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Resistance to 3rd Generation EGFR TKI

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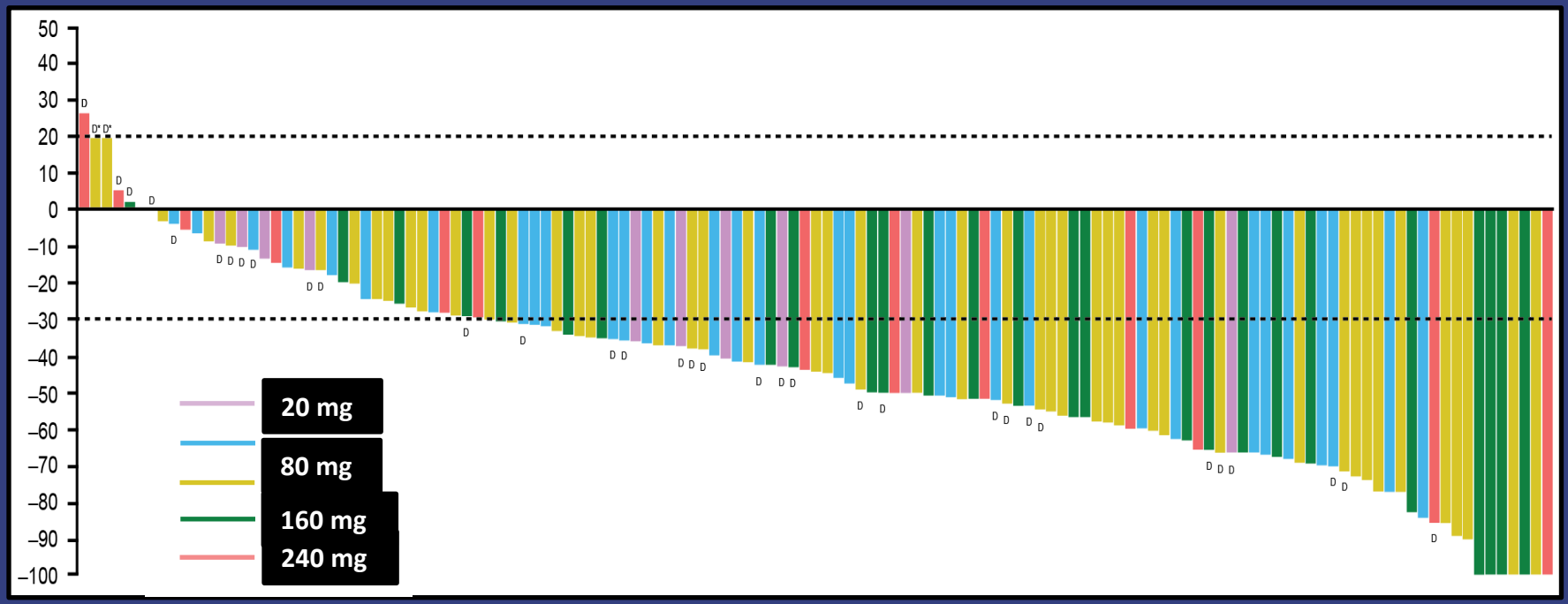
Disclosures

- Ad hoc advisory board
  - Astra Zeneca, Boehringer Ingelheim, Celgene, Genentech, Lilly, Bristol Myers Squibb, Novartis.

Outline

- Clinical activity of T790 Inhibitors
- Resistance mechanisms
- Strategies to overcome resistance
- Treatment algorithm for tertiary resistance

Osimertinib Activity in T790+ve Patients (N=138)



- Confirmed ORR in patients with centrally tested T790M+ tumours was 61% (78/127; 95% CI 52%, 70%)
- Disease control rate (CR+PR+SD) was 95% (121/127; 95% CI 90%, 98%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (127)	10	32	43	28	14
ORR	50%	59%	70%	61%	50%

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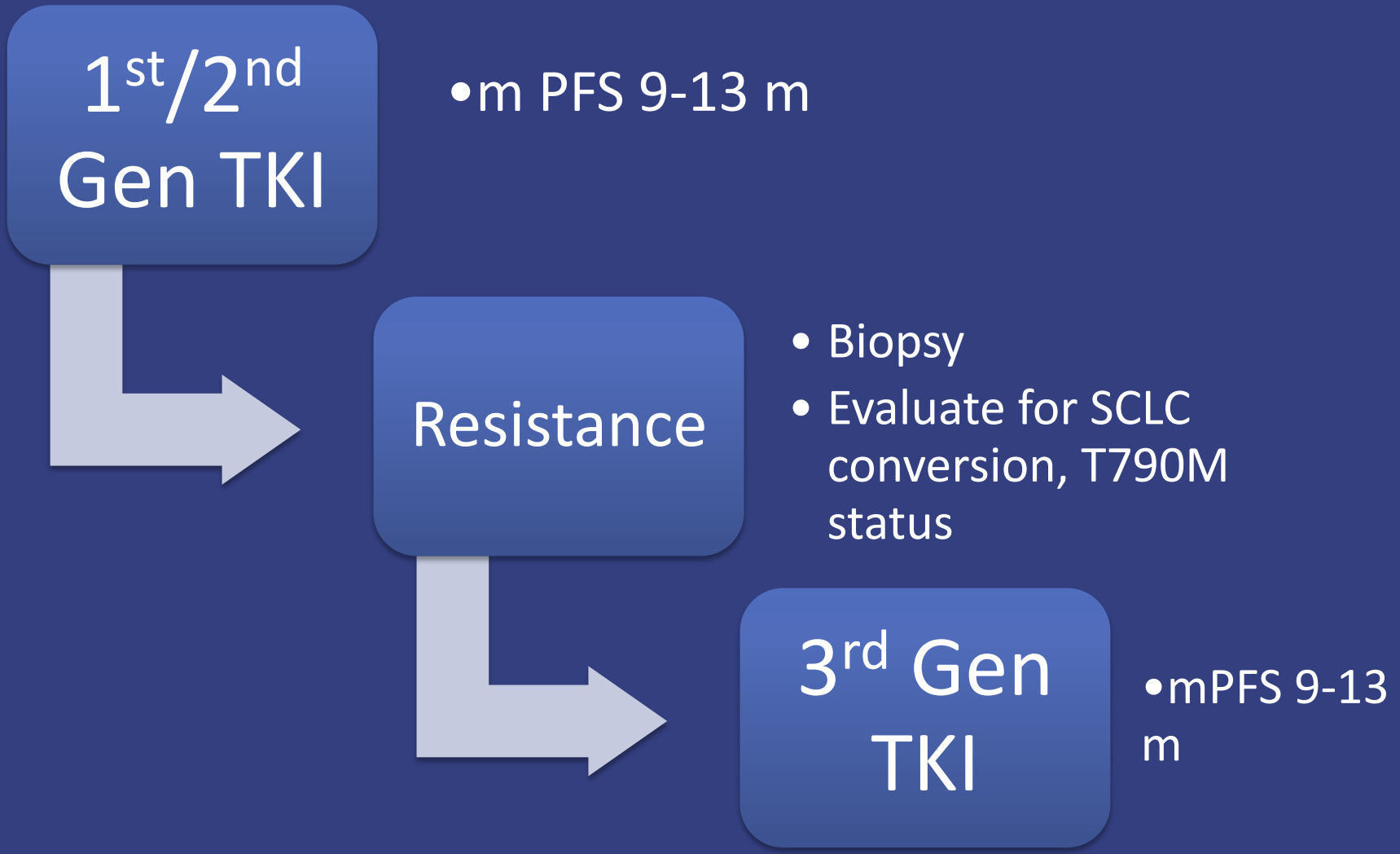
Janne et al, N Engl J Med, 2015

Update on Clinical Outcomes

- LBA2: Osimertinib in pre-treated patients with T790M positive advanced NSCLC: Updated Phase 1 and pooled Phase 2 results.
  - Yang, Ramalingam, Janne, Cantarini, Mitsudomi, et al.
  - April 14, 3.45-4.00 PM

Current Treatment Paradigm for EGFR Mt+ NSCLC



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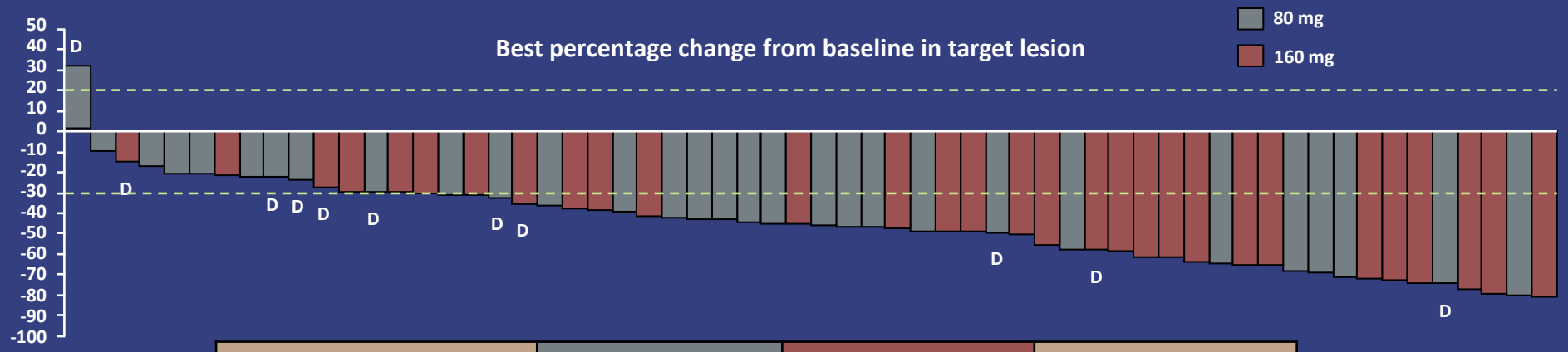
Osimertinib as First-line Therapy for EGFR Mt NSCLC



	80 mg N=30	160 mg N=30	Total N=60
Objective response rate*	**63% (95% CI 44, 80)**	**83% (95% CI 65, 94)**	**73% (95% CI 60, 84)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Best objective response			
Complete response*	0	1	1
Partial response*	19	24	43
Stable disease	9	5	14
Progressive disease	2	0	2

Population: evaluable for response, data cut-off April 15, 2015
Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), programmatically calculated from investigator-recorded tumor measurement
*Confirmed responses only
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; SD, stable disease

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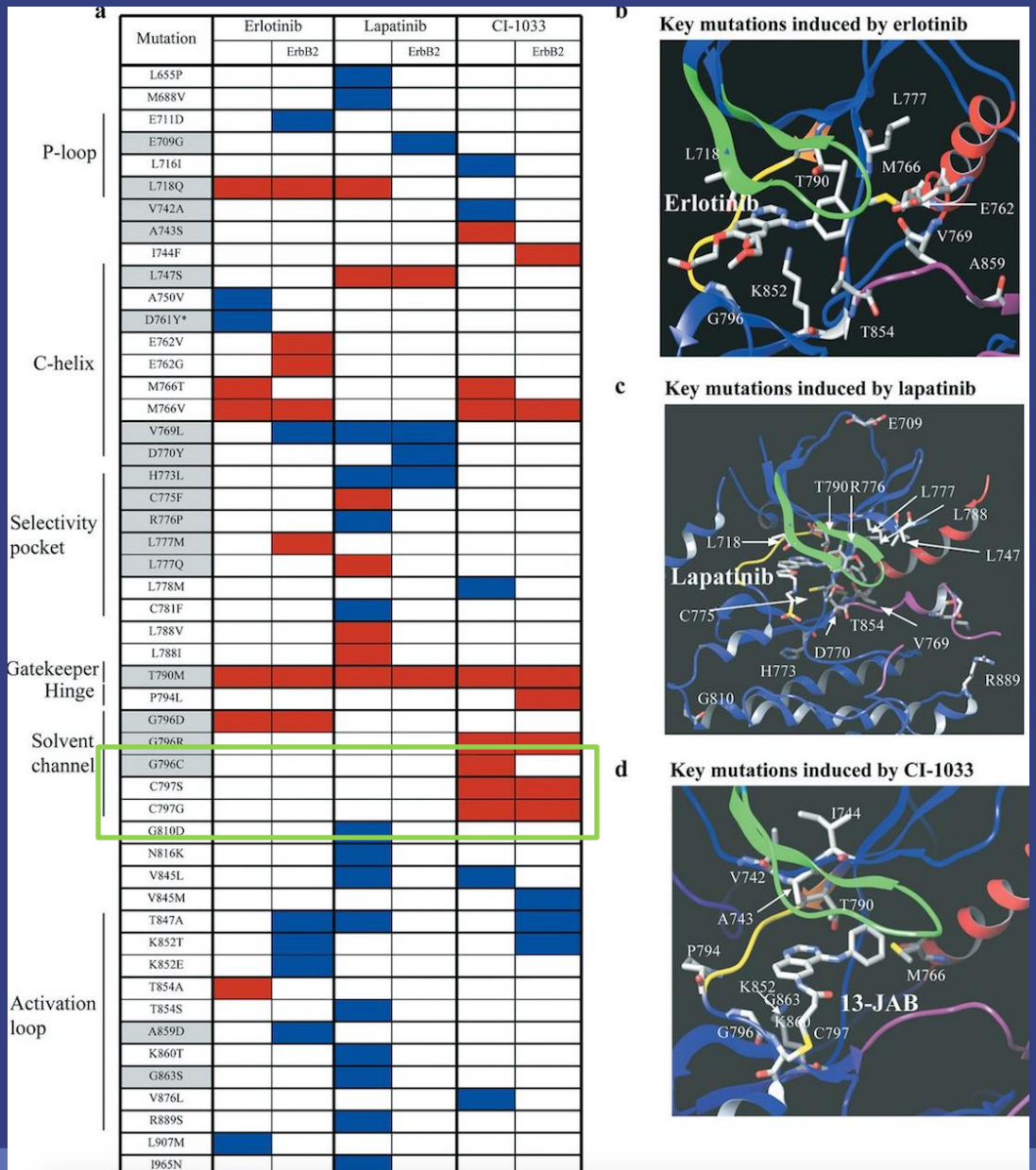
Ramalingam et al, ASCO 2015

Updated First-line Results

- LBA1: Osimertinib as first-line treatment for EGFR mutation positive advanced NSCLC: Updated efficacy and safety results from two phase 1 expansion cohorts
  - Ramalingam, Yang, Lee, Kurata, kim, John, Nogami, Ohe, Janne.
- April 14, 3.30-3.45 PM

EGFR Resistance Profile



Avizienyte et al, Biochemical J, 2008

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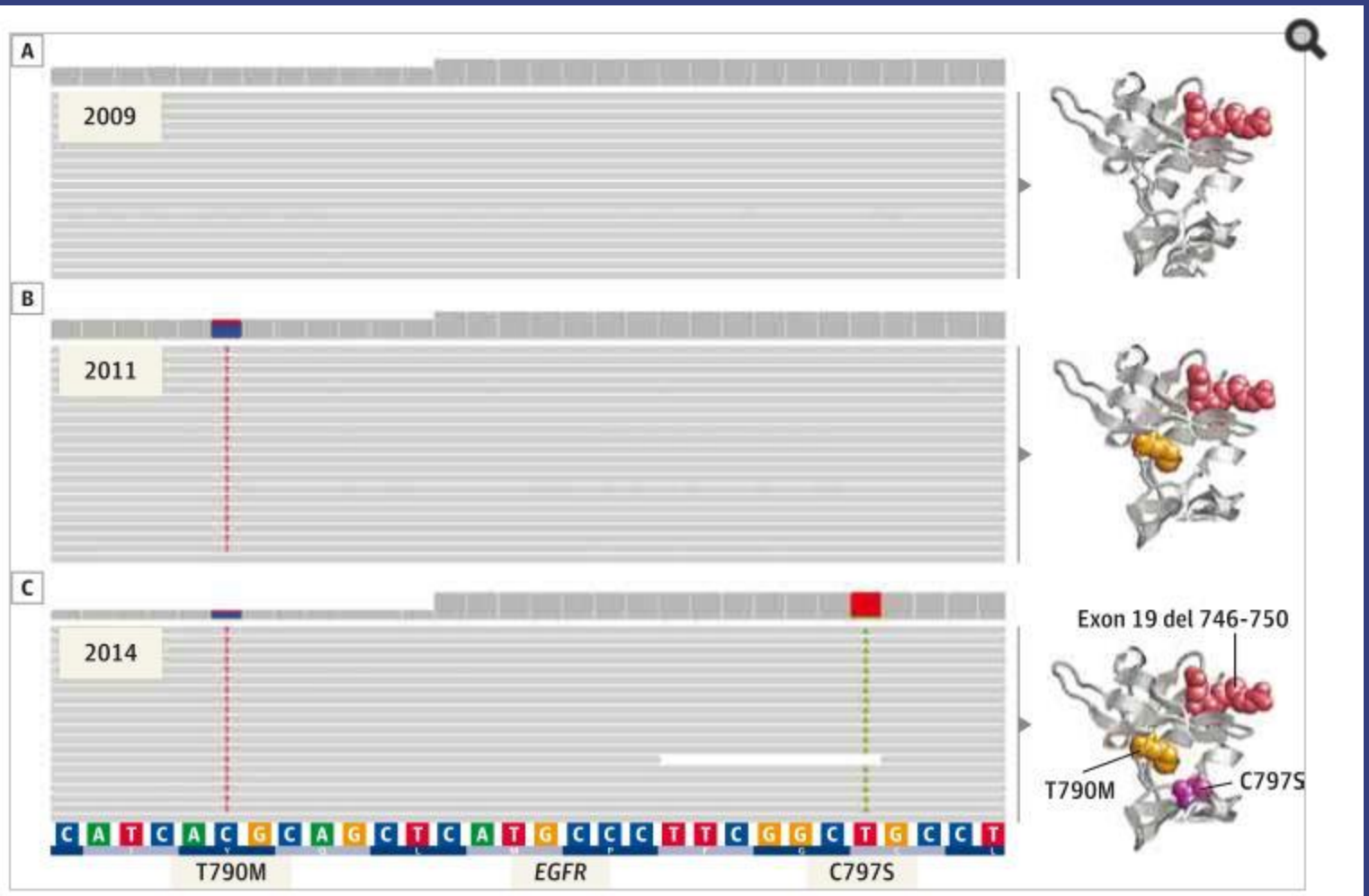
Numerous ErbB family irreversible inhibitors are currently being investigated as a method to overcome clinical resistance driven by the T790M mutation of EGFR [28]. Our screening data with the irreversible inhibitor CI-1033 indicates that clinical resistance to this class of inhibitor is possible and we expect that incidences of EGFR-Gly^{796} and -Cys^{797} mutations will be reported in the clinic following prolonged exposure to irreversible inhibitors. Interestingly, alignment of the ErbB2 and EGFR kinase domains indicates that many of the lapatinib- and CI-1033-resistance residues are conserved in ErbB2 (Supplementary Figure S4). This suggests that clinical resistance (either acquired or intrinsic) due to ErbB2 mutations is a likely possibility in ErbB2-driven tumours treated with either lapatinib or irreversible inhibitors. Based upon the present study, we predict that ErbB2-Cys^{805} will be observed in response to irreversible inhibitors, whereas lapatinib will yield a broad range of mutations that will probably include the gatekeeper (ErbB2-Thr^{798}) and residues clustered deep in the selectivity pocket.

Avizienyte et al,Biochemical J, 2008

Acquired Resistance to Osimertinib



Mutation Analysis of Exon 20 of *EGFR* in the 2009, 2011, and 2014 Tumor Samples

Yu et al, JAMA Oncol, 2015

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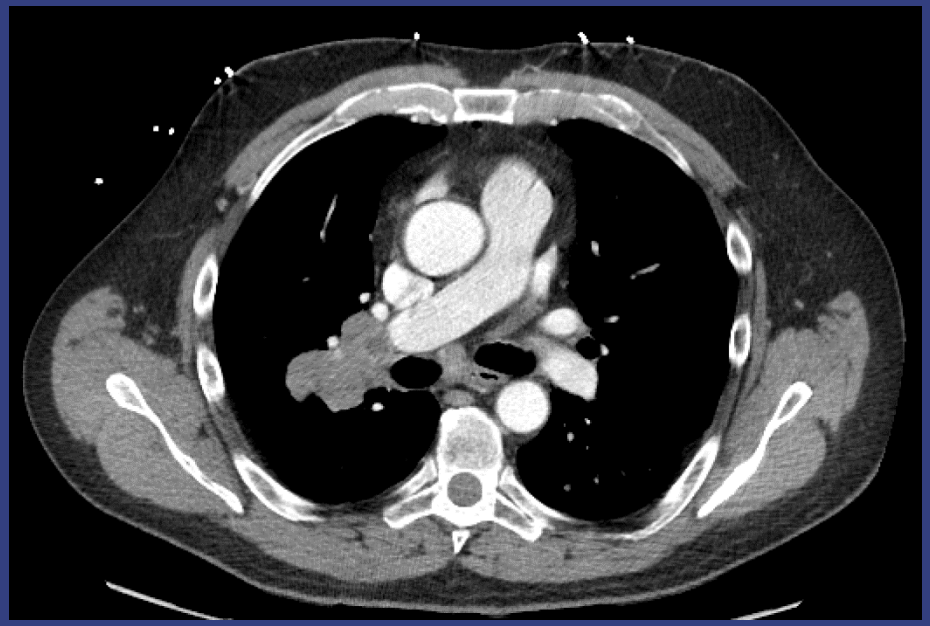
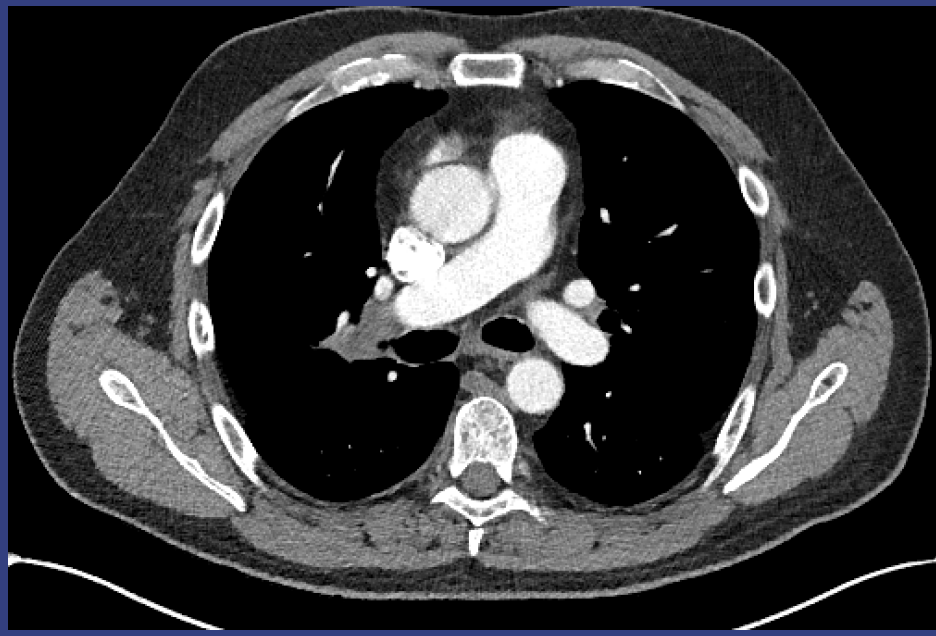
Patient # 1

- 64/M, diagnosed with stage IV lung adeno in Sept' 12
- Exon 19 mutation positive
- Sept'12- Nov'13: Erlotinib
- Dec'13- July'14: Dacomitinib
- T790 +ve



Sept' 2013



Oct 2013

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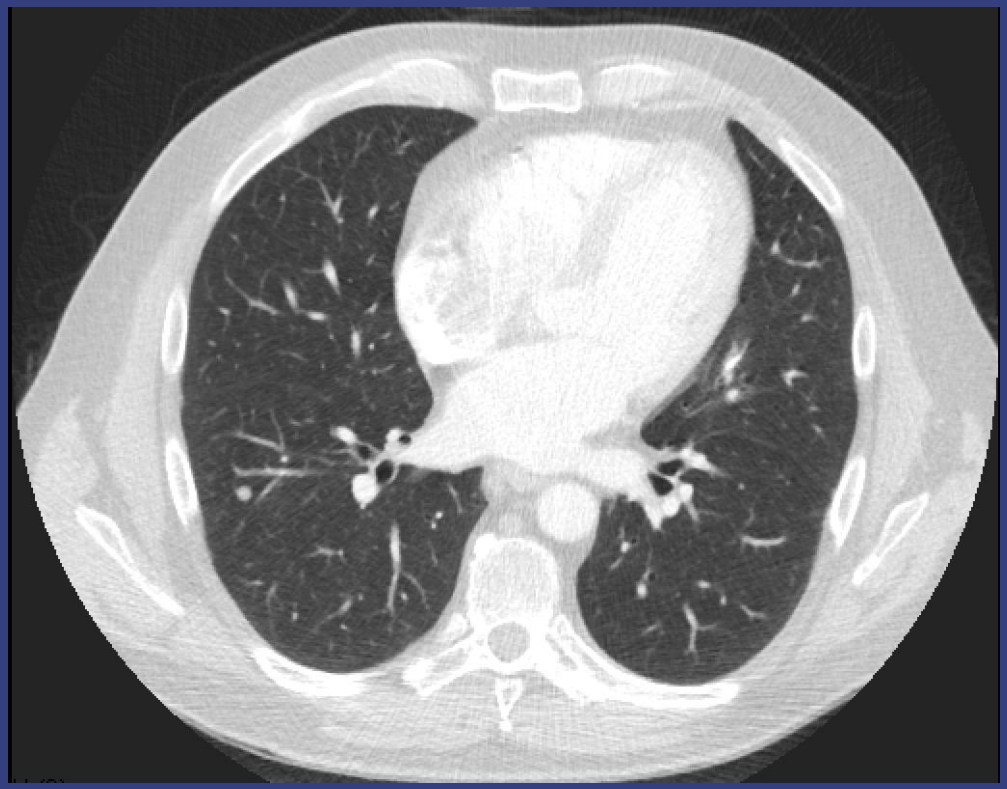
Gradual Progression



- Plasma cfDNA positive for c787S
- Osimertinib was continued
- Patient continues to have gradual PD

June 2014

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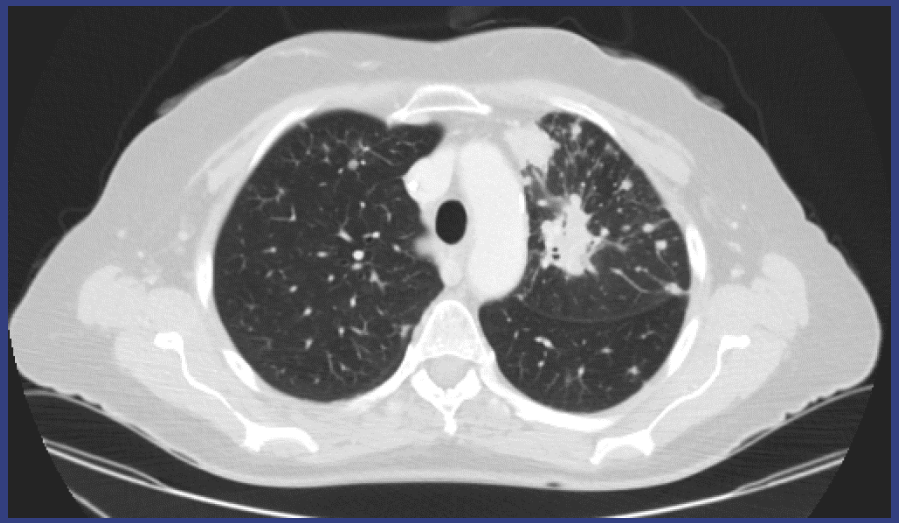
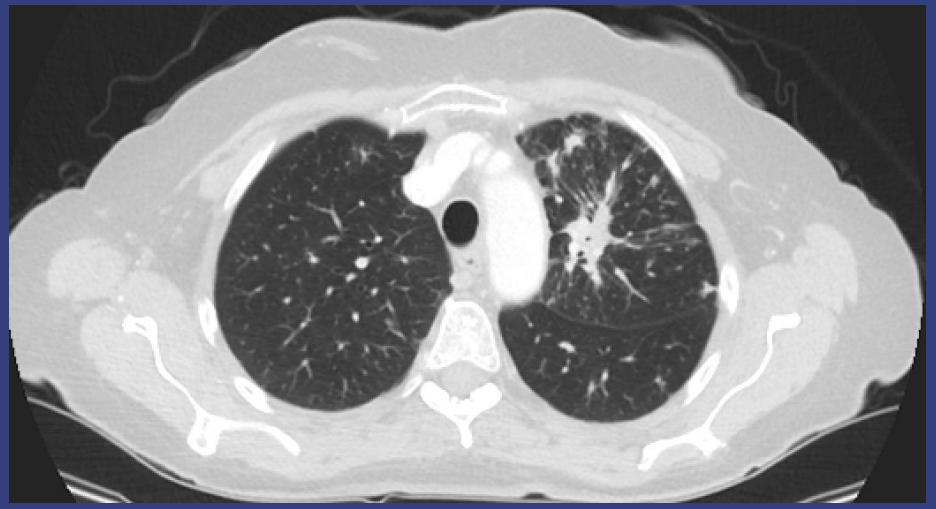
Patient # 2

- 72/F, Diag with Stage IV Lung Adeno in June 2013
- L858R +ve
- June – Aug 2013: Carboplatin + Pemetrexed X 4 cycles
- Sept-March 2014: Erlotinib
- T790+ve- treated with Osimertinib



March 2014



June 2014

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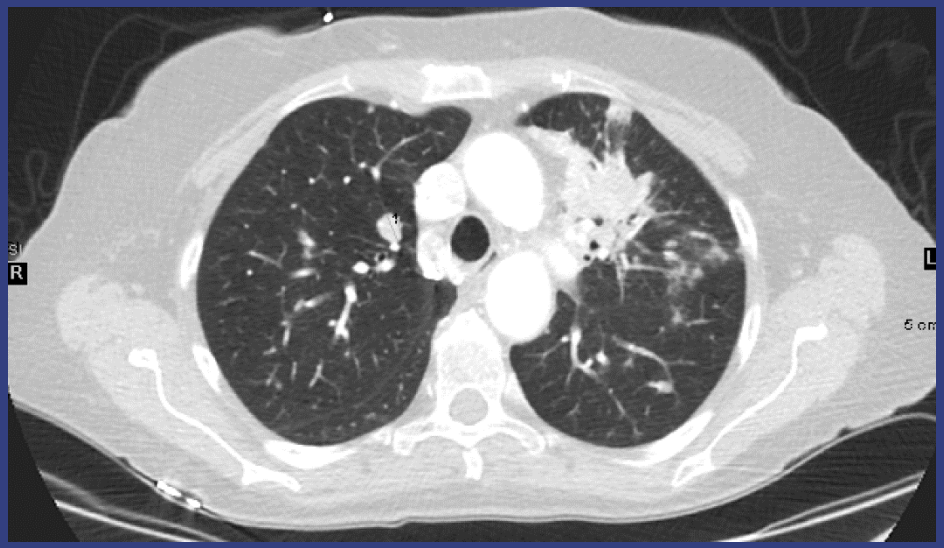
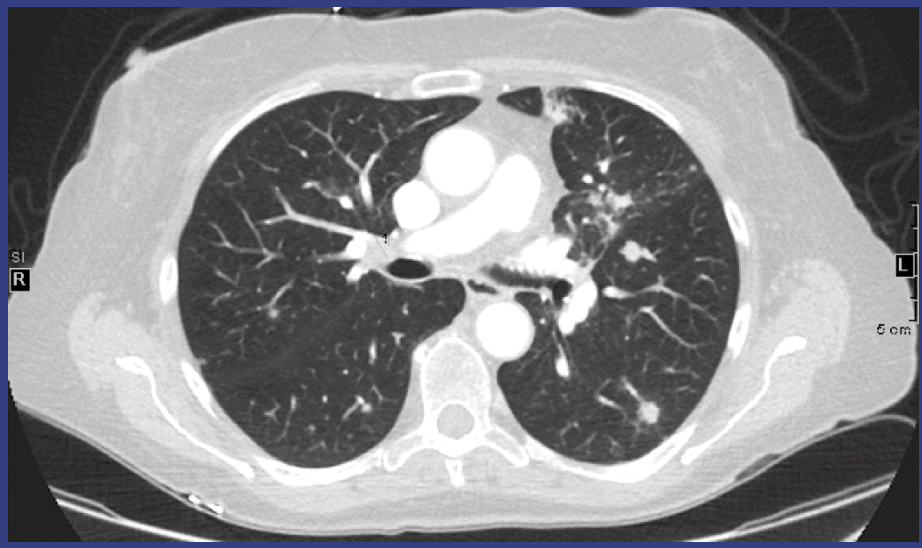
Disease Progression: Widespread Pattern

- Biopsy at progression negative for T790M
- CMET amplificition present





September 2014

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Acquired Resistance to Osimertinib

- Plasma from 67 T790M-positive cases from AURA
- 15 (22%) developed acquired EGFR C797S
- 32 (48%) have loss of T790M at resistance
- Loss of T790M can be mediated by overgrowth of a competing resistance mechanism: MET amp, HER2 amp, BRAF V600E

Oxnard et al, WCLC, 2015

Acquired Resistance to Osimertinib

N=15 Pts

Acquired Resistance to AZD9291

cfDNA testing

Droplet digital PCR

c797S mutation

N=6

T790M present

C797s –ve

N=5

Only original activating mutation

N=4

Thress et al, Nat Med, 2015

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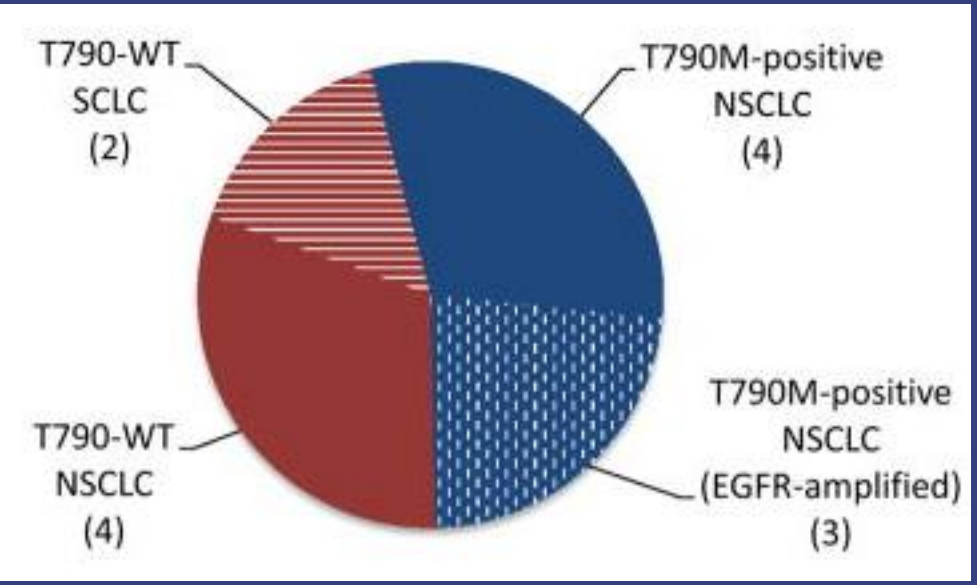
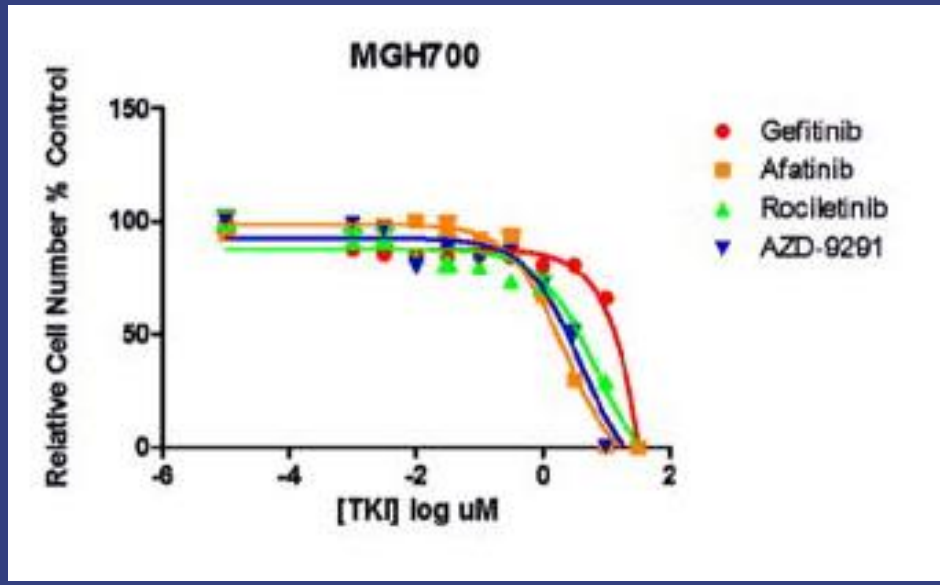
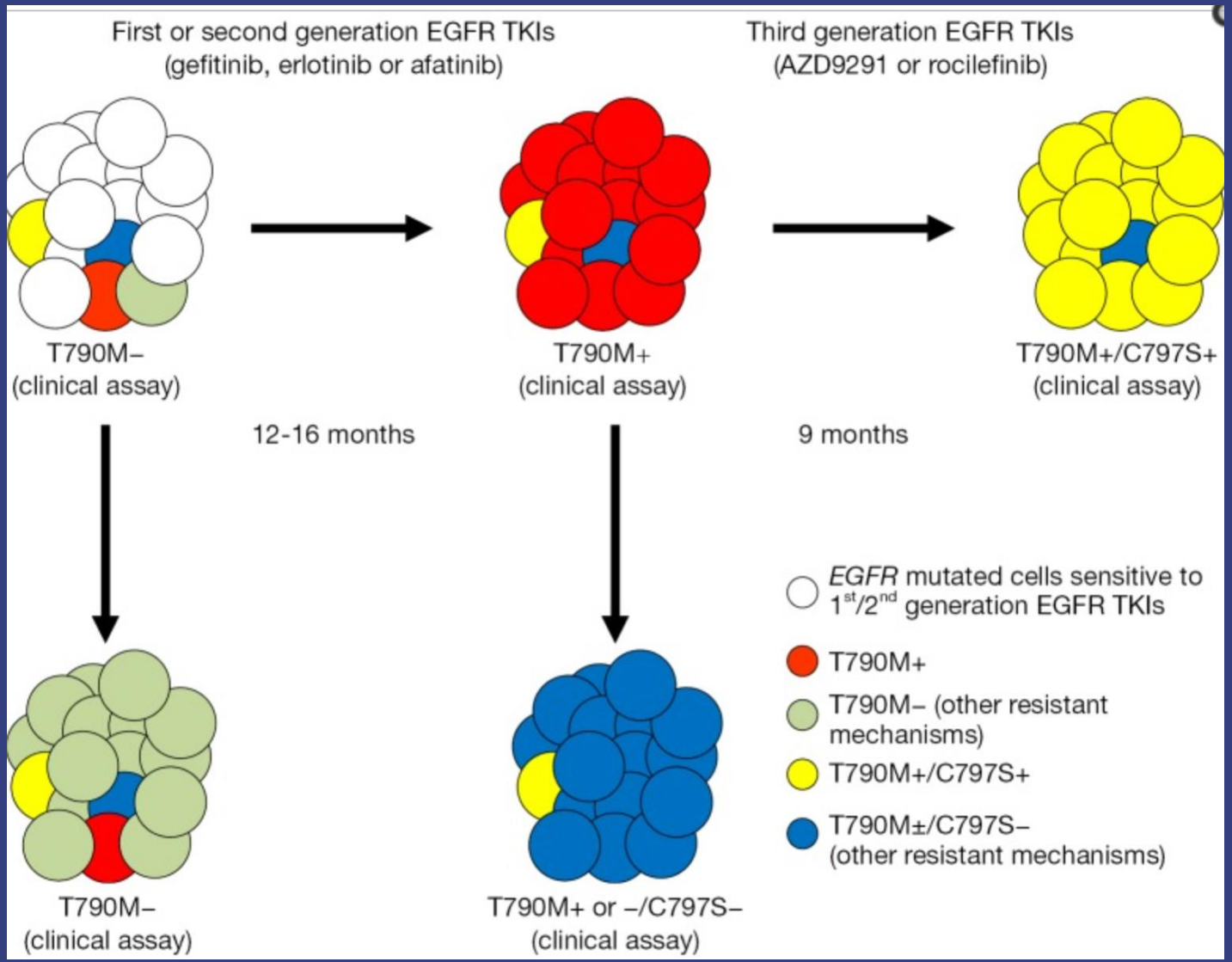
Resistance to Rociletinib





Piotrowska et al, Cancer Discovery, 2015

Evolution of Resistance



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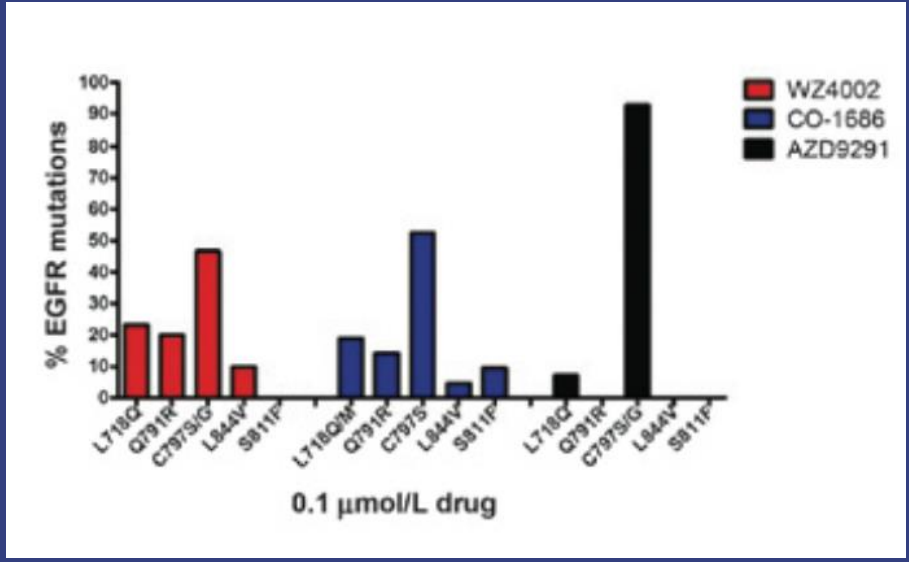
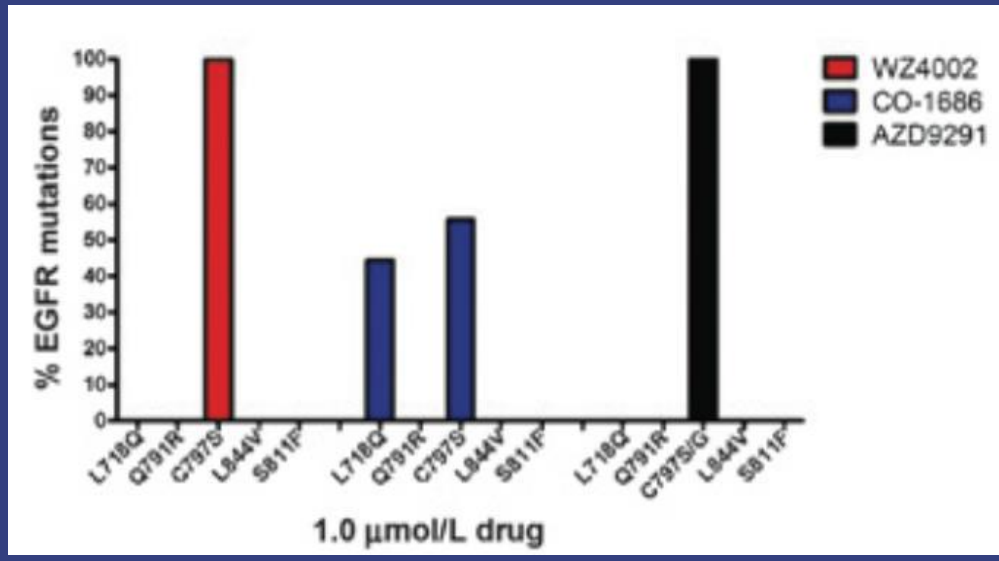
Costa & Kobayashi, Transl Lung Cancer Res, 2015

Resistance to Irreversible Inhibitors





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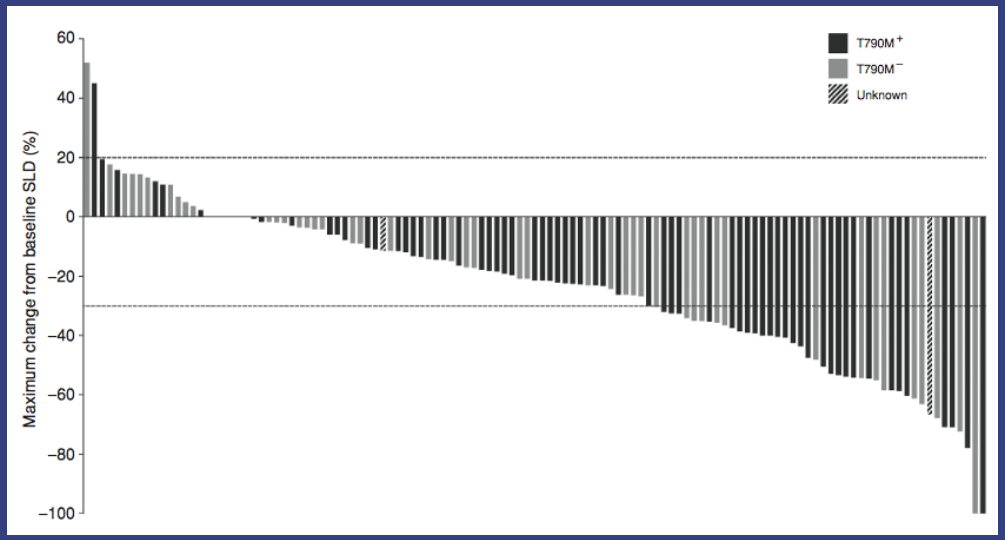
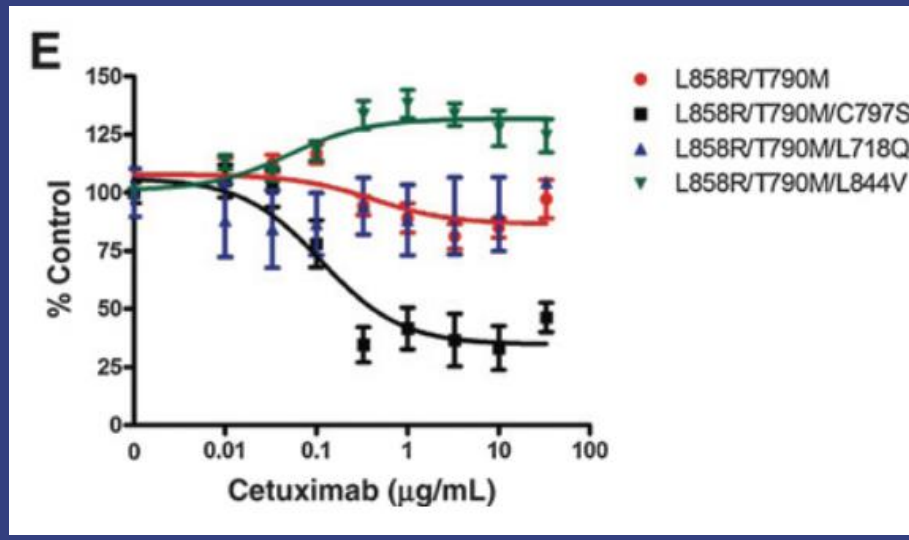
Ercan et al, Clin Cancer Res, 2015

Therapeutic Implications





Afatinib-Cetuximab in EGFR mt+ Pts

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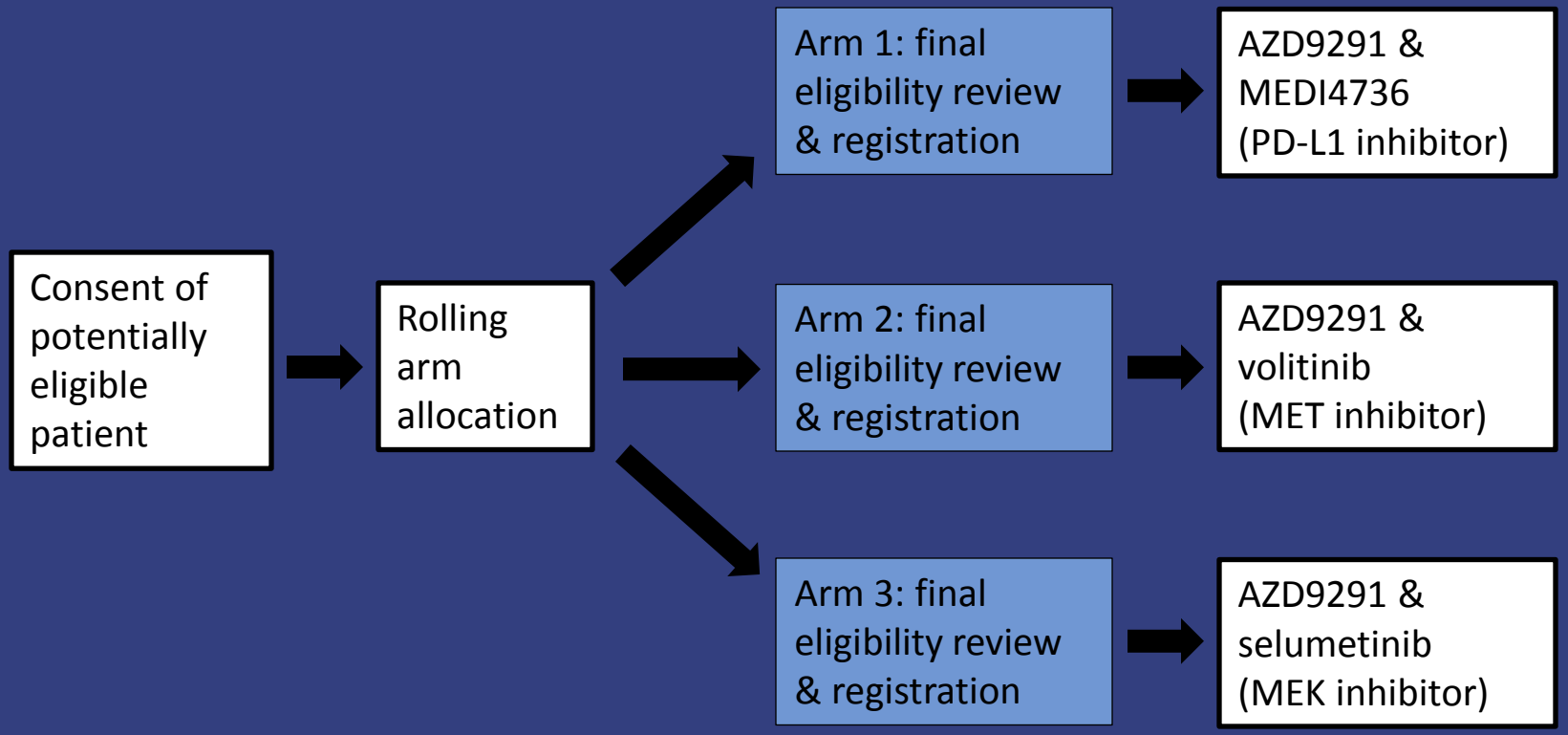
Ercan et al, Clin Cancer Res, 2015
Janjigian et al, Cancer Discovery, 2014

Other Reported Mechanisms of Resistance

- ERK activation
  - Tricker et al, Cancer Discovery, 2015
- MET activation
- Conversion to SCLC

Combination Approaches

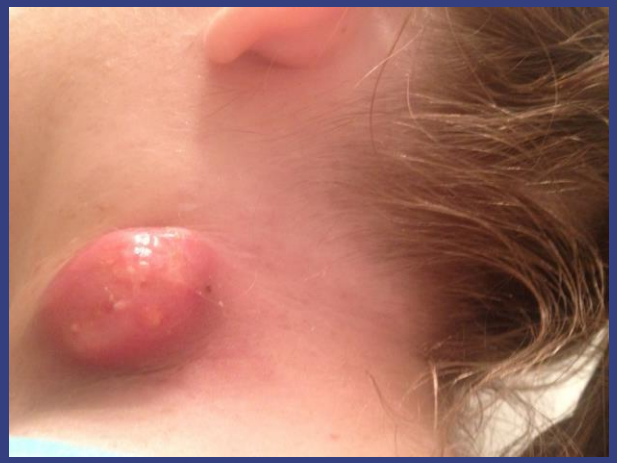
- **Phase IB trial of AZD9291 combined with novel targeted therapies**

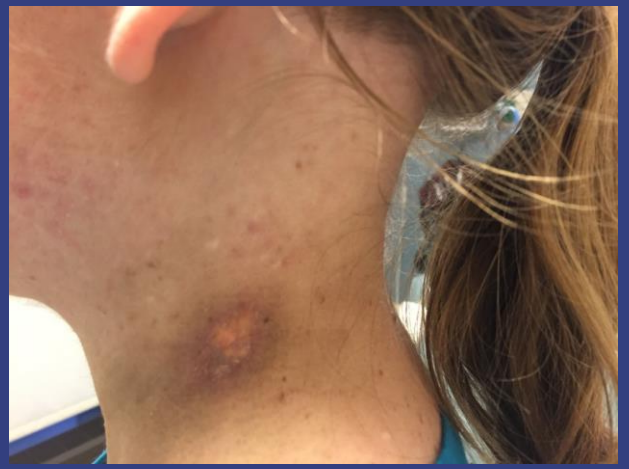


Oxnard et al, ASCO, 2015

TATTON study

- **Dramatic response to AZD9291 & Savolitinib in a patient with T790M neg, MET amplified resistance to EGFR TKI**





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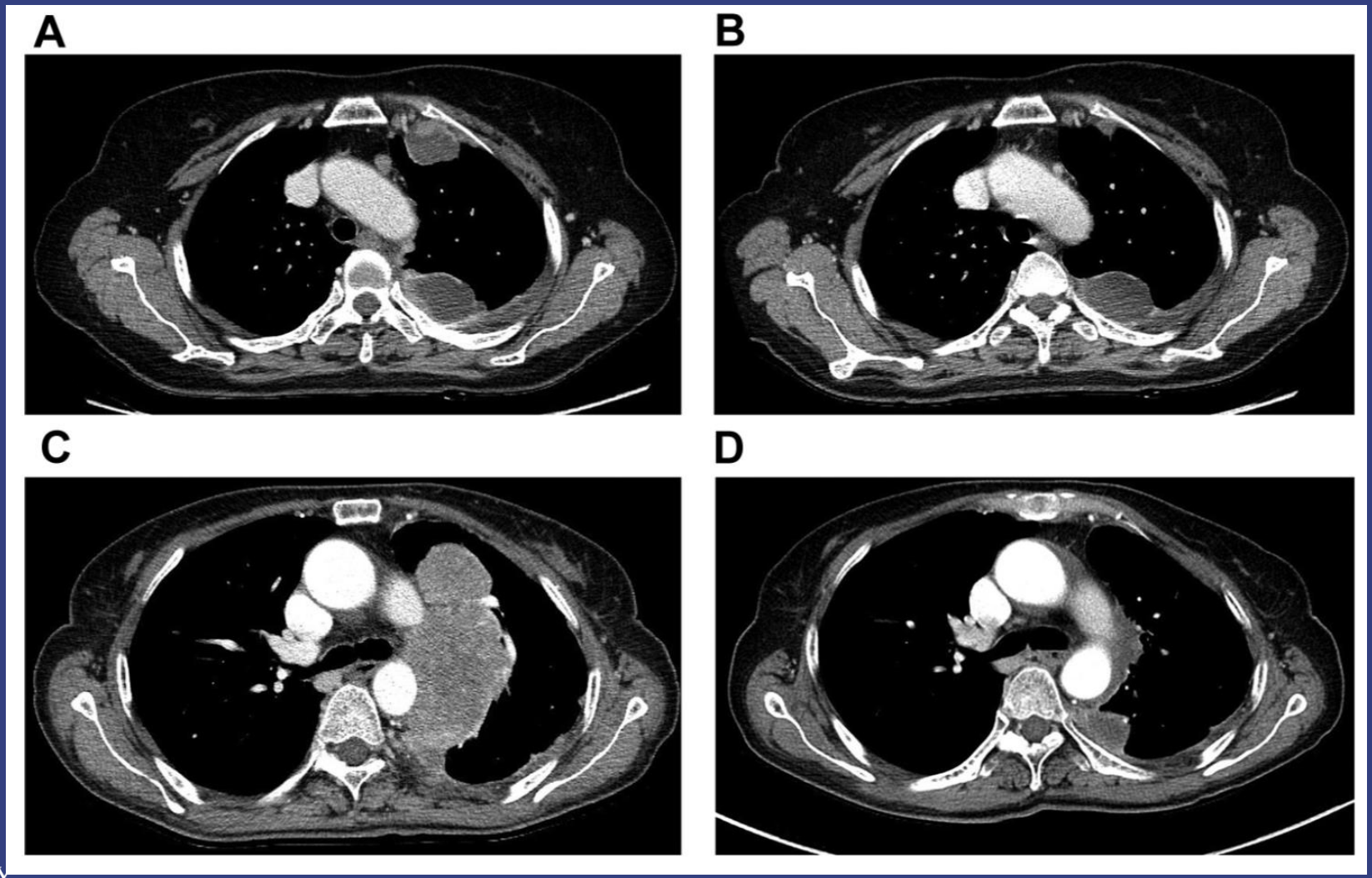
Oxnard et al, ASCO, 2015

Conversion to SCLC Following Osimertinib



Ham et al, J Thorac Oncol, 2015

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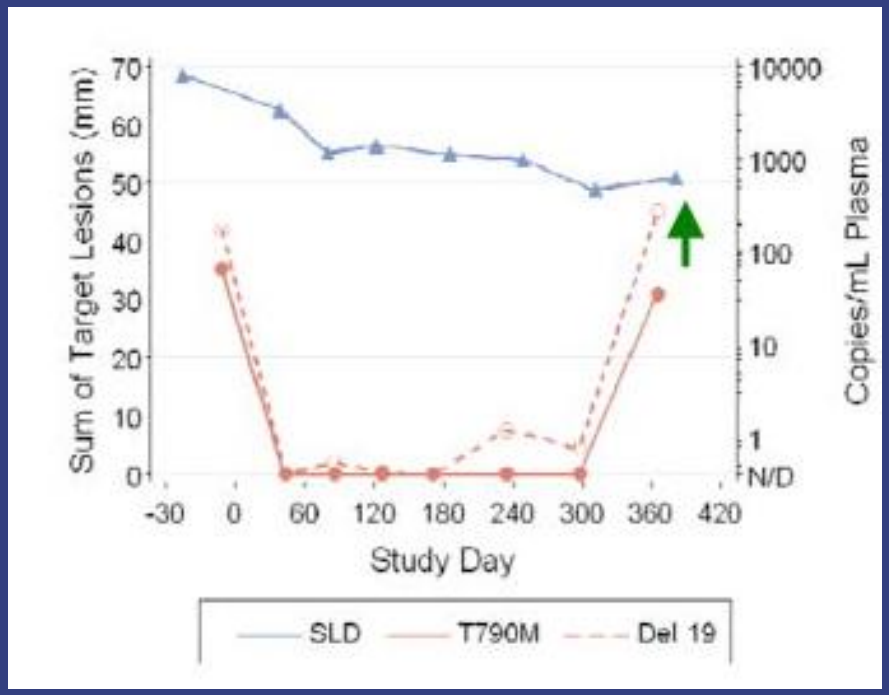
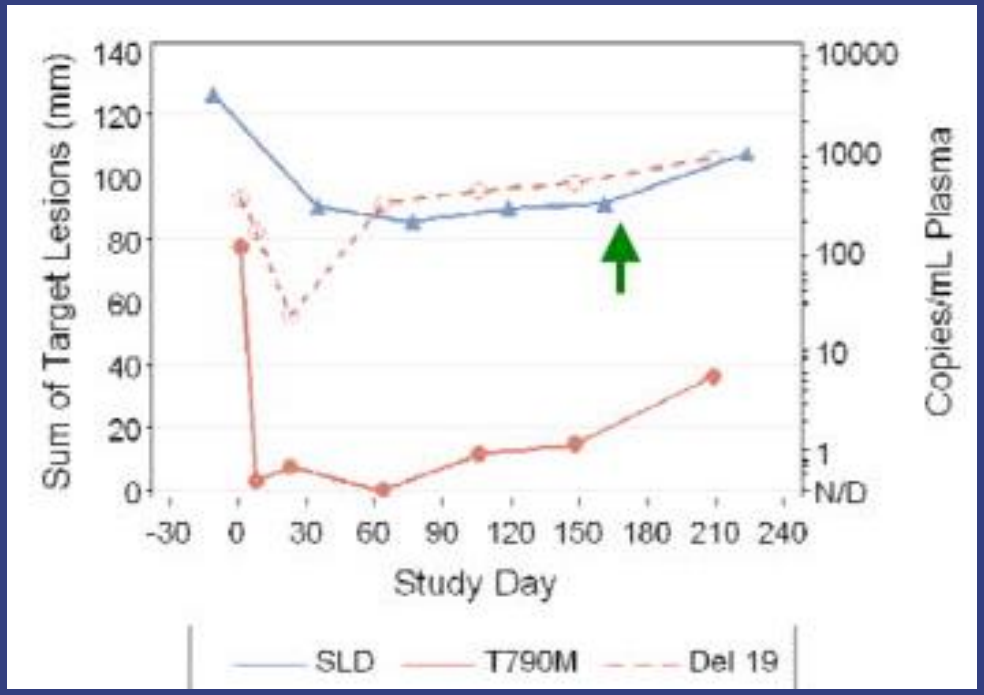
Monitoring Resistance by cfDNA





Piotrowska et al, Cancer Discovery, 2015

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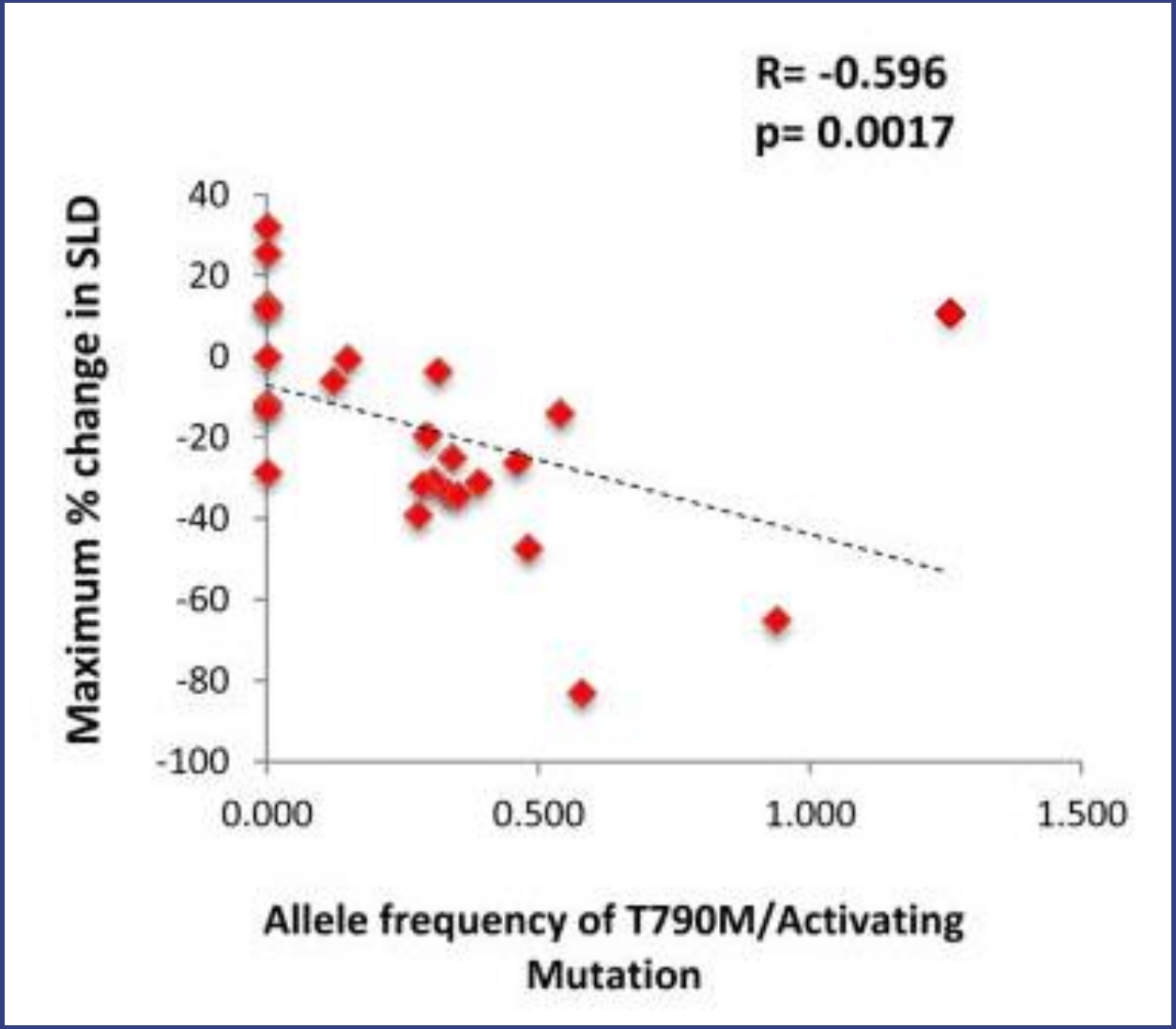
Correlation Between Response and T790M Allele Frequency



Piotrowska et al, Cancer Discovery, 2015

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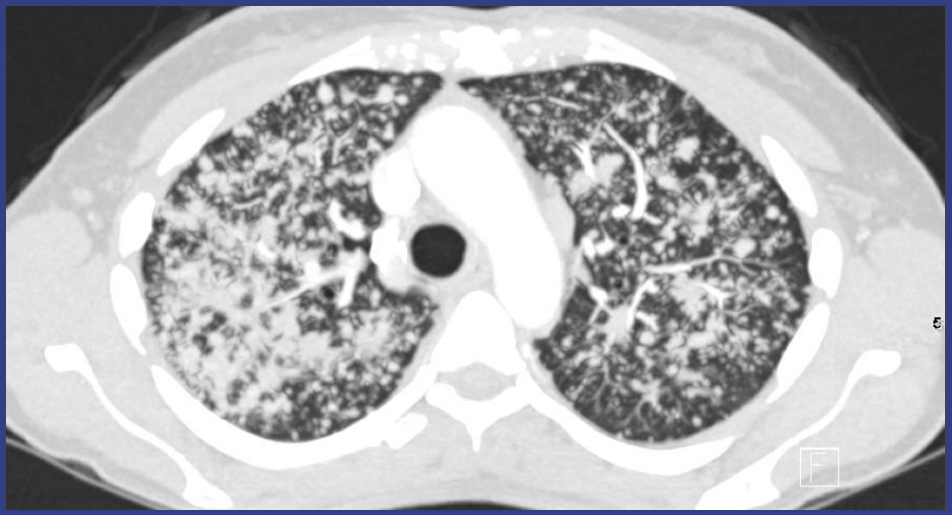
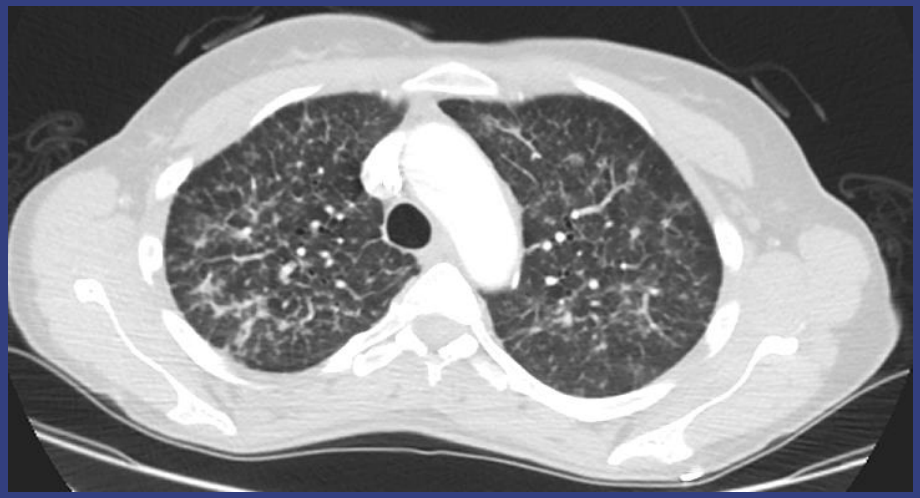
Combination with Immune Checkpoint Inhibitors

60/F, EGFR L858R, S/P erlotinib for 20 months; S/P afatinib 4 months; Repeat biopsy negative for T790M

Enrolled to 'AZD9291 + MEDI 4736 on Phase IB Study of AZD9291 with Ascending Doses of Novel Therapeutics in Patients with EGFRm+ Advanced NSCLC (TATTON)'



Feb 17, 2015
Baseline



Apr 13, 2015
S/P 2 cycles

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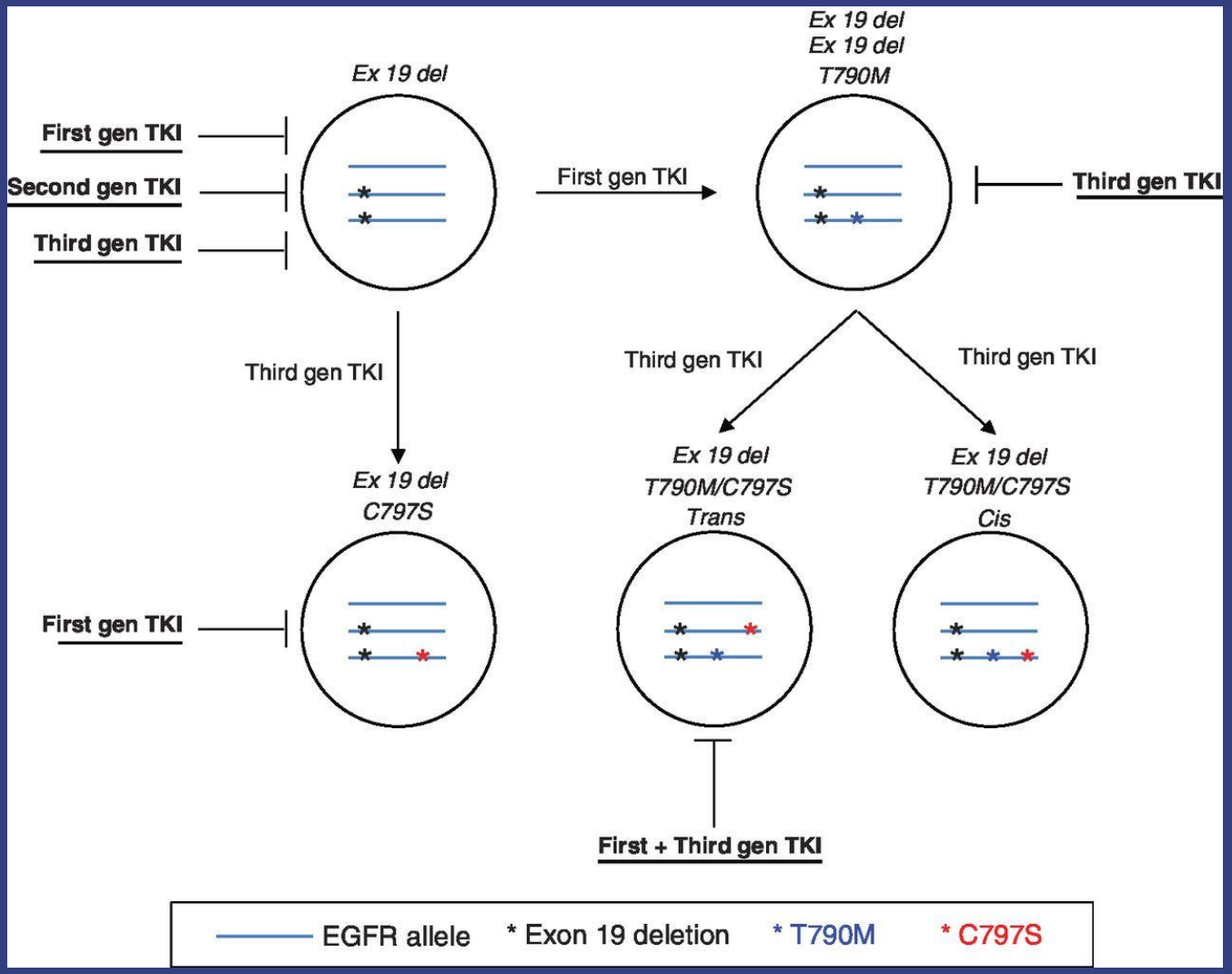
EGFR resistance mutations in response to TKI treatment



Matthew J. Niederst et al. Clin Cancer Res 2015;21:3924-3933

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Resistance: Key Questions

- Determinants of primary versus secondary resistance
- Resistance mechanism based on main EGFR mutation type (exon 19 vs. 21)
- Pattern of progression
  - Localized versus widespread?
  - CNS disease?

Conclusions

- Tertiary C797S mutation confers resistance to T790 inhibitors
- Prevalence of C797S is not well-defined, though it appears that only a third of the patients develop this
- Slow progressors can be continued on therapy with T790 inhibitors
- Utility of plasma cfDNA testing as surveillance remains to be studied