g. gefitinib/erlotinib)
- Known EGFR-mutation positive tumor AND/OR displayed a clinical response to treatment with small molecule kinase inhibitors as defined by either:
 - Radiologic partial or complete response (RECIST or WHO)
- OR:
 - Significant and prolonged (> 6 mos) improvement in symptoms after initiation of small molecule kinase inhibitors as determined by patient's attending physician
- Radiologic progression of disease while on treatment as defined by RECIST or WHO

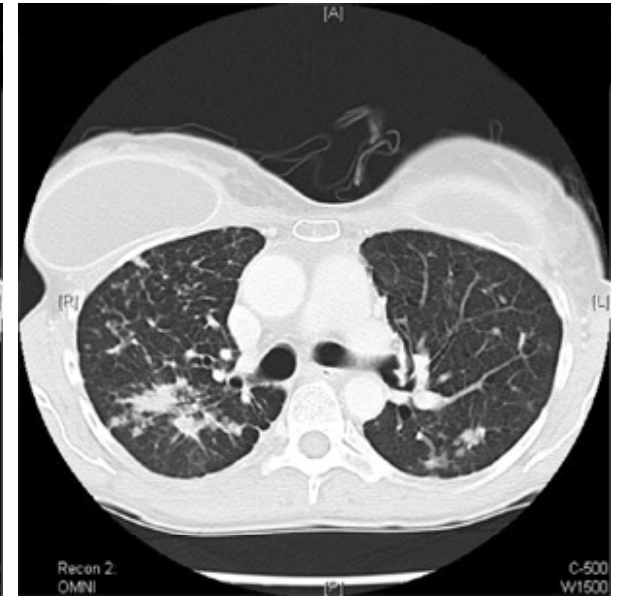
Case Report



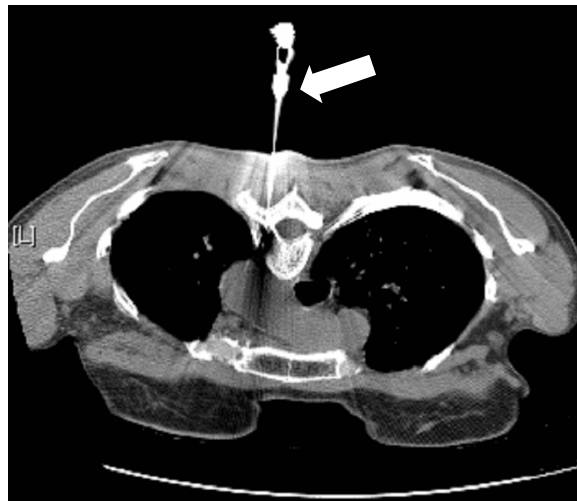
Day 0



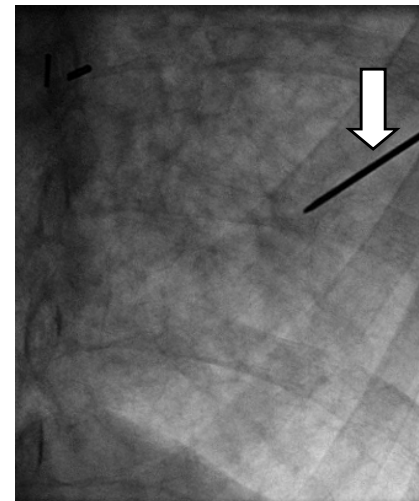
4 months



25 months



Growing bone lesion



Growing lung lesion

EGFR T790M is Frequently Found in Tumor Cells from Patients with Acquired Resistance to EGFR TKIs

Patient	Sex	Smoking	Drug	Duration	Prior chemo	Prior RT	Sites Examined for Acquired Resistance	Primary Mutation	Secondary Mutation	EGFR copy number
1 ^{a,b}	F	Never	E	19	Y	N	Lung, spine	del L747-E749;A750P	T790M	5.7
2	M	Never	G	13	Y	Y	Lung	del L747-S752	T790M	nd
3	M	<u>Oligo</u>	G	11	Y	Y	<u>Omentum</u>	del E746-A750	T790M	5.1 → 6.3
4	F	Never	G	15	Y	N	Lung, pericardial fluid	del L747-P753insS	T790M	9.6 → 11
5	F	Never	E	10	N	N	Pleural fluid	del E746-T751insA	T790M	nd
6	F	<u>Oligo</u>	→E ^c	n/a	Y	N	Lung	del E746-A750	T790M ^f	nd
7 ^a	F	Never	G	10	Y	N	Pleural fluid	L858R	T790M	nd
8	F	Never	G	15	N	N	Lung	L858R	T790M	nd
9	F	Never	G	13	N	N	Lung	L858R	T790M ^e	nd
10	F	Never	G	13	Y	Y	Brain	L858R	D761Y	6.0
11 ^{a,b}	F	Never	E	16	N	<u>N^d</u>	Lung	del L747-P753insQ	<u>None^g</u>	7.1
12 ^a	F	Former	G	11	Y	N	Lung	del L747-E749;A750P	None	nd
13 ^a	M	Never	G	11	Y	<u>N^d</u>	Pleural fluid, ascites	del E746-A750	None	2.9 → 6.1
14	F	<u>Oligo</u>	G	19	Y	N	<u>Ascites</u>	del E746-A750	None	nd
15	F	Never	G	8	N	N	Pleura	del E746-A750	None	8.4
16	F	Never	E	10	Y	N	Lung	del E746-A750	None	5.7
17	M	Never	E	9	N	N	Pleural fluid	del E746-A750	None	7.2
18	F	<u>Oligo</u>	G	7	Y	N	Cervix	del ^e	None	nd
19	M	Former	G	12	Y	Y	Inguinal lymph node	del ^e	None	nd
20	F	<u>Oligo</u>	G	28	N	N	Lung	del ^e	None	nd
21	M	Never	G→E	19	Y	Y	Pleural fluid	L858R	None	nd

Pao et al '05; Balak et al '06

Analogous "Gatekeeper" Mutations in Kinases Associated with Resistance to Kinase Inhibitors

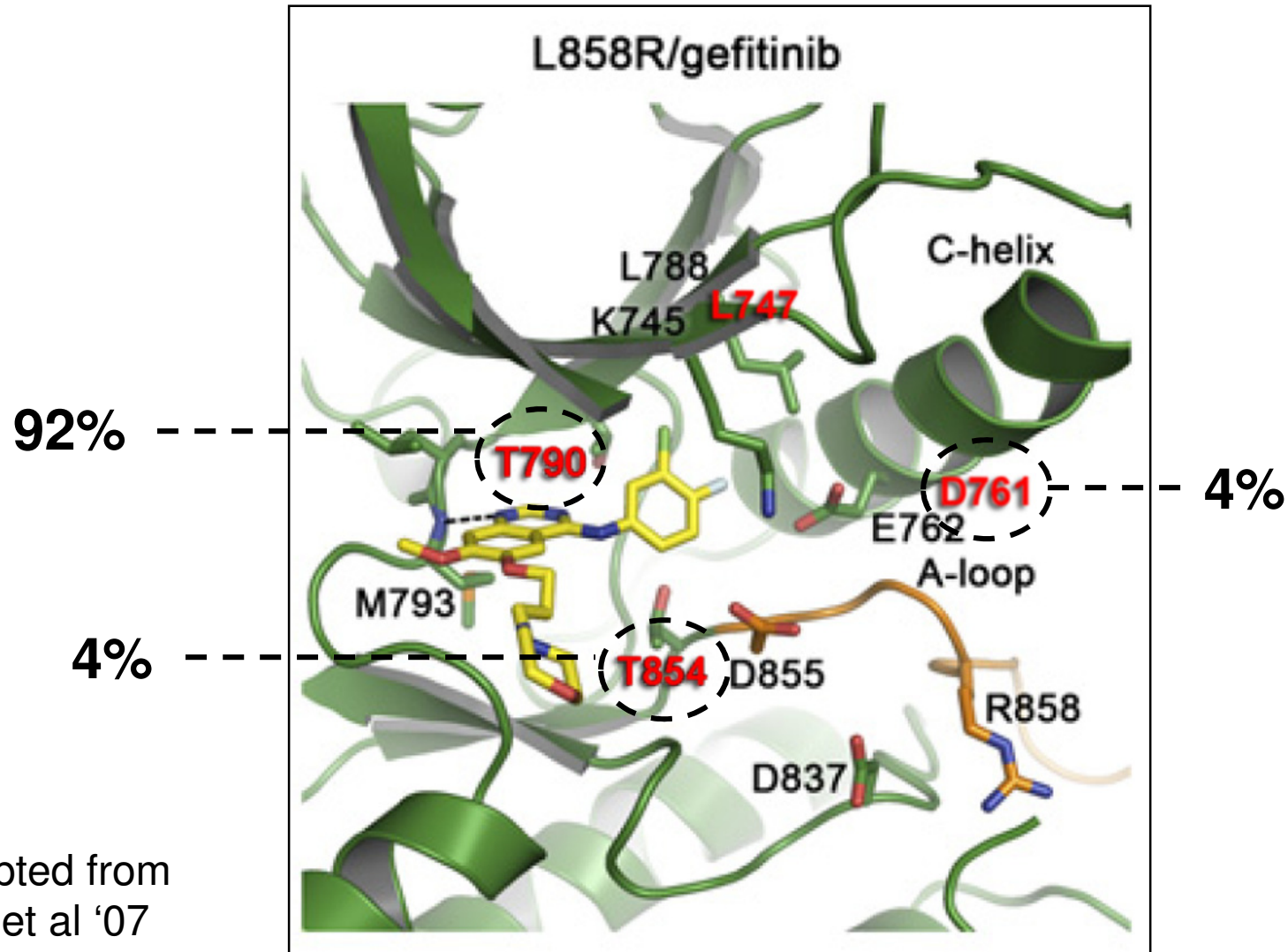
<u>Protein</u>	<u>Mutation</u>	<u>Disease</u>	<u>Drug</u>	<u>Reference</u>
BCR-ABL	T315I	CML	Imatinib	Shah et al, '02
BCR-ABL	T315I	CML	Dasatinib	O'Hare et al, '05
PDGFRa	T674I	HES	Imatinib	Cools et al, '03
KIT	T670I	GIST	Imatinib	Tamborini et al, '04
EGFR	T790M	NSCLC	Gefitinib/ Erlotinib	Pao and Miller et al, '05 Kobayashi et al, '05

For BCR-ABL, T315I leads to steric clash, but for mutant EGFR, T790M may restore affinity of kinase for ATP vs drug (Yun et al '08)

MSKCC Acquired Resistance Experience

- Successfully analyzed tissue specimens from 48 patients with acquired resistance
- All had primary drug-sensitizing mutation (exon 19 del or L858R)
 - 25 had second-site mutation
 - 23 T790M
 - 1 D761Y (Balak et al '06)
 - 1 T854A (Bean et al '08)

T790M and T854A are Drug Contact Residues

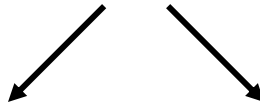


Can We Identify Agents that Overcome T790M-Mediated Resistance?

Screen 47 known kinase inhibitors
for ability to inhibit H1975 proliferation
(>85% inhibition at 2 μ M)



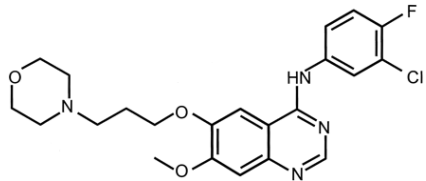
Identify 3 compounds:
CL-387,785; EKB-569; CI-1033



Determine IC_{50}

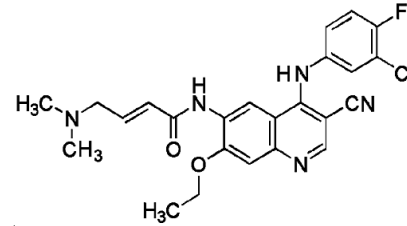
Measure EGFR
autophos inhibition

Current EGFR Inhibitors in the Clinic 2009

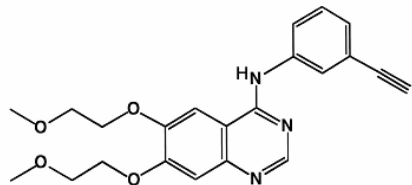


MW 446.9020

Gefitinib/Iressa
(AstraZeneca)

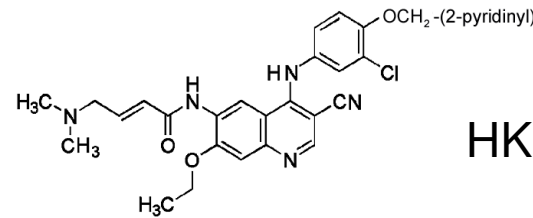


EKB-569
(Wyeth)

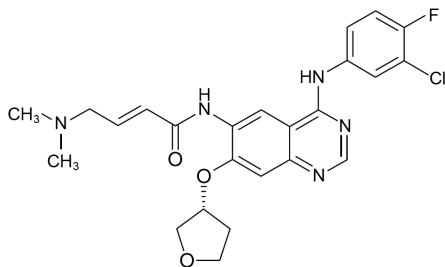


MW: 429.90

Erlotinib/Tarceva
(Genentech)



HKI-272/Neratinib
(Wyeth)



MW: 485.95

BIBW2992
(Boehringer-Ingelheim)

?

XL-647
(Exelixis)

?

PF00299804
(Pfizer)

MET Amplification Occurs in 20% of Cases, With or Without T790M

- *MET* is another receptor tyrosine kinase like *EGFR*
- Using a genomic approach, we found that *MET* amplification was found in 9/43 (21%) acquired resistance patients vs. 2/62 (3%) untreated *EGFR* mutant patients ($p=0.007$, Fisher's Exact Test)
- 4/9 patients with *MET* amplification also had T790M
- Similar findings reported by Engelman et al '07 using a different approach

Potential MET Inhibitors to Overcome Acquired Resistance

- MET inhibitors
 - Small molecule inhibitors
 - ARQ-197 ArQule
 - PF2341066 Pfizer
 - SGX-523 SGX
 - XL-880 Exelixis
 - XL-184 Exelixis
 - Antibodies
 - AV-299 anti-HGF Aveo/Xoma
 - AMG-102 anti-HGF Amgen
 - Anti-MET Genentech

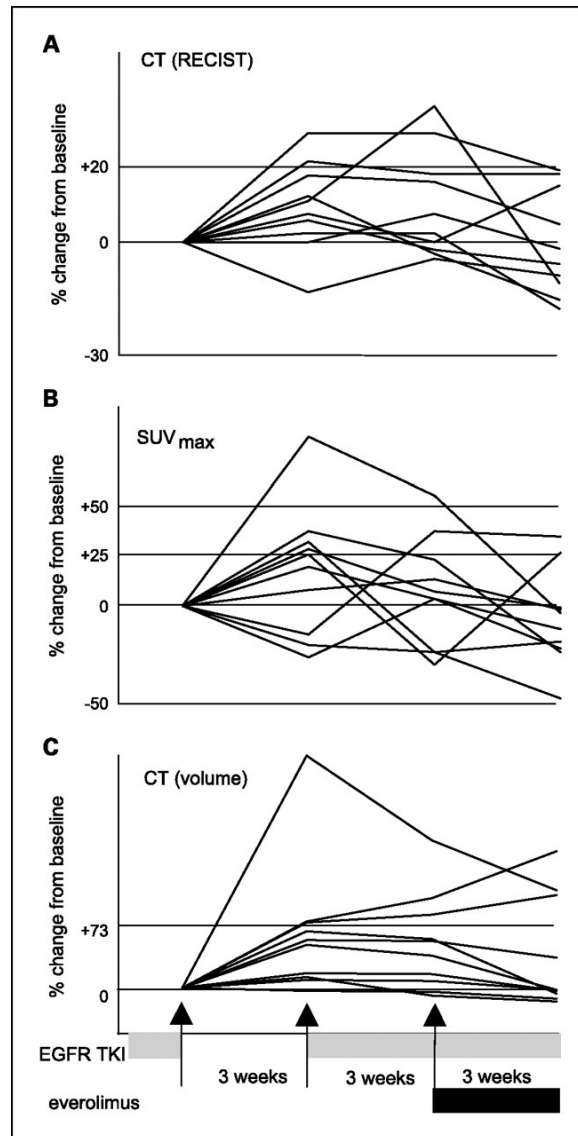
Summary

- Patients with *EGFR* mutant lung adenocarcinomas eventually develop acquired resistance (median ~12 mos)
- ~50% of patients with acquired resistance develop a second-site *EGFR* mutation (T790M) that impairs effectiveness of gefitinib/erlotinib
- ~20% of patients develop *MET* amplification, with or without T790M
- Patients with acquired resistance **SHOULD BE REFERRED** for clinical trials with new targeted agents
 - MSKCC: BIBW-2992 vs placebo; erlotinib plus cetuximab; erlotinib plus dasatinib; IPI-504 with docetaxel
 - MGH/DFCI: PF00299804, others

What Should Be Done Off Trial for Patients with Acquired Resistance?

- Should the EGFR TKI be discontinued?
- Is it safe to add chemotherapy?

Patients with Acquired Resistance May Experience Disease Flare When TKI is Discontinued



- Although patients develop POD, a majority of tumor cells remain sensitive

- Cells with the T790M mutation usually represent a minority of the tumor cell population

- Unknown if there is a role for 'cycling' erlotinib with chemo

What Should Be Done Off Trial for Patients with Acquired Resistance?

- Should the EGFR TKI be discontinued?
 - At MSKCC, we continue the TKI and add additional chemotherapy
- Is it safe to add chemotherapy?
 - YES

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Patients

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