Long term therapeutic plan for NSCLC harboring EGFR mutation

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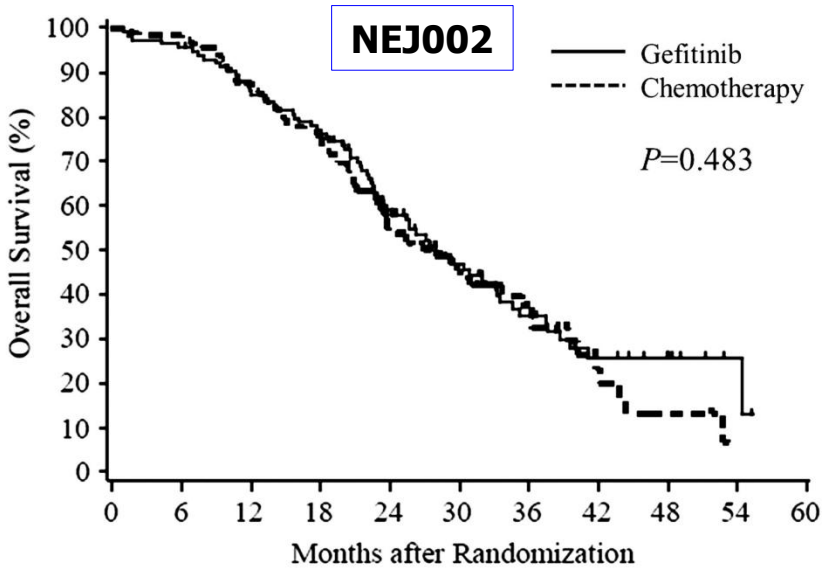
EGFR-TKI therapy is effective as first-line treatment of advanced NSCLC with EGFR^{mut+}

A meta-analysis from six phase III RCTs

Meta-analysis of IPASS, First-SIGNAL, NEJ002, WJTOG3405, OPTIMAL, EURTAC

	First-line therapy				
	N	**EGFR-TKI**	**Chemotherapy**	RR or HR	p-value
RR	1,021	66.6%	30.6%	5.68 [3.17-10.18]	<0.001
PFS	1,006	9.5mo	5.9mo	0.37 [0.27-0.52]	<0.001
OS	852	30.5mo	23.6mo	0.94 [0.77-1.15]	0.57



Data from NEJ002 clinical trial

Stage IV, NSCLC EGFR^{mut+}, Japan

1-year survival	≈ **86%**
2-Year survival	≈ **56%**
3-Year survival	≈ **35%**
4-Year survival	≈ **19%**
5-Year survival	≈ **10% (?)**

Gao G, et al. Int J Cancer. 2012;131:E822-9

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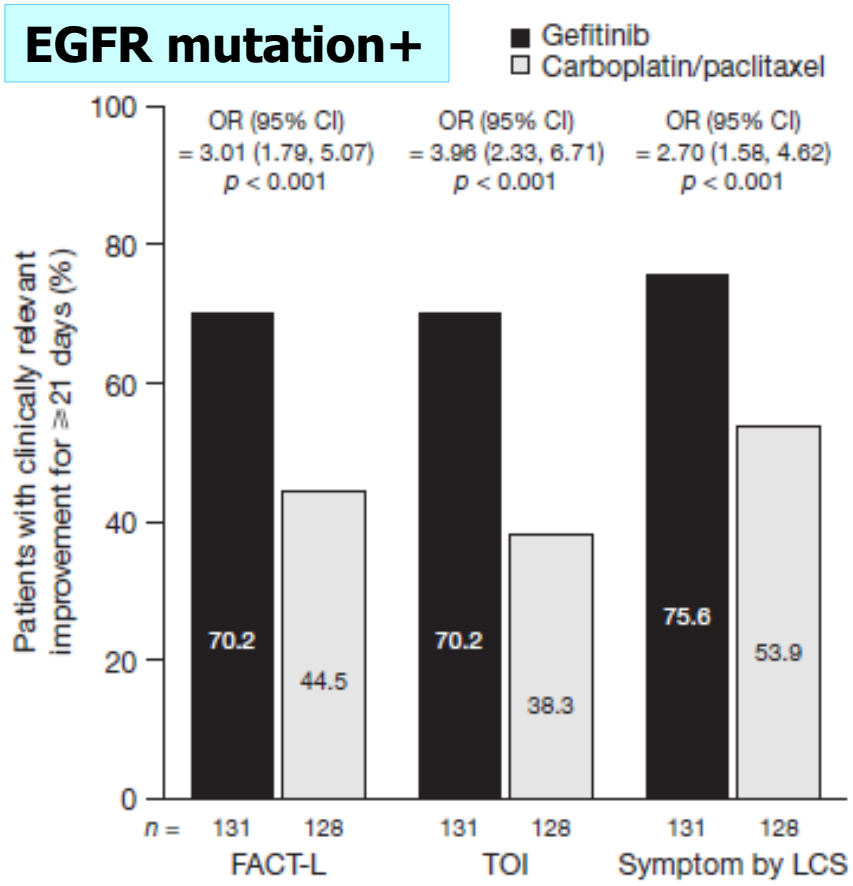
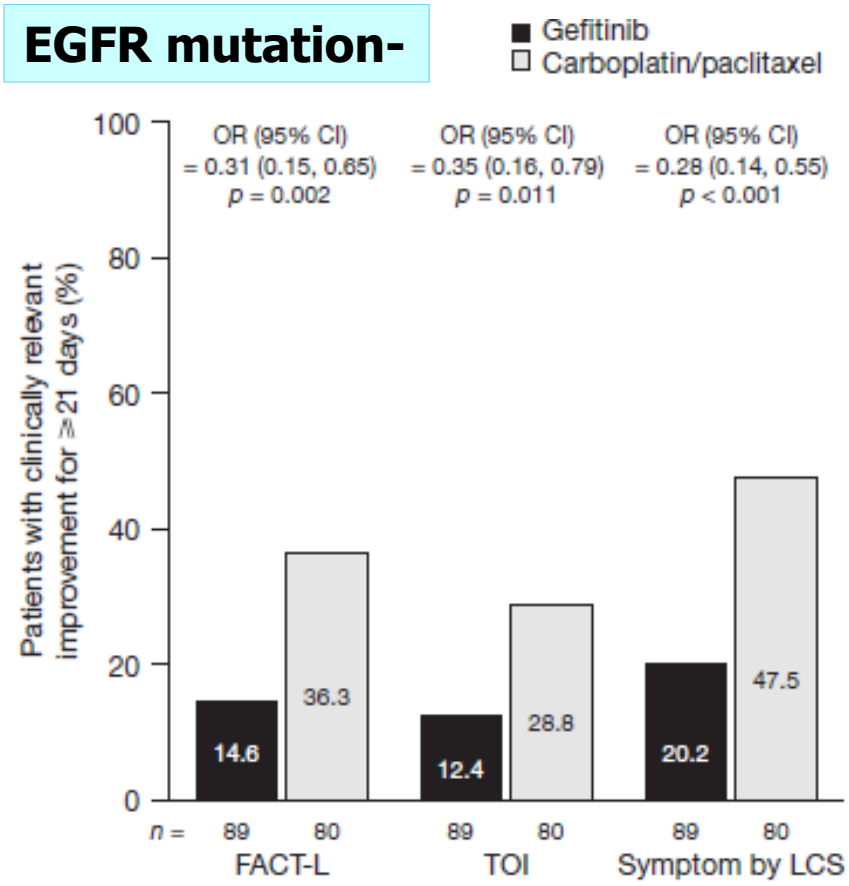
Efficacy of EGFR-TKI or chemotherapy as 1st-line therapy in NSCLC with EGFR^{mut+}

Patient group		N	PFS (months)			OS (months)		
			Gefitinib	Chemotherapy	HR	Gefitinib	Chemotherapy	P
Non-randomized pooled analysis								
I-CAMP[1]	Japanese	148	10.7	6.0	**0.35** [0.23-0.52]	27.7	25.7	**0.78**
Subset analysis of the phase 3 trials for patients selected by clinical background								
IPASS[2,3]	East Asian	261	9.5	6.3	**0.48** [0.36-0.64]	21.6	21.9	**0.99**
First-SIGNAL[4]	Korean	42	8.4	6.7	**0.61** [0.31-1.22]	30.6	26.5	
Phase 3 trials for patients selected by EGFR mutation status								
NEJ002[5,9]	Japanese	194	10.8	5.4	**0.30** [0.22-0.41]	27.7	26.6	**0.48**
WJTOG3405[6,10]	Japanese	172	9.2	6.3	**0.49** [0.34-0.71]	36.0	39.0	**NS**
			Erlotinib	**Chemotherapy**	**HR**	**Erlotinib**	**Chemotherapy**	**P**
Phase 3 trials for patients selected by EGFR mutation status								
OPTIMAL[7,11]	Chinese	154	13.1	4.6	**0.16** [0.10-0.26]	HR 1.065		**0.68**
EURTAC[8]	European	173	9.7	5.2	**0.37** [0.25-0.54]	19.3	19.5	**0.87**

[1]Morita S, et al. Clin Cancer Res. 2009;15:4493-8
[2]Mok TS, et al. N Engl J Med 2009;361:947-57
[3]Fukuoka M, et al. J Clin Oncol. 2011;29:2866-74
[4]Lee JS, et al. J Thorac Oncol. 2009;4(suppl):abstr PRS.4.
[5]Maemondo M, et al. N Engl J Med. 2010;362:2380-8
[6]Mitsudomi T, et al. Lancet Oncol. 2010;11:121-8
[7]Zhou C, et al. Lancet Oncol. 2011;12:735-42
[8]Rosell R, et al. Lancet Oncol. 2012;13:239-46
[9]Inoue A, et al. Ann Oncol. 2013;24:54-59
[10]Mitsudomi T, et al. J Clin Oncol 30, 2012 (suppl; abstr 7521)
[11]Zhou C, et al. J Clin Oncol 30, 2012 (suppl; abstr 7520)

Health-related quality of life in patients on IPASS





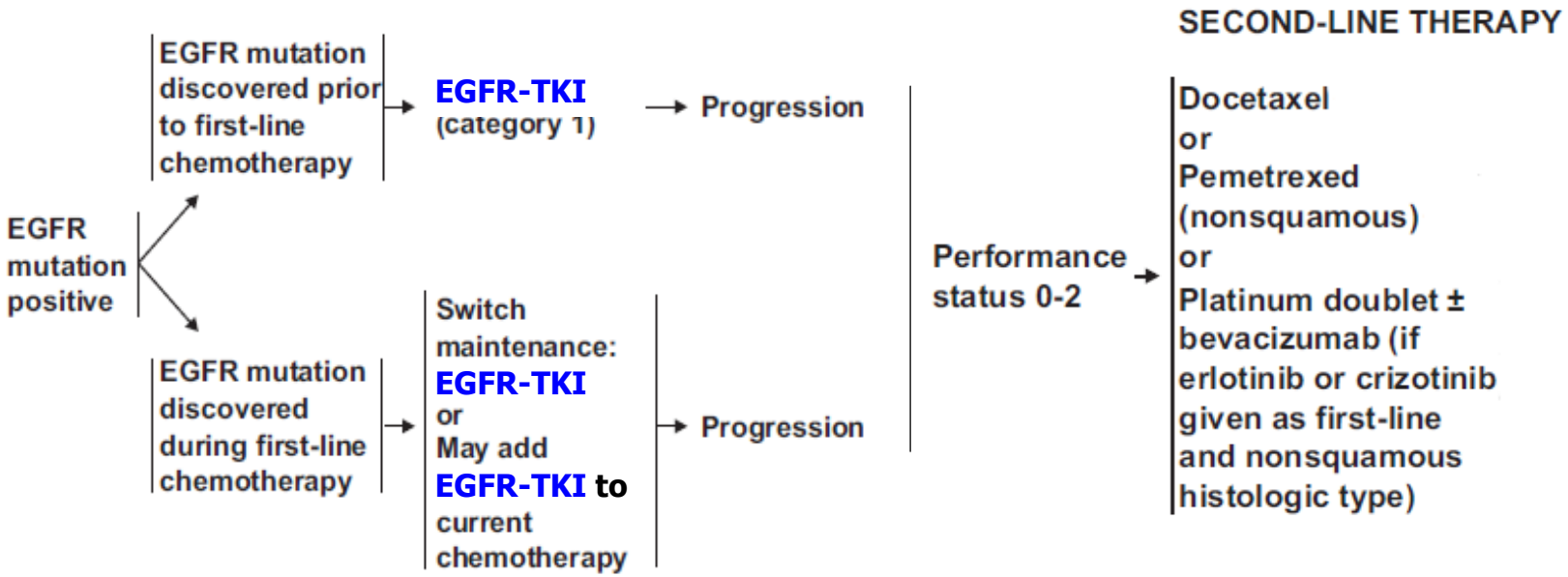
Thongprasert S, et al. J Thorac Oncol. 2011;6:1872-80

Efficacy of switch maintenance to EGFR-TKI in NSCLC

Trial	Drug	Eligibility	N	Subgroup	PFS [Primary EP]	OS [Secondary EP]
SATURN[1]	**Erlotinib**	① Stage IIIB-IV	889	Overall	HR **0.71** [0.62-0.82]	HR **0.81** [0.70-0.95]
▯ Caucasian 84%		② Non-PD after			2.87 vs. 2.59 mo	12.0 vs. 11.0 mo
		1st-line CT, 4 cycles		EGFR^{mut+}	HR **0.10** [0.04-0.25]	HR **0.83** [0.34-2.02]
		③ PS 0-1		EGFR^{WT}	HR **0.78** [0.63-0.96]	HR **0.77** [0.61-0.97]
INFORM[2]	**Gefitinib**	① Stage IIIB-IV	296	Overall	HR **0.42** [0.33-0.55]	HR **0.84** [0.62-1.14]
▯ Chinese 100%		② Non-PD after			4.8 vs. 2.6 mo	18.7 vs. 16.9 mo
		1st-line CT, 4 cycles		EGFR^{mut+}	HR **0.17** [0.07-0.42]	
		③ PS 0-2		EGFR^{WT}	HR **0.86** [0.48-1.51]	

[1]Cappuzzo F, et al. Lancet Oncol. 2010;11:521-9
[2]Zhang L, et al. Lancet Oncol. 2012;13:466-475

Treatment guideline for EGFR^{mut+} NSCLC



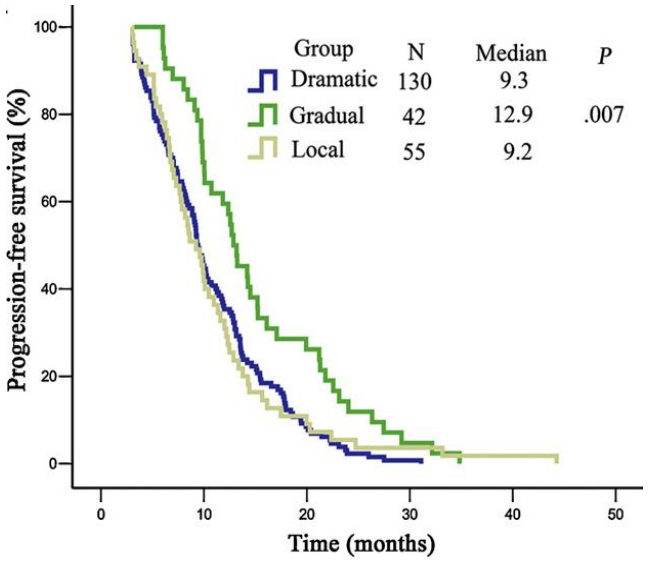
NCCN Practice Guidelines for Non-small-cell Lung Cancer v.2.2013

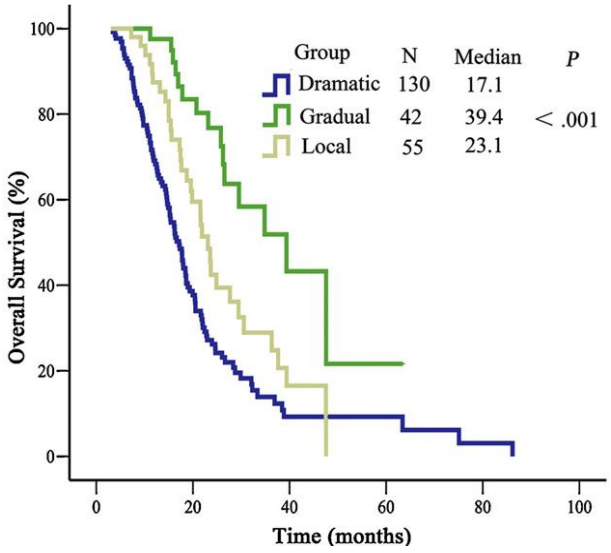
Clinical modes of EGFR-TKI failure and subsequent management in advanced NSCLC

- Stage III-IV NSCLC, First-line EGFR-TKI
- Duration of disease control ≥ 3 mo on EGFR-TKI

EGFR-TKI failure

Discriminating factors	**Dramatic** progression	**Gradual** progression	**Local** progression
Disease control on TKI	≥ 3mo	≥ 6mo	≥ 3mo
Tumor burden increment [**Doubling time**]	Rapid	Minor	Solitary extra-cranial or limitation in intra-cranial lesion
Symptom score	≥ 2	≤ 1	≤ 1



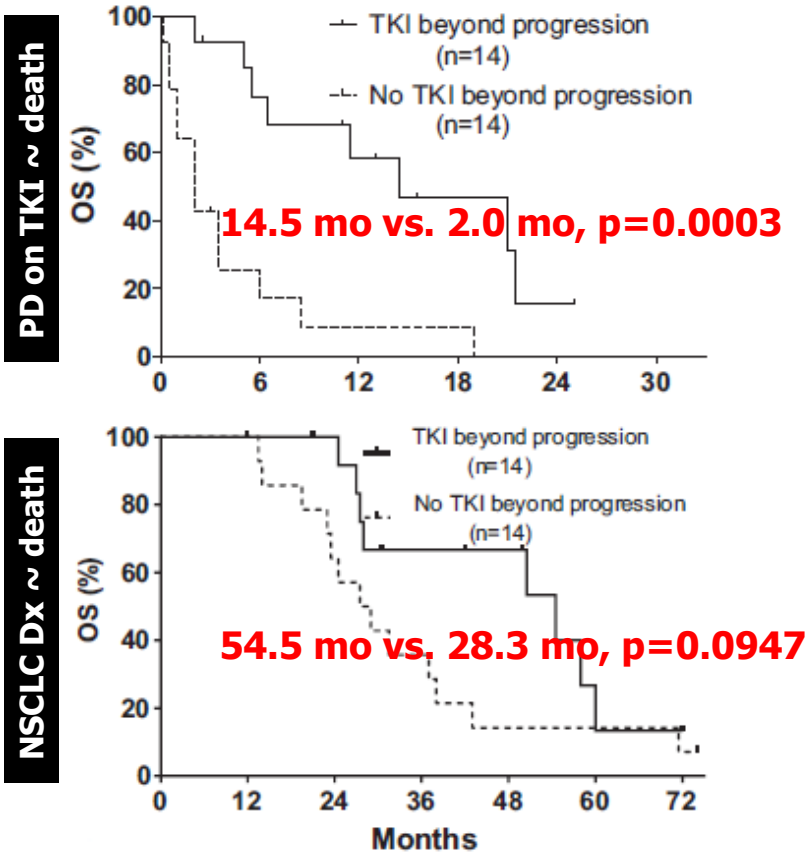


Yang JJ, et al. Lung Cancer. 2013;79:33-9

EGFR-TKI treatment beyond progression in long-term Caucasian responders to erlotinib in advanced NSCLC

- A retrospective **case-control analysis** of **pairs matched** for sex, PS, smoking, histology
- Patients with stage IIIB-IV NSCLC, **at least SD on erlotinib ≥ 6 months**

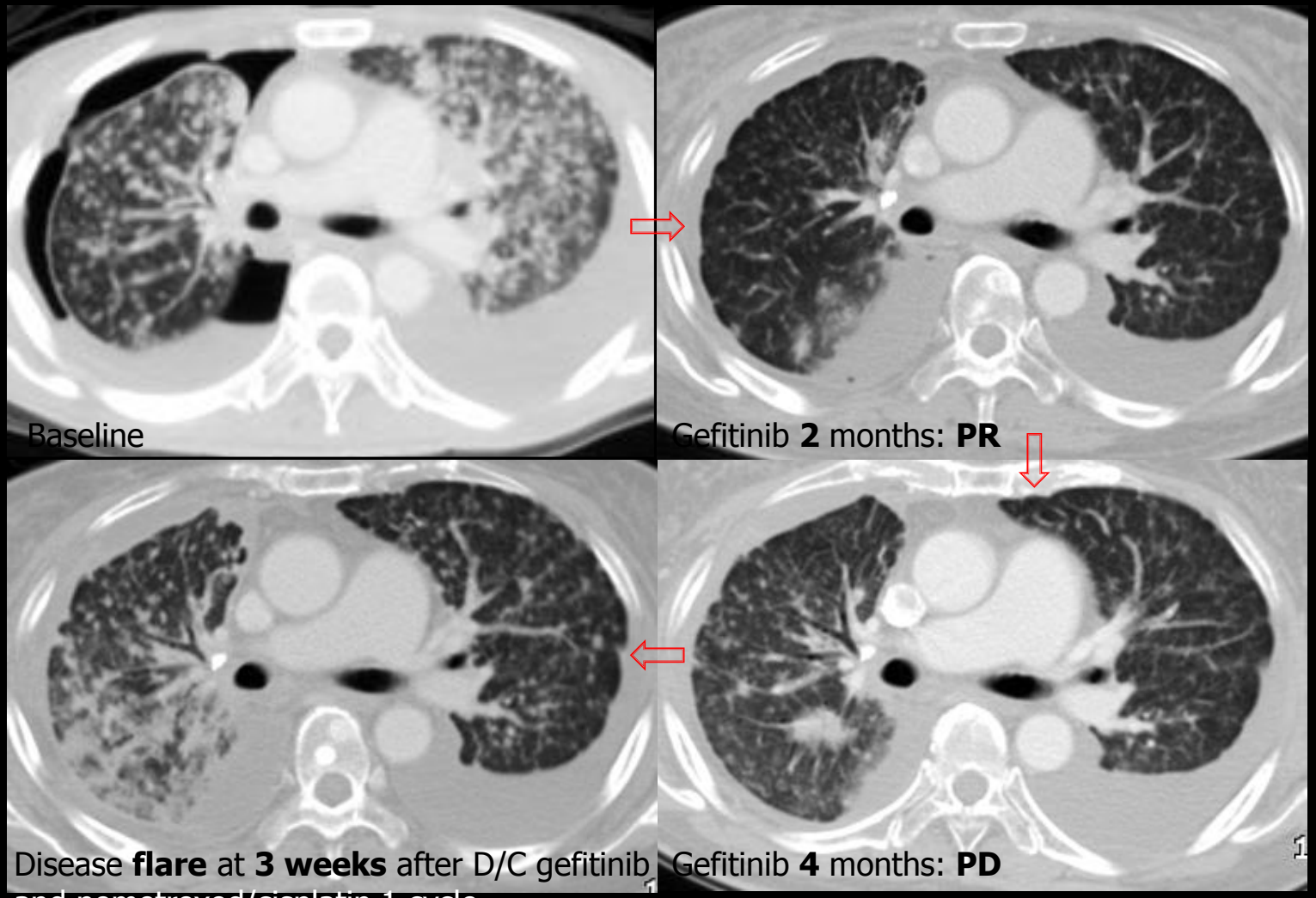
	Continue TKI [n=14]	D/C TKI [N=14]
EGFR mutation		
(+) exon 19	4	1
(+) exon 21	0	1
(+) exon 18	1	0
Negative	6	3
Unknown	3	9
Best response to erlotinib		
CR	1	1
PR	10	9
SD	3	4
PFS	12.5 mo	12.0 mo
Treatment after progression on TKI		
Chemotherapy	11	9
Radiotherapy	4	3
BSC	4	5



Faehling M, et al. Lung Cancer. 2013 doi: 10.1016

A case of flare phenomenon after stopping EGFR-TKI

F/60, adenocarcinoma, EGFR exon19 del_E746-A750



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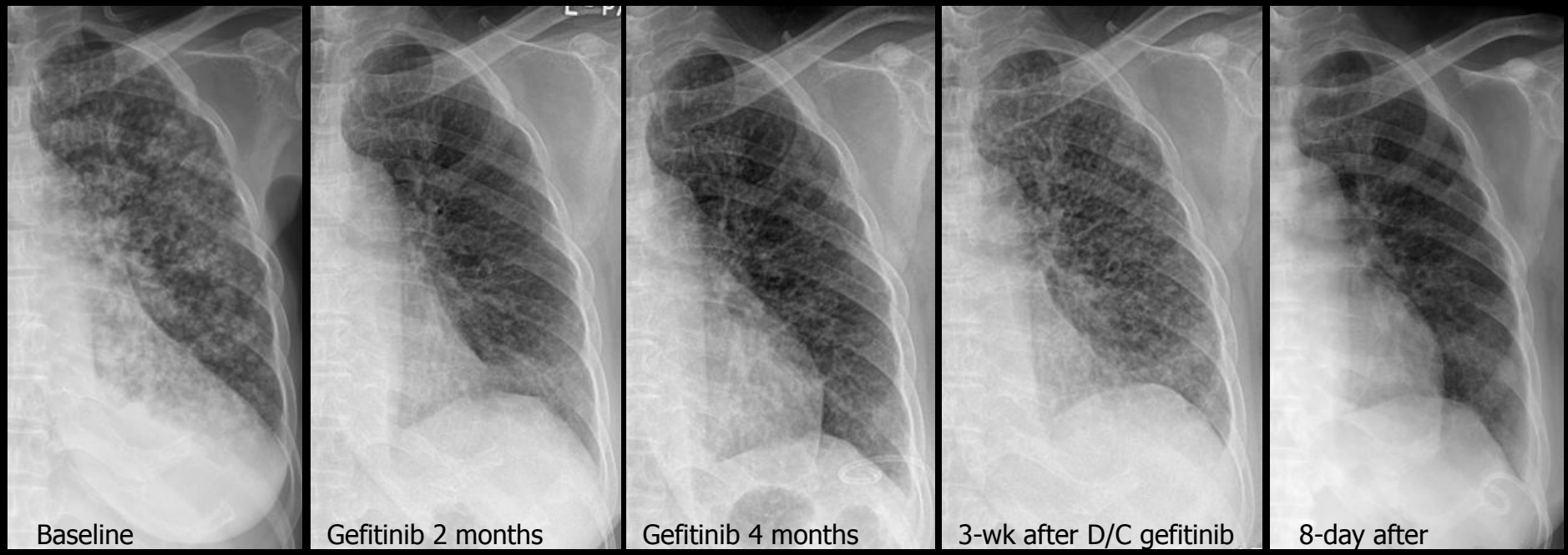


Disease flare after TKI discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib

- A retrospective analysis (N=61)
- Patients with ❶ Lung cancer harboring a sensitizing mutation (G719X, exon 19 del, L858R)
  ❷ Acquired EGFR-TKI resistance after initial benefit
- Definition of "**disease flare**": hospitalization or death attributable to disease progression after stopping TKI

- 14/61 (**23%**, 95% CI: 14-35) experienced a disease flare
- Median time to disease flare after TKI discontinuation was **8 days** (range 3-21)
- Factors associated with disease flare: ❶ **shorter time to progression on initial TKI** (p=0.002)
  ❷ presence of **pleural involvement** (p=0.03)
  ❸ presence of **CNS involvement** (p=0.01)
- No association with mutation type, presence of T790M, performance, sex, TKI, smoking status

Chaft JE, et al. Clin Cancer Res. 2011;17:6298-303

Prospective assessment of discontinuation and reinitiation of erlotinib(E) or gefitinib(G) in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus

Patients with stage IV NSCLC, ≥ 6mo on **E**rlotinib or **G**efitinib **AND**
❶ At least decreasing SD on **E** or **G** **OR**
❷ EGFR mutation (exon 19 or 21)

→ Documented **PD** (RECIST) on **E** or **G**

CT and PET-CT → **Stop E or G** for **3 weeks** → **CT and PET-CT** → **Restart E or G** for **3 weeks** → **CT and PET-CT** → **Add** everolimus† 5mg/day for **3 weeks** → **CT and PET-CT**

†mTOR inhibitor (Novartis)

13 patient s were enrolled, and **10 patients completed the course**

- Adenocarcinoma (11)/ NSCLC (2)
- Erlotinib (6)/ Gefitinib (7)
- Median time on erlotinib or gefitinib 16 months (8~79)
- EGFR L858R (2)/ exon 19 deletion (6)/ not available (5)

	After **stopping** E or G	After **restarting** E or G	After **adding** **everolimus**
Median Δ Tumor diameter	+9% (-13~+29%)	-1% (-14~+23%)	-8% (-34~+15%)
Mean Δ Tumor diameter	**+9%**	**1%**	**-9%**
Median Δ Tumor volume	+50% (-4~+260%)	-1% (-27~15%)	-11% (-40~+26%)
Mean Δ Tumor volume	**+61%**	**-4%**	**-10%**
Median Δ SUV_{max}	+18% (-17~+87%)	-4% (-45~+62%)	-18% (-39~+82%)
Mean Δ SUV_{max}	**+23%**	**-11%**	**-11%**
Symptoms	Generally aggravated	Generally stable or improved	

Riely GJ, et al. Clin Cancer Res. 2007;13:5150-5

Retreatment of gefitinib in patients with NSCLC who previously controlled to gefitinib

- A single arm, open-label, prospective phase II trial
- Advanced or metastatic NSCLC **previously controlled (CR/PR or SD ≥3mo) by gefitinib**
- **At least one prior cytotoxic chemotherapy after a previous EGFR-TKI failure**
- Retreatment with gefitinib 250mg/day until PD or intolerant AE

□ Baseline characteristics (n=23)

Clinical factor		Value
Sex	Female	20 (86.9%)
	Male	3 (13.0%)
Histology	ADC	22 (95.7%)
	SQC	1(4.3%)
Smoking	Ex-smoker	2 (8.7%)
	Never	21 (91.3%)
Response to initial gefitinib		
	PR	10 (43.5%)
	SD	13 (56.5%)
Gefitinib holiday	≤ 6mo	9 (39.1%)
	6-12mo	8 (34.8%)
	≥ 12mo	6 (26.1%)

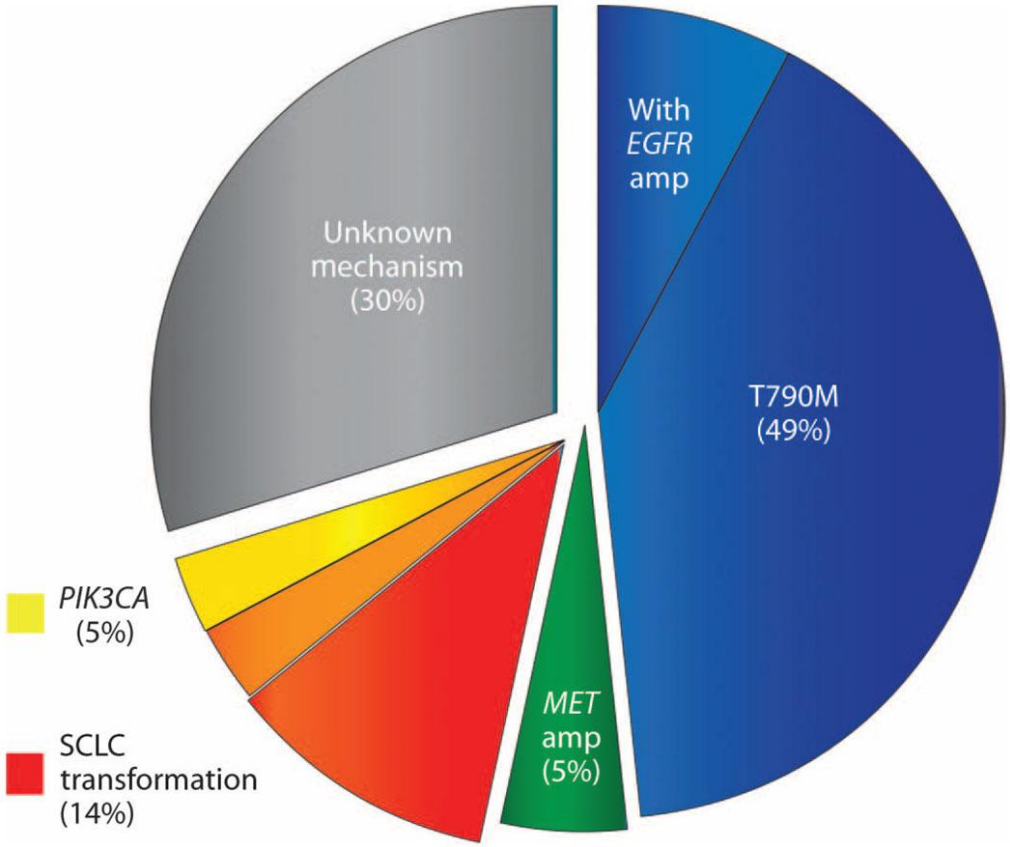
Initial diagnosis ~ gefitinib retreatment, **median 25.5 mo**

□ Outcomes of gefitinib retreatment

Index	Outcome
ORR	21.7% (5/23)
DCR	65.2% (15/23)
TTP	103 day (95% CI, 70-134)
OS	343 day (95% CI, 235-409)
Favorable factor for better TTP	
	DC on retreatment
	Good PS
	PR on initial gefitinib
	Skin rash
Favorable factor for better OS	
	DC on retreatment
	Good PS

Oh IJ, et al. Lung Cancer. 2012;77:121-7

Frequency of observed EGFR-TKI resistance mechanisms



Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will **transform to SCLC** at progression

Sequist LV, et al. Sci Transl Med. 2011;3:75ra26

Molecular basis of dug resistance

❶ **Drug efflux**

❷ Acquisition of drug binding **target-deficient** mutants

❸ Engagement of **alternative survival pathways**

❹ Cancer **stem cells**

❺ **Epigenetic mechanisms**

"One gene-one outcome" models may be an oversimplification of acquired resistance. Instead, clinical drug resistance may be due to changes in expression of **a large number of genes** that have a **cumulative impact on chemosensitivity**

Redmond KM, et al. Front Biosci. 2008;13:5138-54
Trumpp A, et al. Nat Clin Pract Oncol. 2008;5:337-47
Glasspool RM, et al. Br J Cancer. 2006;94:1087-92

Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment

- A retrospective analysis
- Stage IV NSCLC with an **initial response** to EGFR-TKI (n=14: erlotinib 10, erlotinib+sorafenib 3, gefitinib 1)
- **Platinum based chemotherapy** after initial EGFR-TKI failure
- Retreatment with erlotinib at renewed progression

Baseline characteristics (n=14)

Clinical factor		Value
Sex	Female	9 (64%)
	Male	5 (36%)
Initial EGFR	Exon 19 del	11 (79%)
	L858R	1 (7%)
	Unknown	2 (14%)
Rebiopsy EGFR	Exon 19 del	6 (43%)
	Exon 19 del **+ T790M**	**5 (36%)**
	L858R	1 (7%)
	Unknown	2 (14%)
Response duration to initial EGFR-TKI		
	12.5 mo (95% CI,7-34)	
TKI holiday	9.5 mo (range, 3-36)	

Outcomes of erlotinib retreatment†

Index	Outcome
ORR	36% (5/14)
DCR	86% (12/14)
PFS	6.5 mo (range, 1-16+)

†3 patients received erlotinib + cetuximab
2/3 showed PD, 1/3 PR

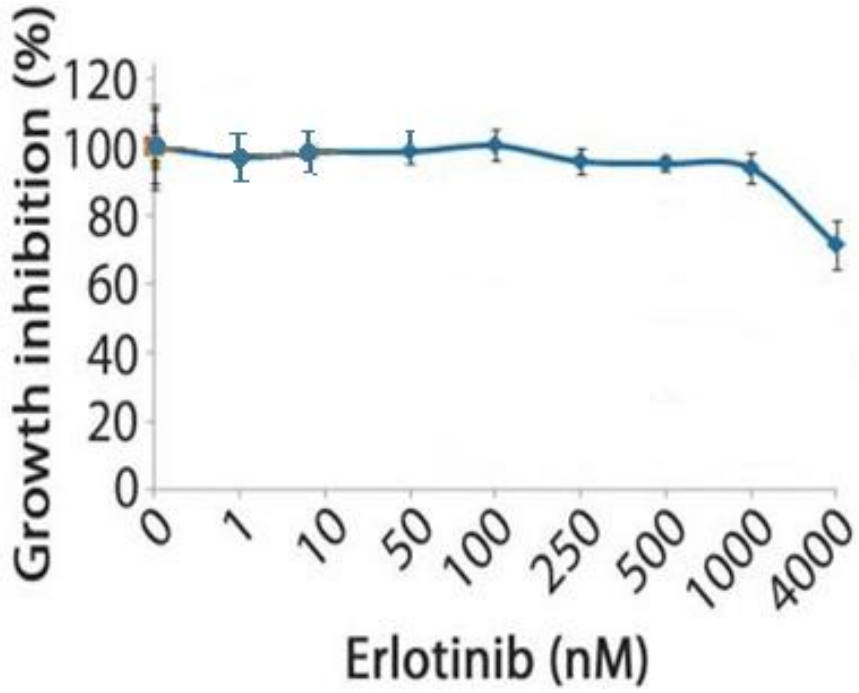
Response in patients with **EGFR$^{ex19\ del+T790M}$**

PR	**40% (2/5)**
SD	20% (1/5)
PD	40% (2/5)

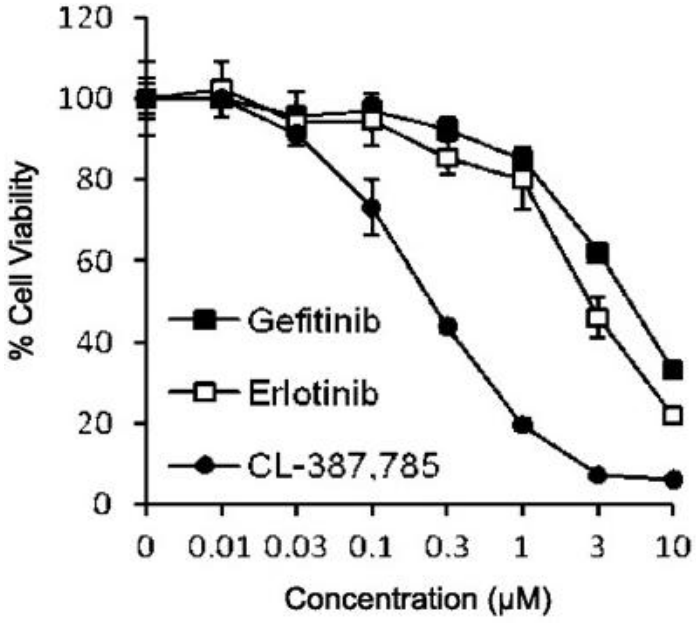
Becker A, et al. Eur J Cancer. 2011;47:2603-6

Cancer cells harboring dual EGFR mutation (sensitizing+T790M) have resistance to EGFR-TKI

PC-9 (EGFR exon19 del/T790M)



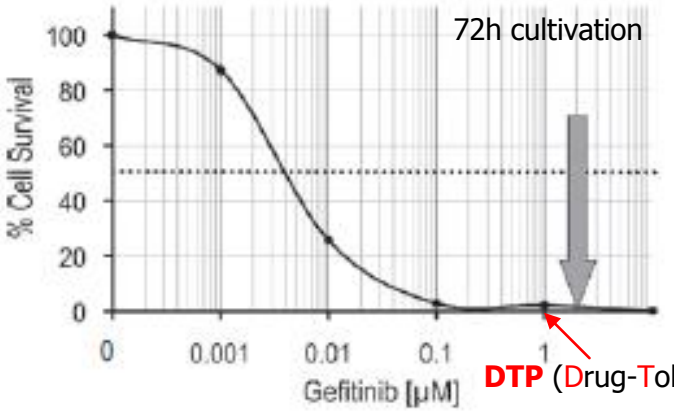
H1975 (EGFR L858R/T790M)



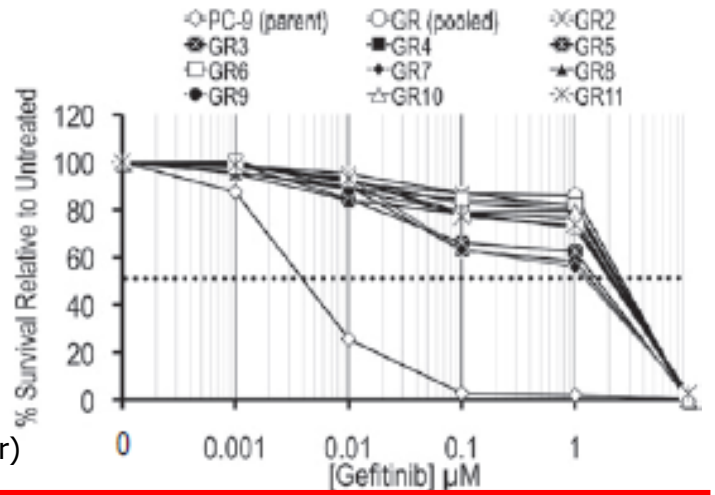
Chmielecki J, et al. Sci Transl Med. 2011;3:90ra59
Yamada T, et al. Clin Cancer Res. 2010;16:174-83

A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations

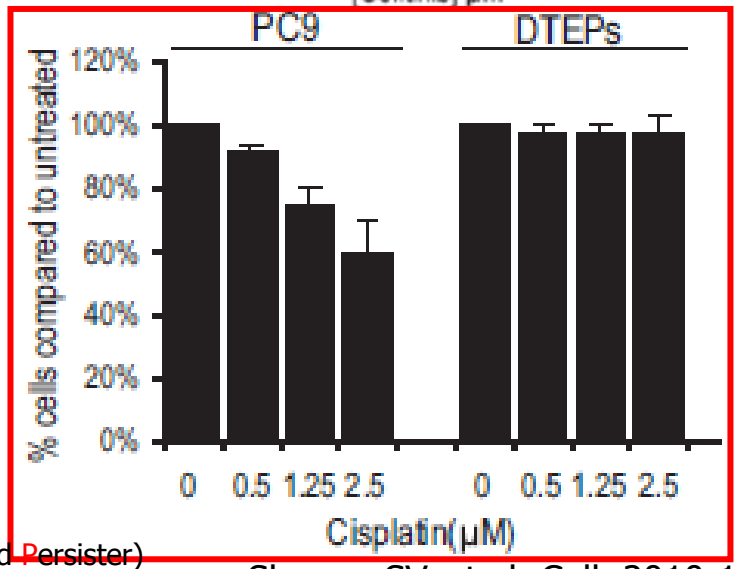
PC-9 (harboring **EGFR exon19 deletion**)



DTP (Drug-Tolerant Persister)



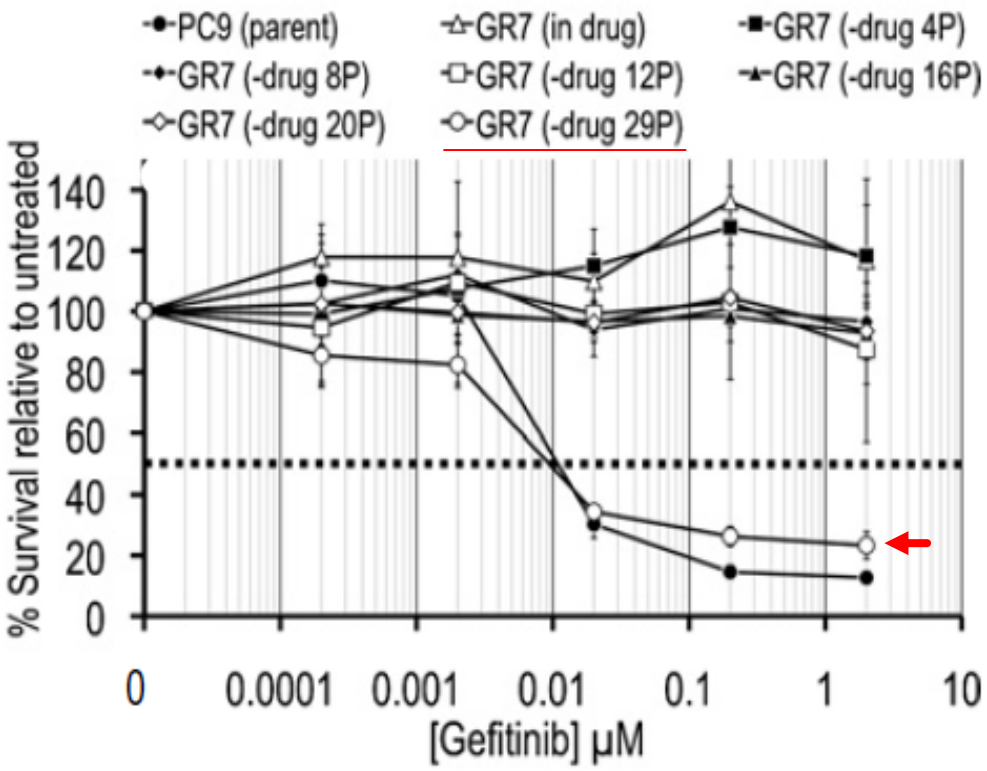
DTP **DTEP** (DT Expanded Persister)



Sharma SV, et al. Cell. 2010;141:69-80

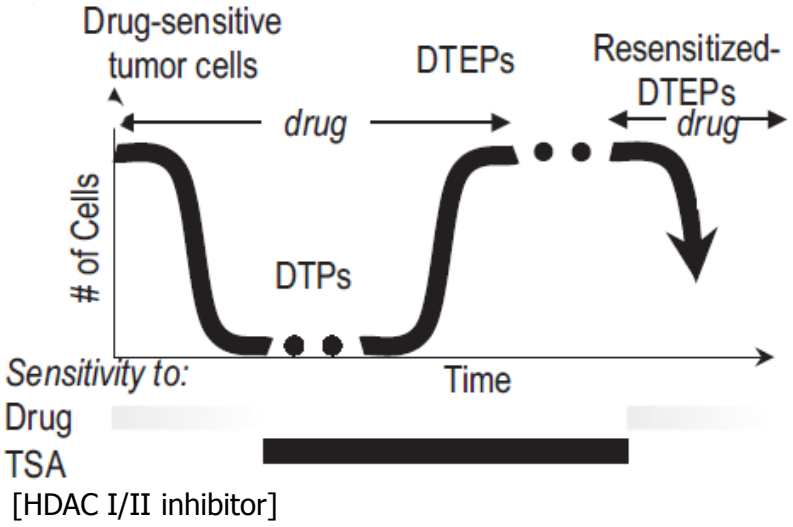
A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations

Indicated number passage **in drug free media**



Involved mechanisms establishing DTEPs

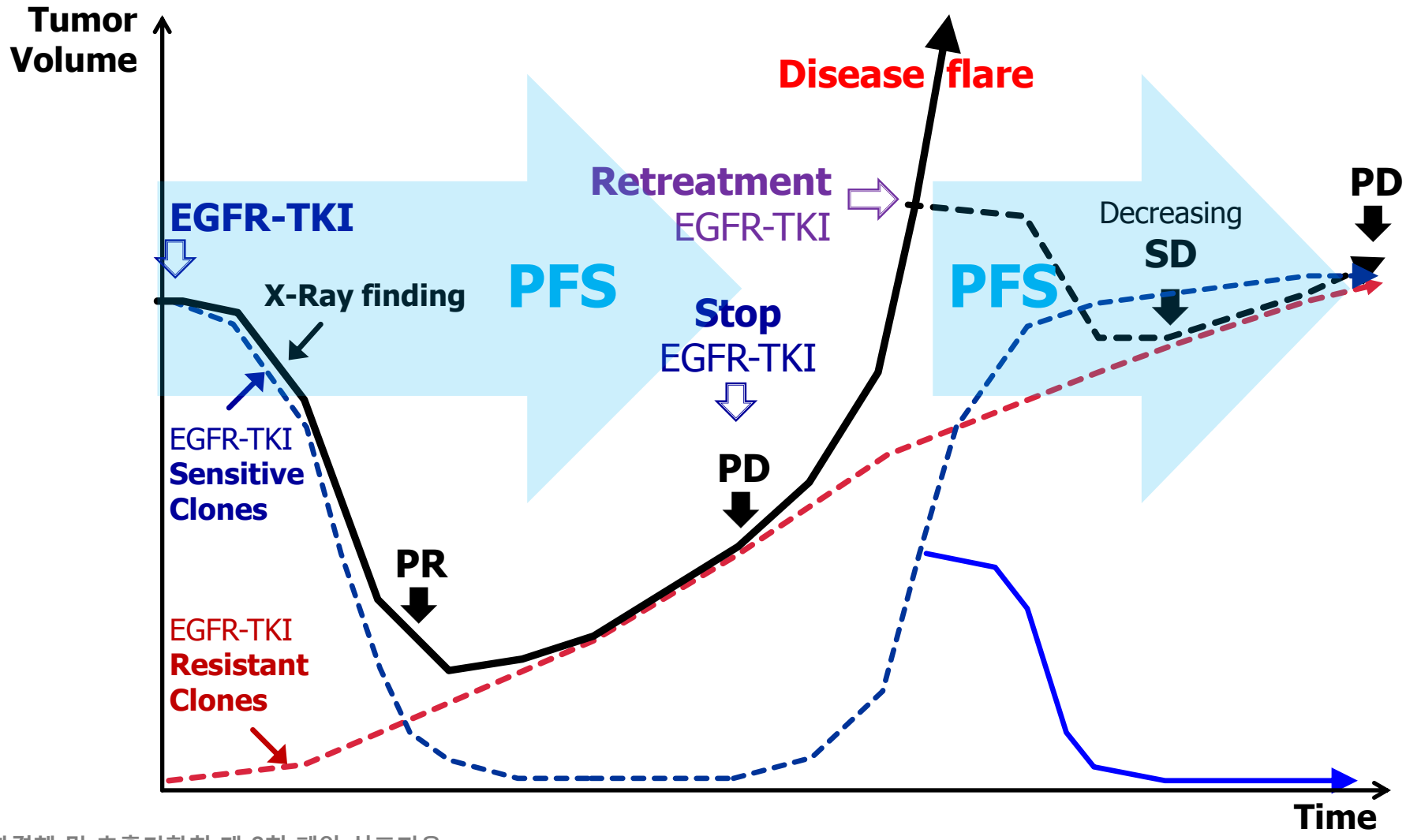
① Stem cell marker+ (CD133)
② Histone demethylation, deacetylation
③ IGF-1R signaling
④ EGFR T790M in several weeks later(?)



Dynamic phenotypic heterogeneity of a nongenetic nature under a lethal drug exposure

Sharma SV, et al. Cell. 2010;141:69-80

Real practice for EGFR-mutant NSCLC



EGFR-TKI in the treatment of EGFR mutant NSCLC metastatic to the brain

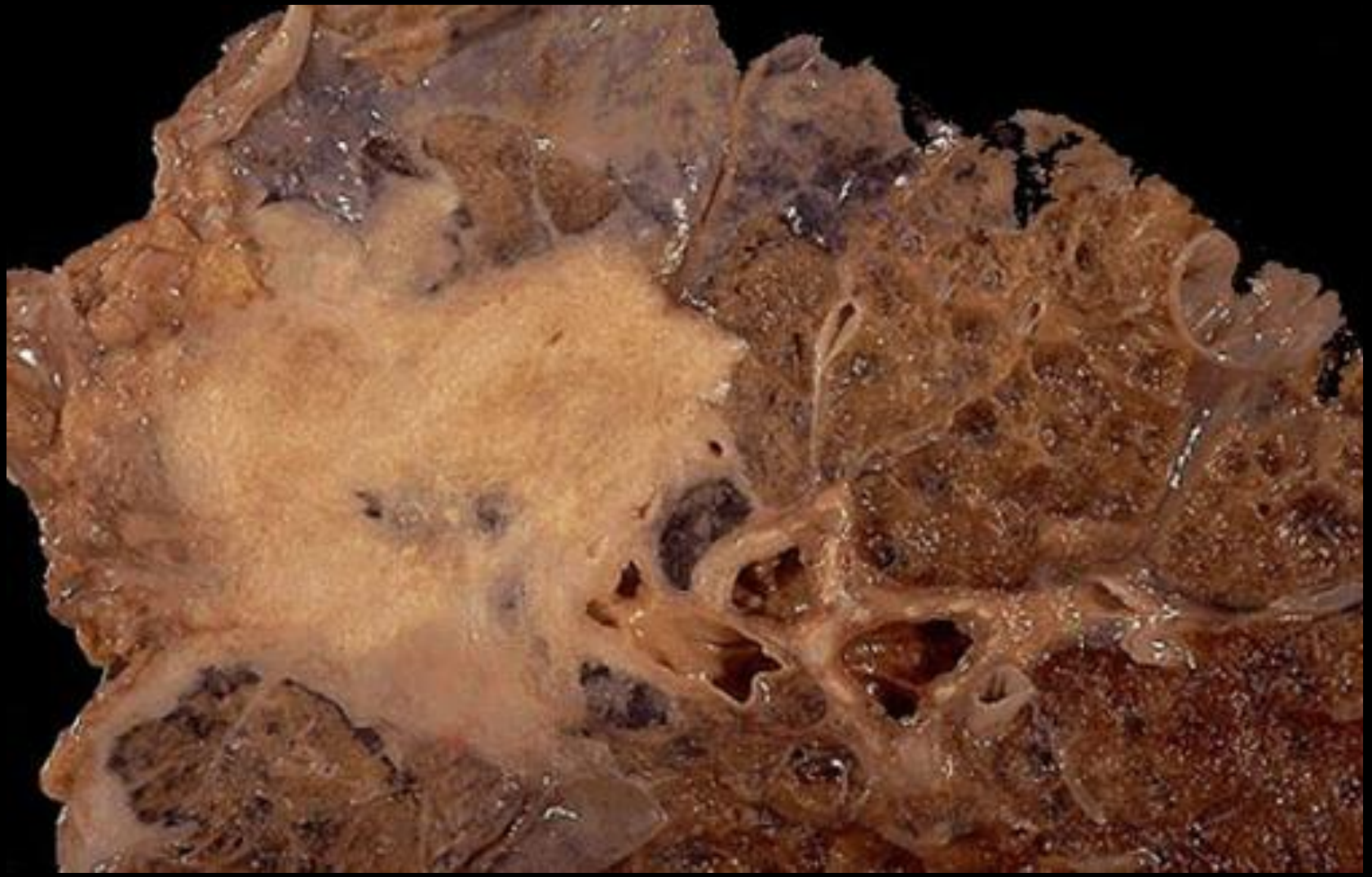
- Incidence of brain metastases (BM) in patients with NSCLC: approximately **25~30%**[1]
- Different incidence of BM: EGFR **mutant: 64%** (9/14) vs. **wild type: 31%** (30/96)[2]
- Local therapy: Surgery/SRS/WBRT
- Systemic therapy: **EGFR-TKI** > chemotherapy in NSCLC **with EGFR-mutation**

	N	Drug	ORR of Brain metastasis
Porta R, et al.[3]	17	Erlotinib	**82.4%** (14/17)
Park SJ, et al.[4]	28	Erlotinib or Gefitinib	**82.1%** (23/28)
Li Z, et al.[2]	9	Gefitinib	**88.9%** (8/9)

- **Dose escalation** for **refractory** brain metastases to standard-dose EGFR-TKI
  - ① Switching: Erlotinib > Gefitinib in ratio of CSF/Serum EFGR-TKI[5]
  - ② Gefitinib: 500mg ▸ 750mg ▸ 1,000mg ▸ 1,250mg[6]
  - ③ Erlotinib: Alternating 300mg/d ◂▸ 150mg/d[7]
  - ④ Erlotinib: Weekly 1,000~1,500mg pulse[8]

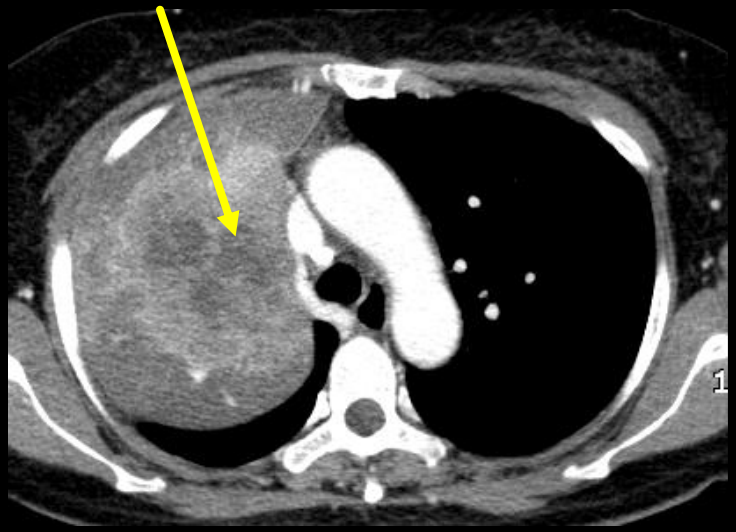
[1]Langer CJ, et al. J Clin Oncol. 2005;23:6207-19
[2]Li Z, et al. J Clin Oncol. 2011;29:e18065
[3]orta R, et al. Eur Respir J. 2011;37:624-31
[4]Park SJ, et al. Lung Cancer. 2012;77:556-60
[5]Katayama T, et al. J Thorac Oncol. 2009;4:1415-9
[6]Jackman DM, et al. J Clin Oncol. 2006;24:4517-20
[7]Hata A, et al. J Thorac Oncol. 2011;6:653-4
[8]Clarke JL, et al. J Neurooncol. 2010;99:283-6

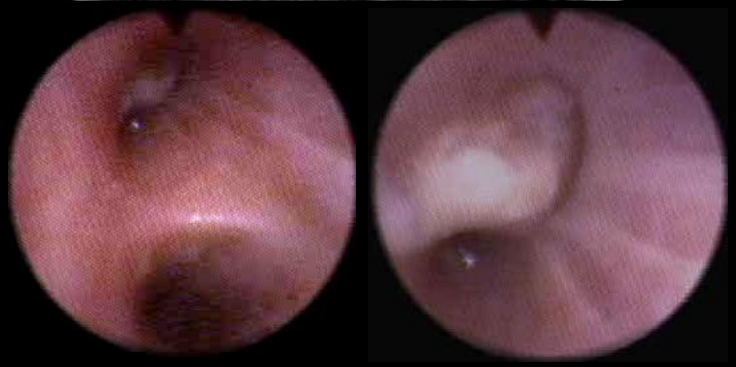
Intratumoral heterogeneity in NSCLC, probably be!

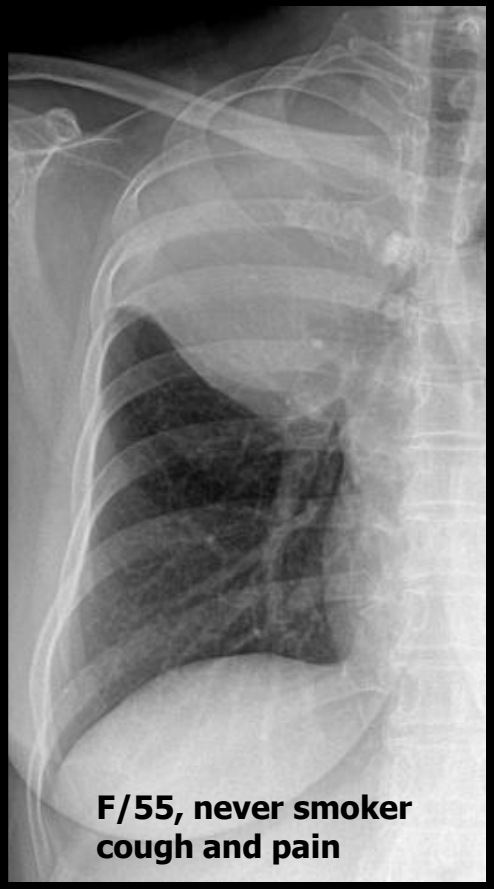


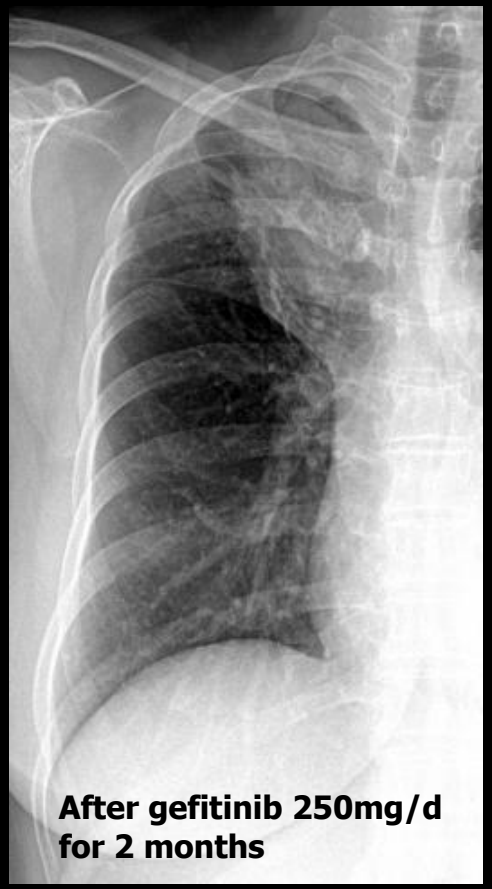
A case of intratumoral heterogeneity in NSCLC

Lung percutaneous needle biopsy:
Adenocarcinoma, well differentiated
EGFR: positive, TTF-1: positive, ALK: negative









Bronchoscopic biopsy: Squamous cell carcinoma
P63: positive, TTF-1: negative

PNA Clamping for EGFR
Deletion mutation in exon 19
No mutation in exon 18, 20, 21

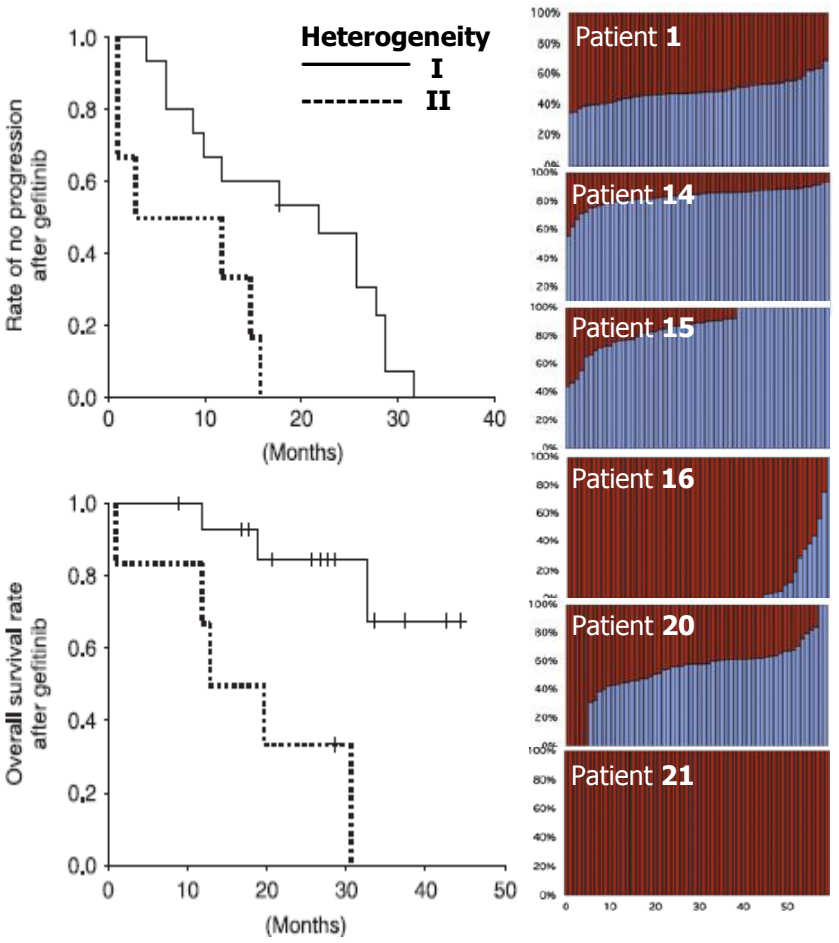
Squamous cell carcinoma, molecular testing recommendation:
EGFR mutation and ALK testing are not routinely recommended
except in never smokers and small biopsy specimens

NCCN Practice Guidelines for Non-small-cell Lung Cancer v.2.2013

Intratumor heterogeneity of EGFR mutations in lung cancer and its correlation to the response to gefitinib

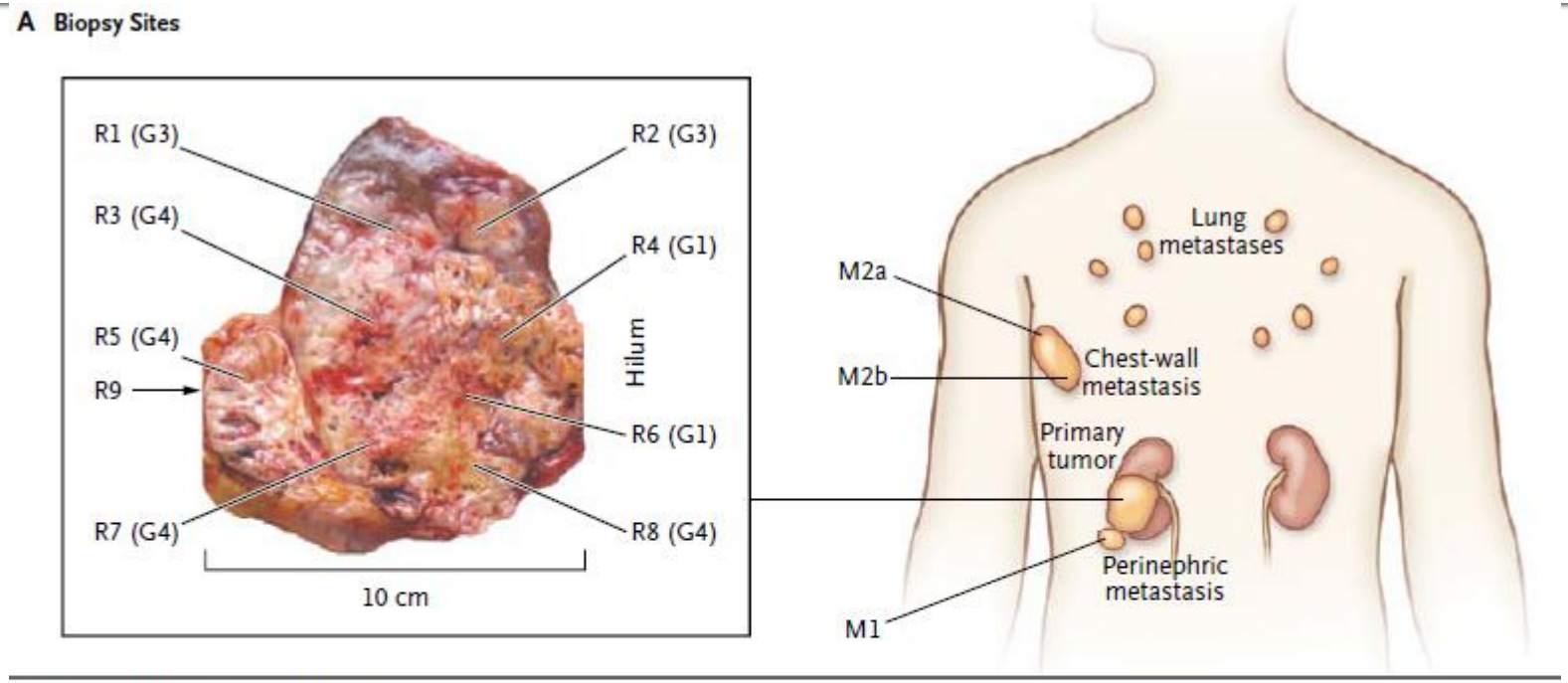
- 21 patients **with EGFR^{mut+}** NSCLC treated with gefitinib for **postoperative recurrence**
- Multipoint microsampling (laser capture microdissection: 50-60 area, 30-50 cells/area) and SNaP shot assay

No.	Histo	EGFR mutation	Wild type area(%)	Mutated allele(%)	Hetero-geneity	Gefitinib response
1	Ad	L858R	0.00	47.9	**I**	PR
2	Ad	L858R	0.00	48.0	**I**	PR
3	Ad	L858R	0.00	50.4	**I**	CR
4	Ad	L858R	0.00	53.2	**I**	CR
5	Ad	L858R	0.00	53.9	**I**	CR
6	Ad	delE746-A750	0.00	58.6	**I**	CR
7	Ad	delE746-A750	0.00	58.7	**I**	PR
8	Ad	delE746-A750	0.00	61.5	**I**	PR
9	Ad	L858R	0.00	74.2	**I**	PR
10	Ad	delE746-A750	0.00	75.1	**I**	PR
11	Ad	delE746-A750	0.00	81.2	**I**	PR
12	Ad	delE746-A750	0.00	82.8	**I**	PR
13	Ad	L861Q, G719S	0.00	82.9	**I**	PR
14	Ad	delL747-T751	0.00	84.5	**I**	PR
15	Ad	delE750-K758	0.00	93.9	**I**	PR
16	Ad	L858R	74.07	24.1	**II**	SD
17	Ad	delE746-A750	6.67	48.3	**II**	PR
18	Ad	delE746-A750	11.54	49.8	**II**	CR
19	Ad	delE746-T751 insIP	8.77	54.3	**II**	PR
20	Ad	delE746-A750	8.62	58.1	**II**	PR
21	AdSq	delA859-L883 insV	100.00	0.0	**II**	PD



Taniguchi K, et al. Cancer Sci. 2008;99:929-35

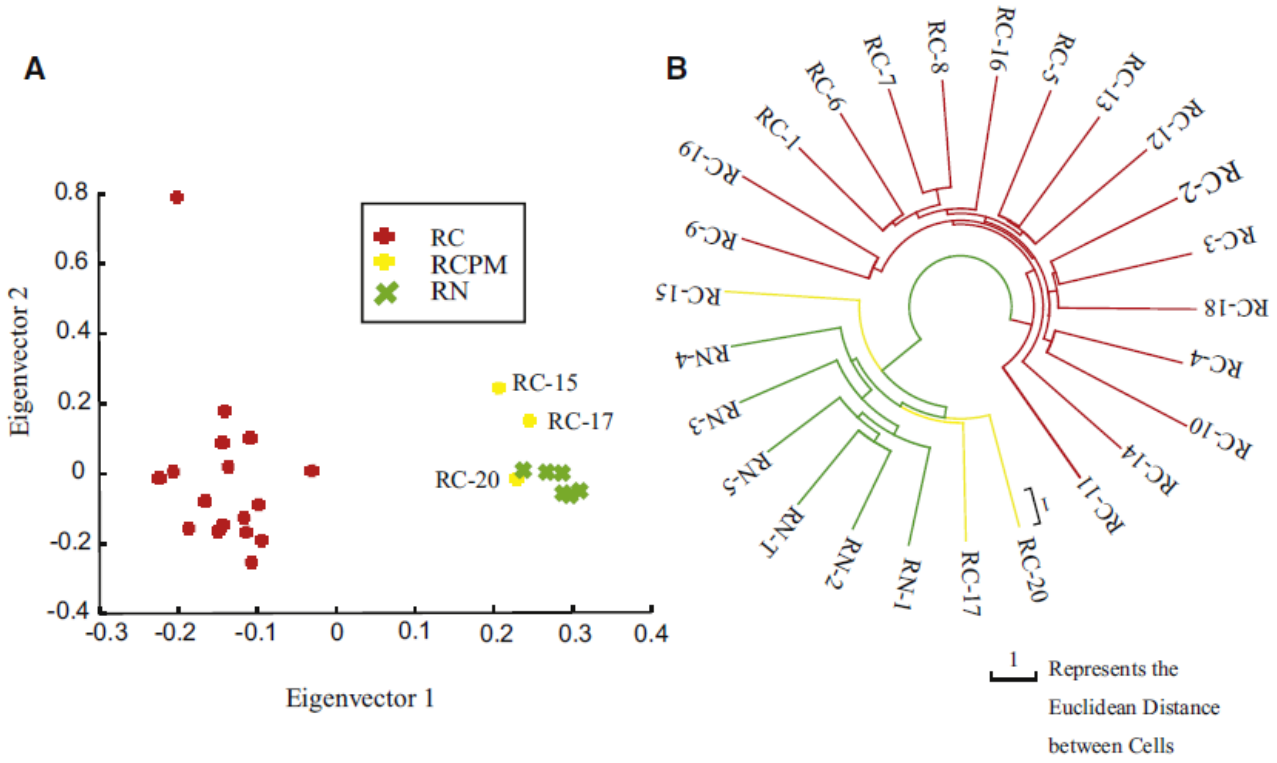
Intratumor heterogeneity and branched evolution revealed by multiregion sequencing



Gerlinger M, et al. N Engl J Med. 2012;366:883-92

Single-cell exome sequencing reveals single-nucleotide mutation characteristics of a kidney tumor

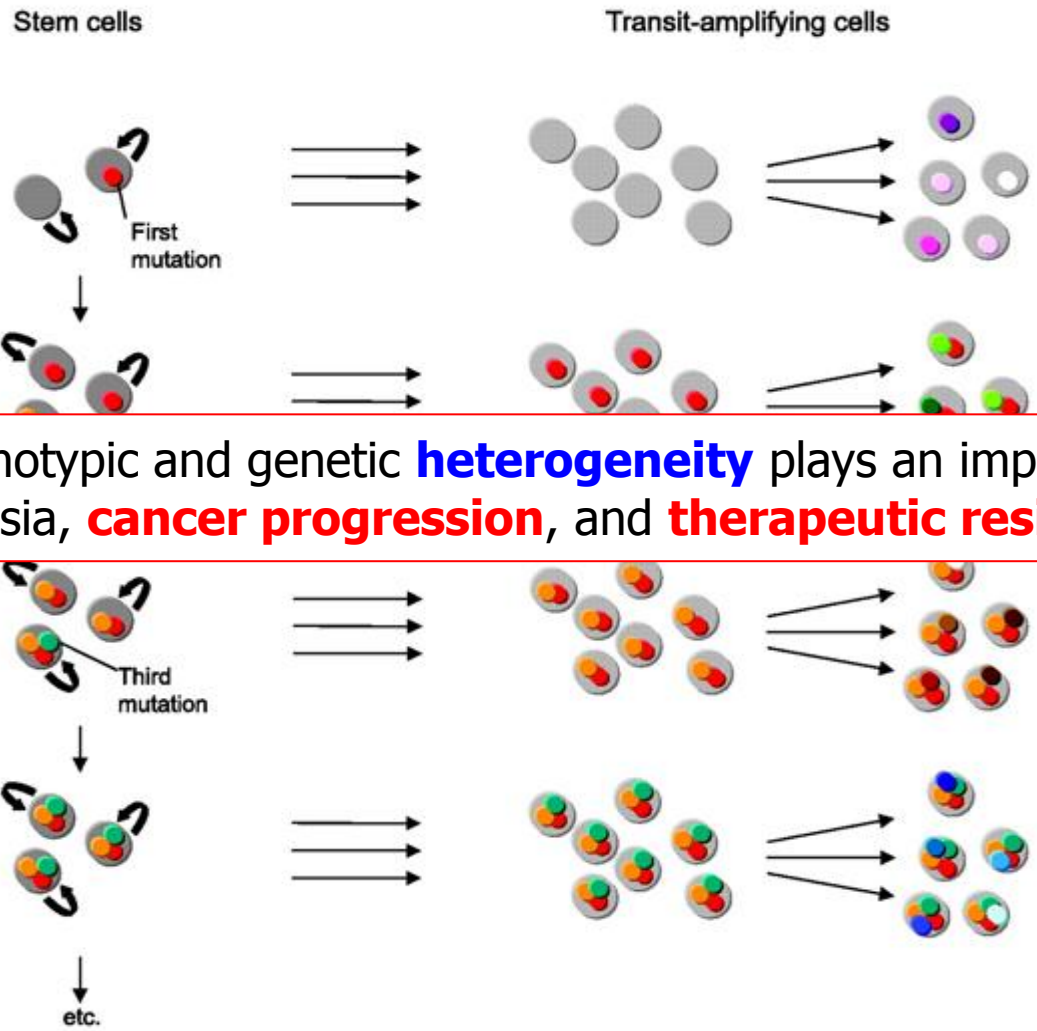
- A 59-year-old Chinese male with stage IV clear cell renal cell carcinoma (ccRCC)
- Isolation of single cells (20 cancer cells: RC1~20 and 5 normal cells: RN1~5) under inverted microscope
- Principle component analysis (PCA) mutation profiling on the 260 somatic mutation sites



(A) PCA of cancer cell (RC), normal control cell (RN), and normal cells picked as cancer cells (RCPM)
(B) Neighbor joining phylogenic tree constructed using sites of somatic mutation data by Euclidean distance
RN-T (normal tissue DNA) as control

Xu X, et al. Cell. 2012;148:886-95

Emergence and maintenance of tumor diversity
Intratumor heterogeneity



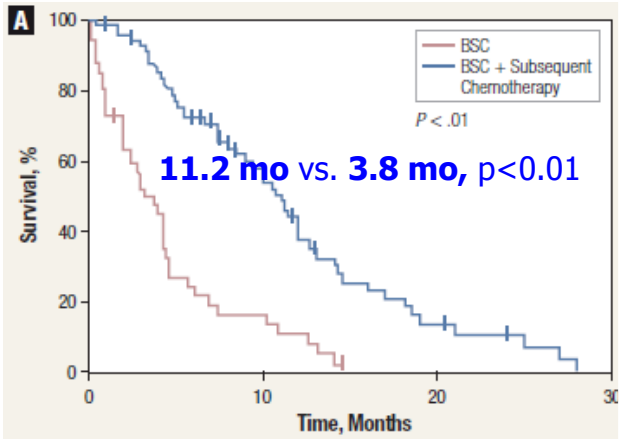
This phenotypic and genetic **heterogeneity** plays an important role in neoplasia, **cancer progression**, and **therapeutic resistance**!

Michor F, et al. Cancer Prev Res 2010;3:1361-4

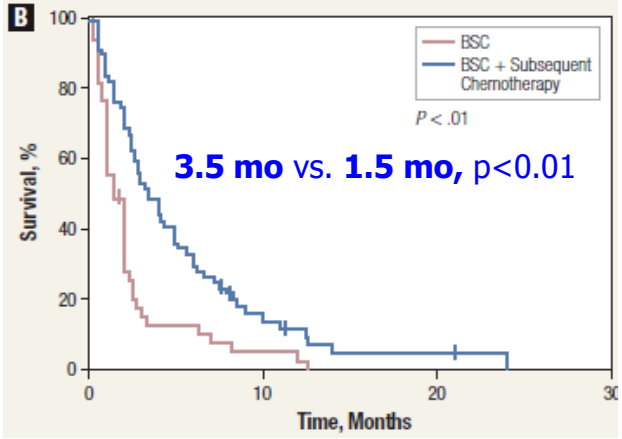
Subsequent chemotherapy improves survival outcome in advanced NSCLC with acquired TKI resistance

- A retrospective analysis in Taiwan
- 114 patients with stage IIIB-IV NSCLC, disease control on EGFR-TKI

Overall survival [TKI failure~Death]



Progression free survival [Subsequent chemotherapy]

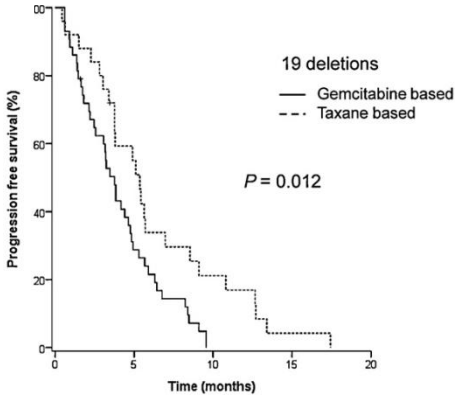


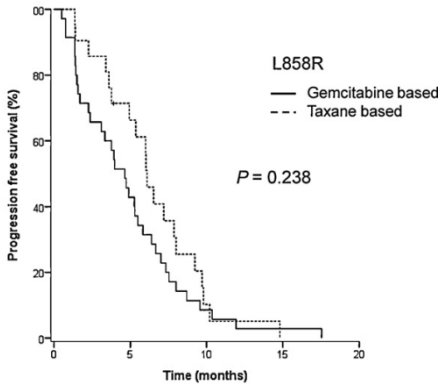
Kuo CH, et al. Clin Lung Cancer. 2010;11:51-6

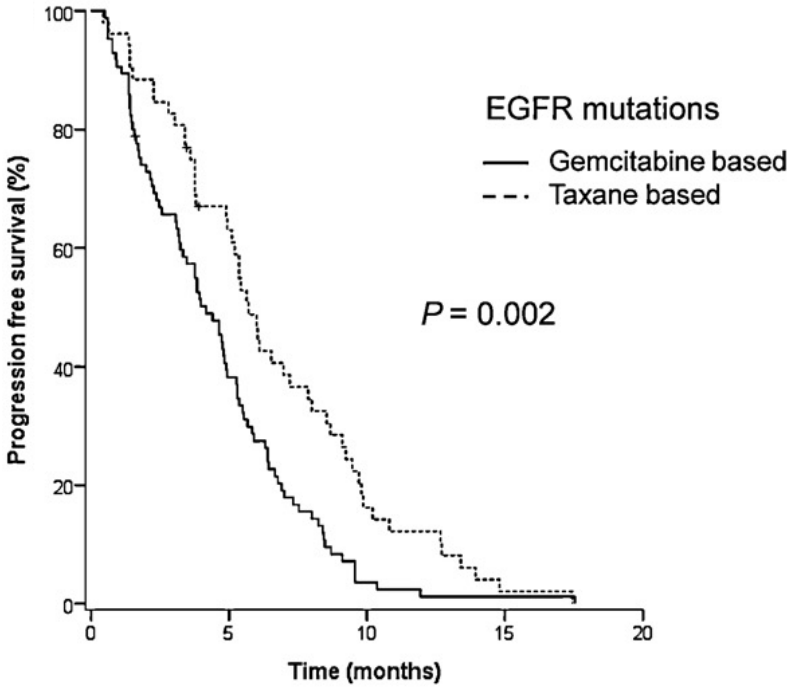
EGFR mutations as a predictive marker of cytotoxic chemotherapy

- A retrospective analysis, **1st-line chemotherapy**, Year 2005-2010, in Korea
- Advanced/metastatic NSCLC (n=217: ADC 174, SQC 4, Others 39)
- **Gemcitabine**-based **vs. Taxane-**based regimen**: ORR** and **PFS** according to **EGFR mutation status**

		GEM	TAX	P-value
Wild type EGFR	N	46	34	
	ORR	34.8%	35.3%	0.962
	DCR	78.3%	73.5%	0.623
	PFS	4.4mo	4.4mo	0.362
Mutant EGFR	N	85	52	
	ORR	30.6%	38.5%	0.344
	DCR	**71.8%**	**88.5%**	**0.022**
	PFS	**4.1mo**	**5.7mo**	**0.002**







Park JH, et al. Lung Cancer. 2012;77:433-7

Retreatment of patients with same chemotherapy: implications for clinical mechanism of drug resistance

- Advanced cancer patients **retreated with same chemotherapy** previously received
- **Retreatment** for the progressive disease **after complete remission**
- Medline review of 15 reports

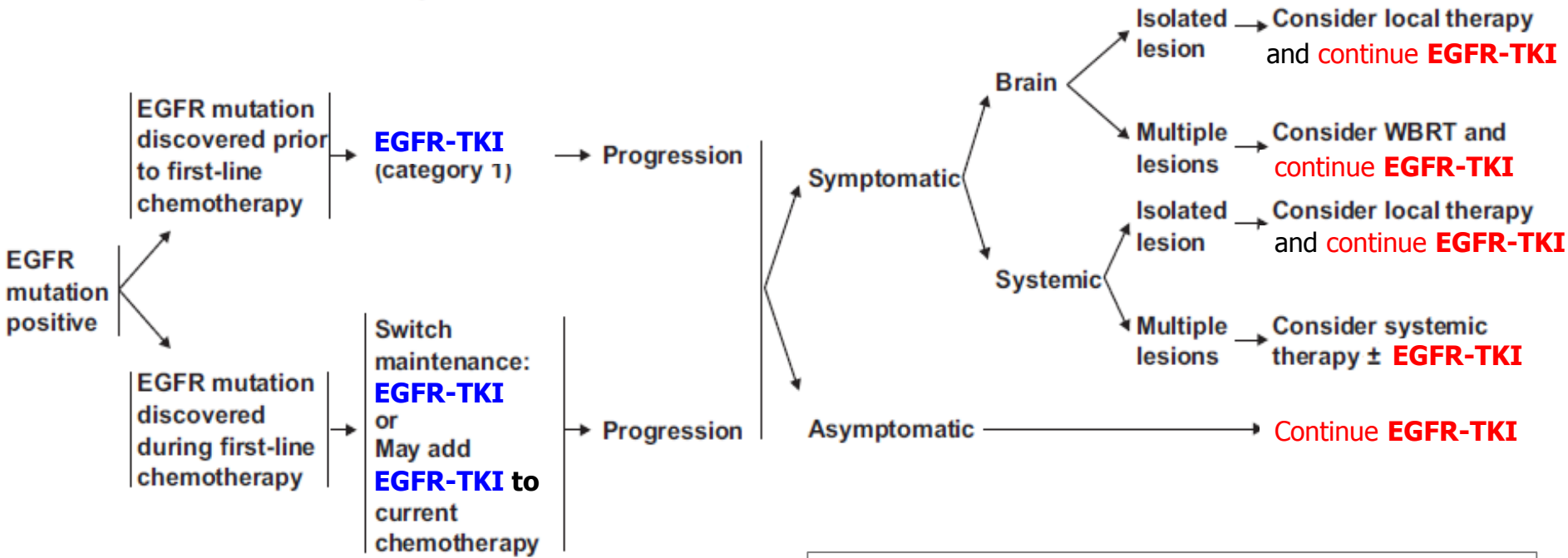
- Median off-treatment 48 weeks, **Response rate 18-100% (median 51%)**

Cancer type	Drug	Number	**Holiday**	**Response**	Duration
AML	Cytosine, ADR	24	31 wk	37% CR	13 wk
AML	Cytosine, daunorubicin	136	46 wk	51% CR	20 wk
Harry cell leukemia	Chlorodeoxyadenosine	4	76 wk	50% CR, 25% PR	72 wk
CML	Chrorodeoxyadenosine	6	58 wk	16% CR, 32% PR	-
Multiple myeloma	Melphalan, procabazine, PD, VCR	20	>48 wk	80% PR	-
HD					84 wk
Breast cancer					12 wk
SCLC					-
SCLC	Cytoxan, ADR, etoposide	37	34 wk	16% CR, 45% PR	26 wk
SCLC	Cytoxan, ADR, etoposide or VCR	12	30 wk	16% CR, 33% PR	19 wk
SCLC	Carboplatin, epirubicin, etoposide	6	58 wk	33% CR, 67% PR	-
Ovarian cancer	Platinum, paclitaxel	10	36 wk	30% CR+PR	10 wk
Ovarian cancer	Cytoxan, ADR, cisplatin, methylmelamine	11	88 wk	36% CR, 36% PR	38 wk
Colorectal cancer	5-FU, leucovorin	49	50 wk	18% CR+PR	21 wk
Urothelial cancer	MTX, VBL, ADR, cisplatin	8	52 wk	71% PR	-

Transient resistance to chemotherapy!

Cara S, et al. Ann Oncol. 2001;12:23-7

Summary



Flare phenomenon or **after EGFR-TKI holiday**, consider **retreatment with EGFR-TKI**!

Chemotherapy! **Singlet vs. platinum doublet?** **Taxane** seems to be more efficacious than non-taxane: if so**, taxane vs. pemetrexed?**


Thank you for your attention…