Interesting Case of Chemotherapy

Eun Young Kim

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Department on Internal Medicine
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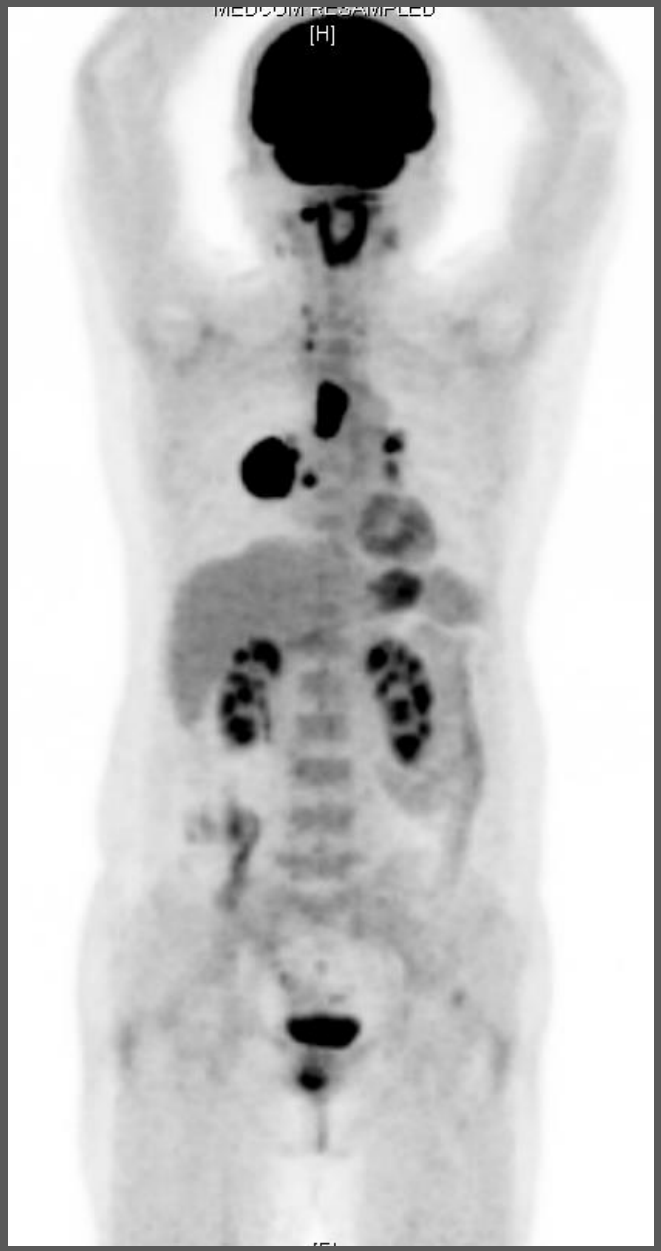
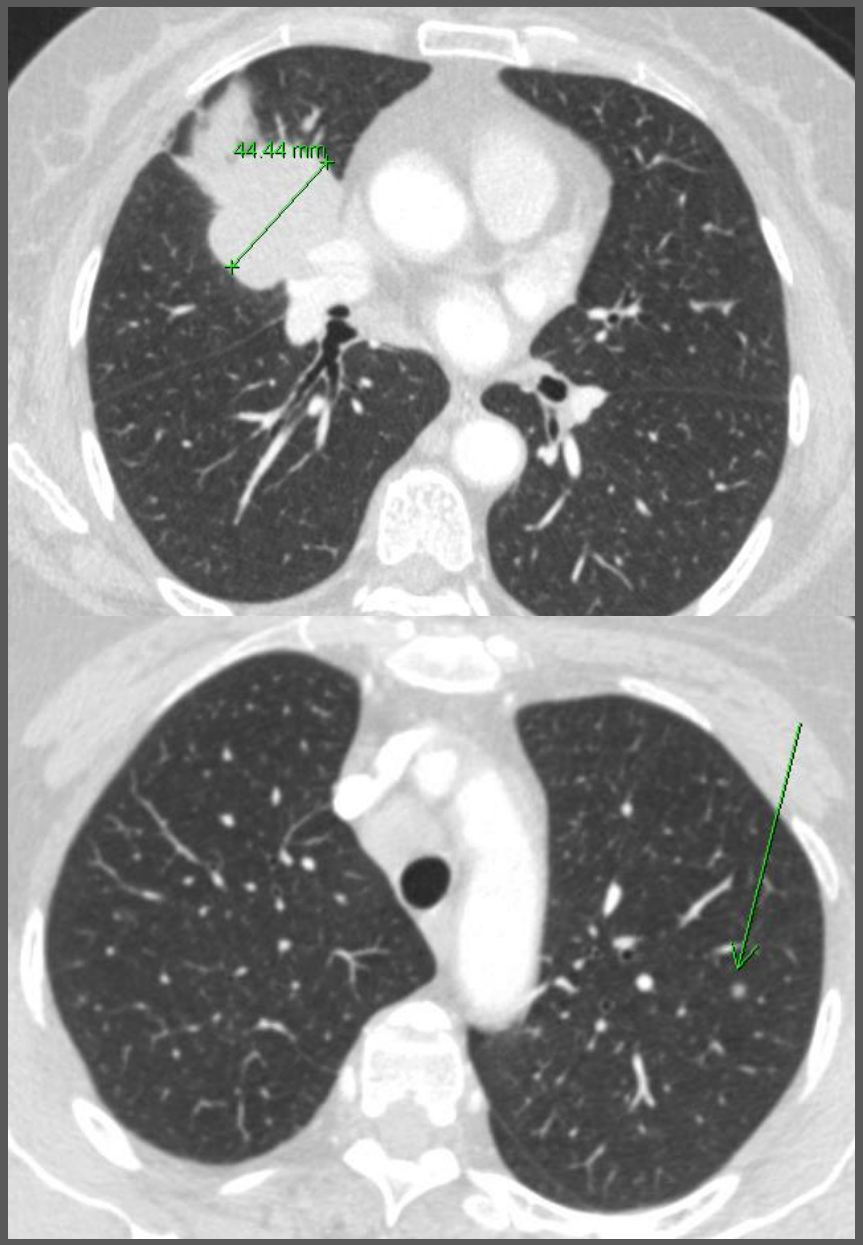
F/69, never smoker





F/69

- ✓ Never smoker
- ✓ ECOG 0
- ✓ Lung cancer, cT4N3M1b, stage IV
  lung to lung metastasis
  metastasis to adrenal gland

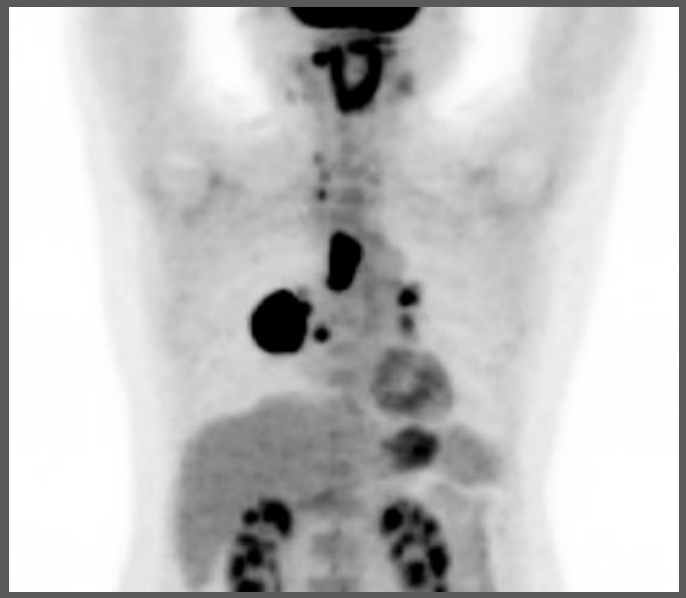
- ✓ TBLB at RUL mass
  : Non-small cell carcinoma, favoring adenocarcinoma.

  EGFR mutation (PNA real time PCR): wild
  KRAS mutation: wild
  ALK/ROS1 IHC: -/-

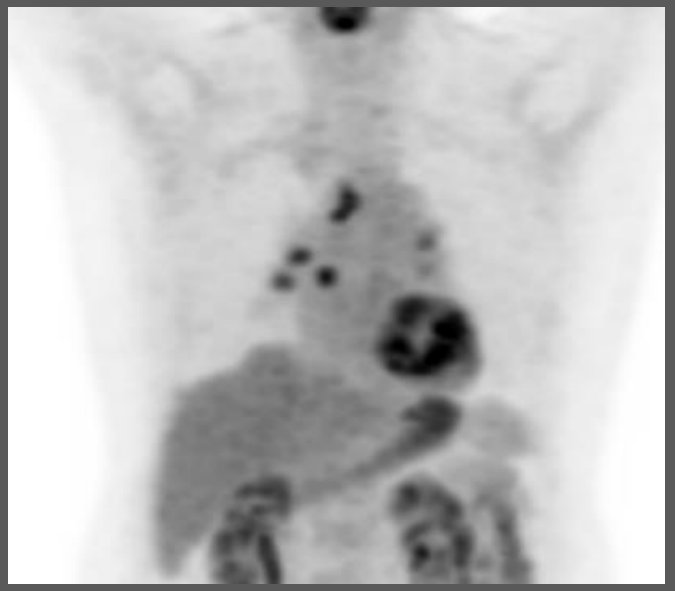
F/69

- ✓ Never smoker
- ✓ ECOG 0
- ✓ Lung cancer, cT4N3M1b, stage IV (2013.01)
  lung to lung metastasis
  metastasis to adrenal gland

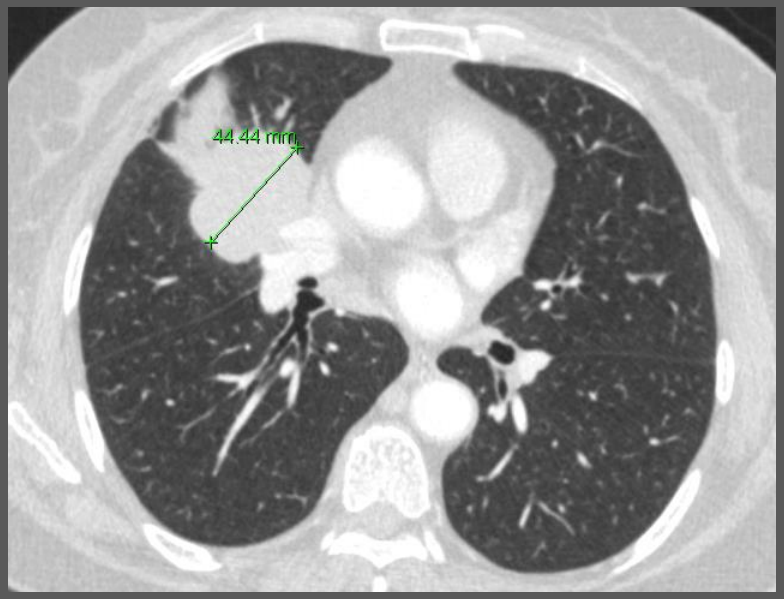
- ✓ s/p 1st line 4th Pemetrexed/Cisplatin CTx (2013.04) → PR
  s/p 16th Pemetrexed maintenance CTx → q4wks (2014.4)
  s/p 62th Pemetrexed maintenance CTx (2017.07)



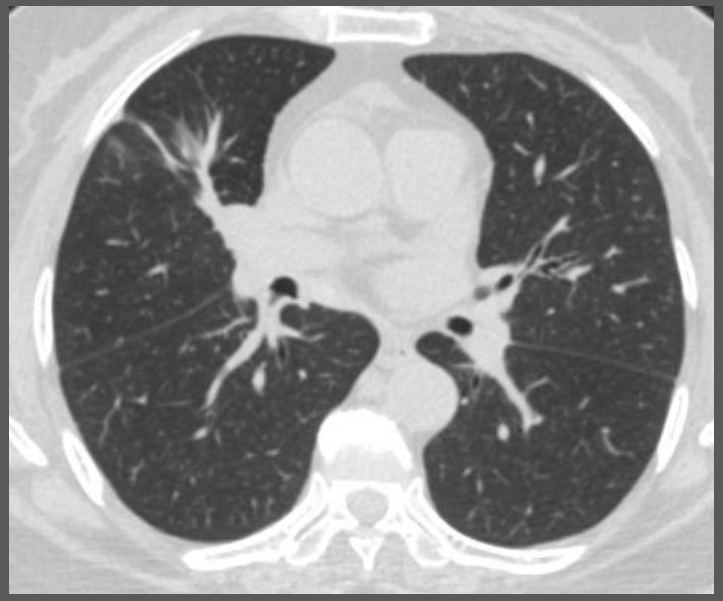
2013.01



2016.01



2013.01



2017.04

RESEARCH ARTICLE Open Access

Predictive factors for a long-term response duration in non-squamous cell lung cancer patients treated with pemetrexed

Sojung Park[1], Hyun Jung Kim[2], Chang–Min Choi[1,3], Dae Ho Lee[3], Sang–We Kim[3], Jung–Shin Lee[3], Woo Sung Kim[1], Se Hoon Choi[4], Jin Kyung Rho[5] and Jae Cheol Lee[3*]

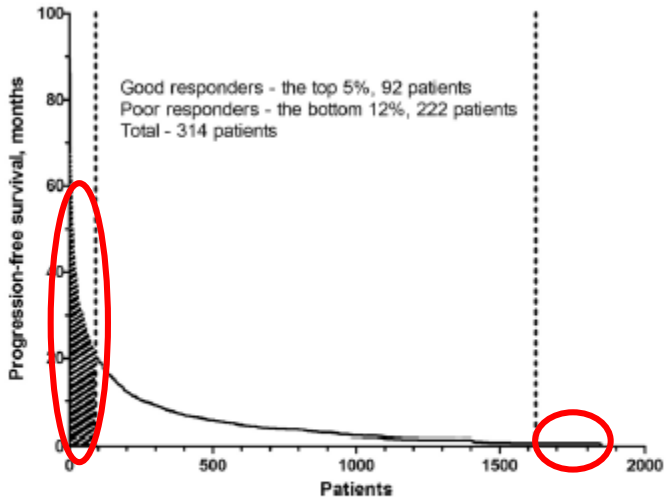


Fig. 1 Distribution of non-small-cell lung cancer patients. Distribution of non-small-cell lung cancer patients arranged in order of the duration of pemetrexed therapy. The dotted lines indicate the cutoff for the top 5 % and bottom 12 % of patients

- ✓ between 2006 and 2015
- ✓ 1,848 non-squamous NSCLC patients
- ✓ retrospective study
- ✓ Good responder: top 5% (n=92)
- ✓ Poor responder: bottom 12% (n=222)

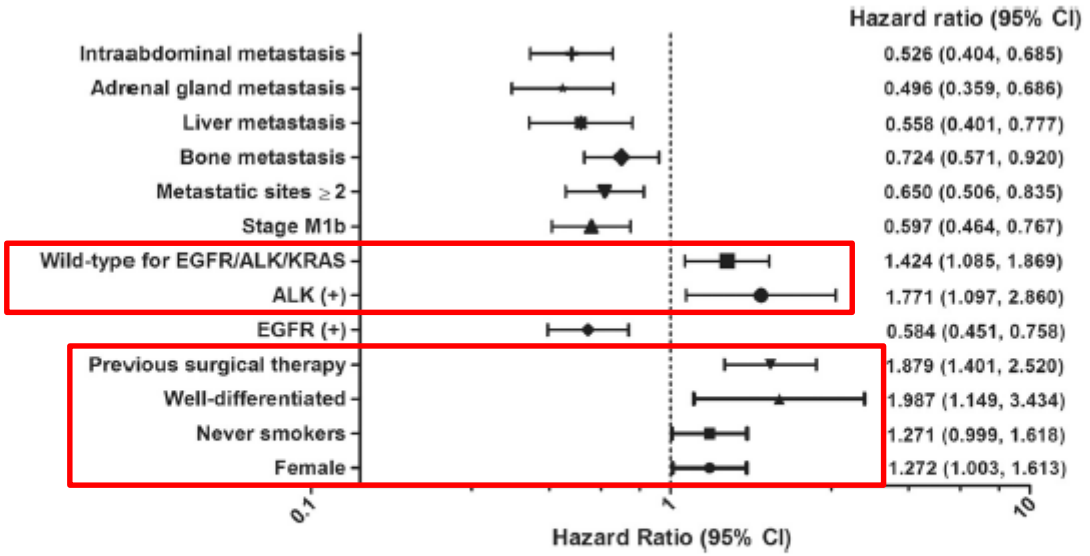


Fig. 2 Prognostic factors by univariate analysis. The Forest plot of prognostic factors for non-small-cell lung cancer patients treated with pemetrexed-containing therapy. The Forest plot shows the hazard ratio and 95 % confidence interval of the prognostic factors by univariate analysis. *W/D* well-differentiated cancer; *EGFR* epidermal growth factor receptor; *ALK* anaplastic lymphoma kinase; *KRAS* Kirsten rat sarcoma viral oncogene homolog; *CI* confidence interval

- ✓ The median PFS of the good responders : 29.9 months (range; 20.9–90.0)
- ✓ The median number of cycle : 37 (range; 18–129)

- ✓ In the good responder group, 46.7 % showed PR, 53.3% showed SD (median PFS in SD, 29.6 months).

- ✓ ALK translocation was more frequently seen in the good responder group (22.2 % versus 4.2 %, P <0.001).

British Journal of Cancer (2011) 104, 1594 – 1601

www.bjcancer.com

Thymidylate synthase as a determinant of pemetrexed sensitivity in non-small cell lung cancer

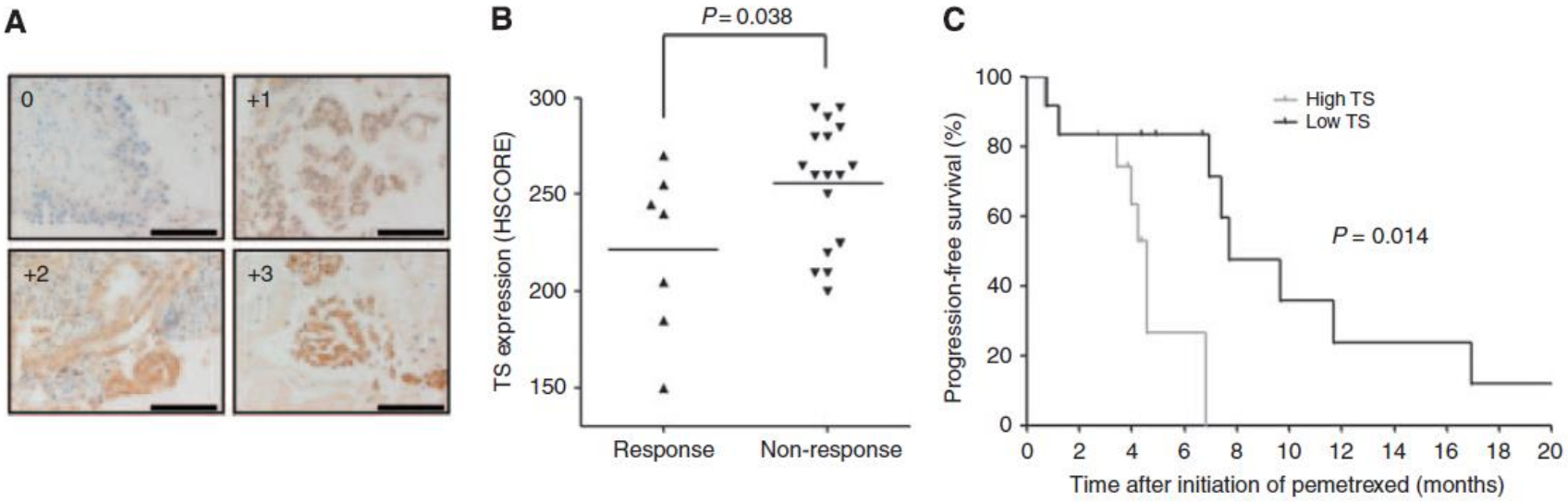


Figure 6 Relation of TS expression level to tumour response in NSCLC patients treated with pemetrexed and either carboplatin or cisplatin. (**A**) Representative sections of carcinomas including cells with the indicated intensities of TS immunostaining. Scale bars, 125 μm. (**B**) TS expression level (HSCORE) for the clinical specimens of 24 patients classified according to tumour response (response = CR or PR, $n = 7$; non-response = SD or PD, $n = 17$). Horizontal lines indicate mean values. The P value was determined by Student's two-tailed t test. (**C**) Progression-free survival of the NSCLC patients according to the expression level of TS in tumour specimens. The P-value was determined with the log-rank test.

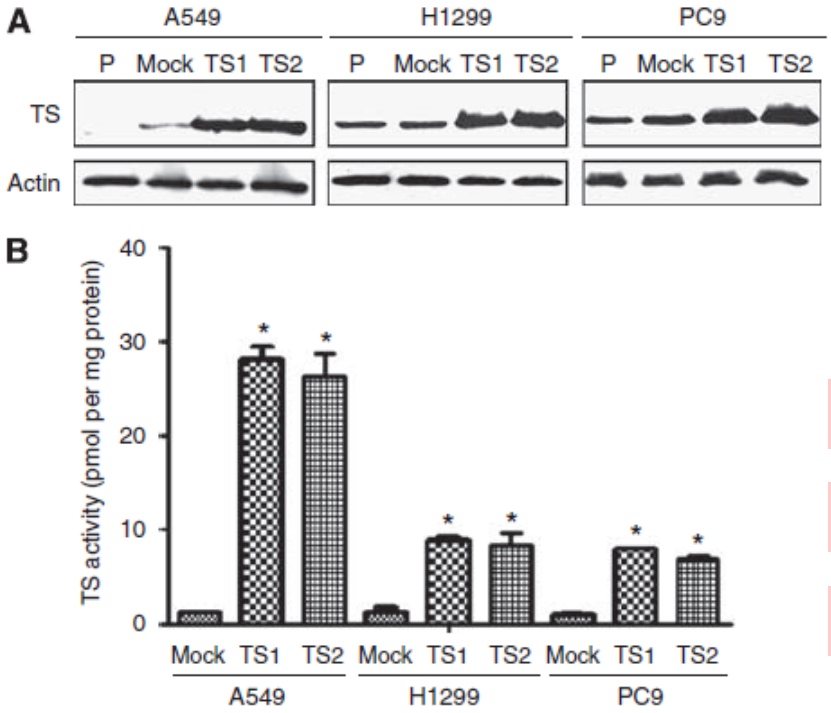


Figure 1 Abundance and enzymatic activity of TS in TS-overexpressing NSCLC cell lines.

Table I Median inhibitory concentrations (μM) for the antiproliferative effects of chemotherapeutic agents in TS-overexpressing NSCLC cells *in vitro*

Cell line	Pemetrexed	Cisplatin	Docetaxel
A549/Mock	0.07	2.62	0.12
A549/TS1	0.38	2.37	0.12
A549/TS2	0.44	2.21	0.13
H1299/Mock	0.08	2.93	0.32
H1299/TS1	0.22	2.98	0.30
H1299/TS2	0.22	2.90	0.30
PC9/Mock	0.03	0.72	0.18
PC9/TS1	0.11	0.72	0.18
PC9/TS2	0.10	0.65	0.17

Abbreviations: NSCLC = non-small cell lung cancer; TS = thymidylate synthase.

PFS

7.1 mo (low TS) vs. 2.6 mo (high TS) (p<0.01; HR=0.28)

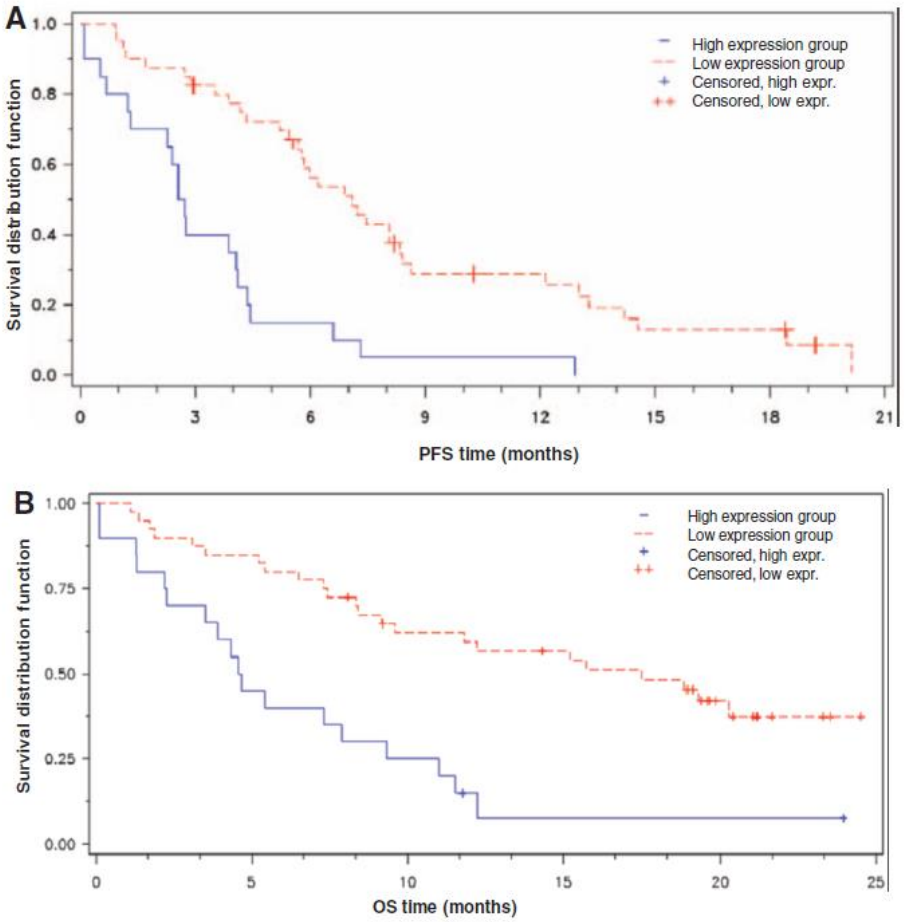
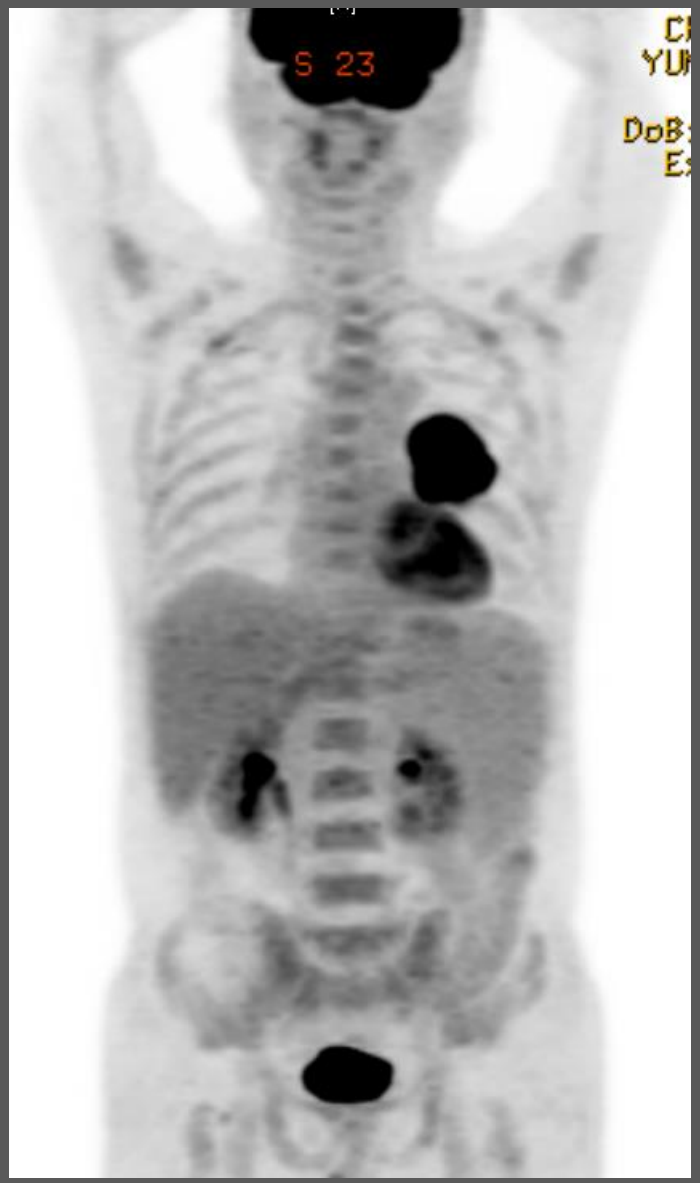
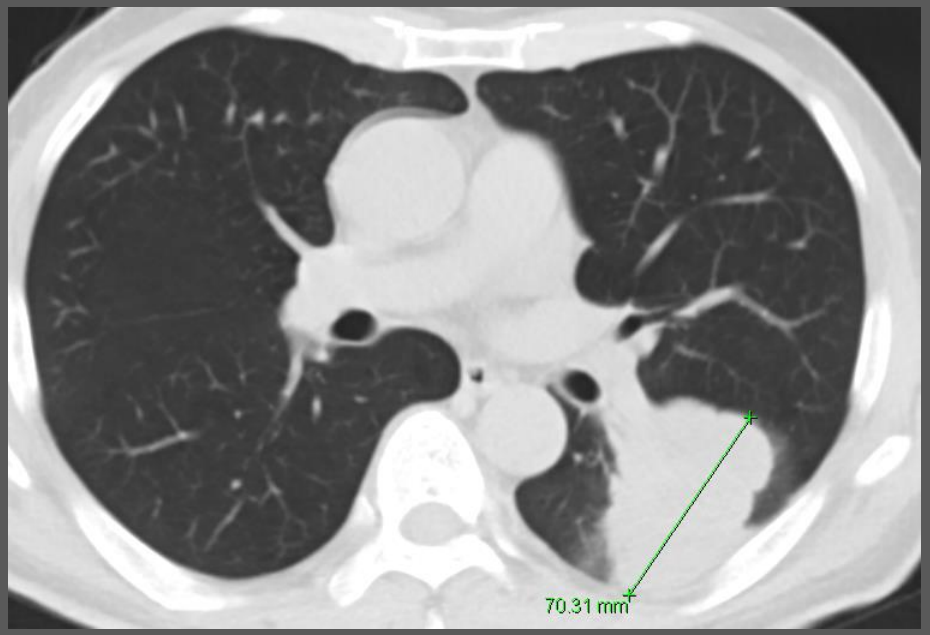


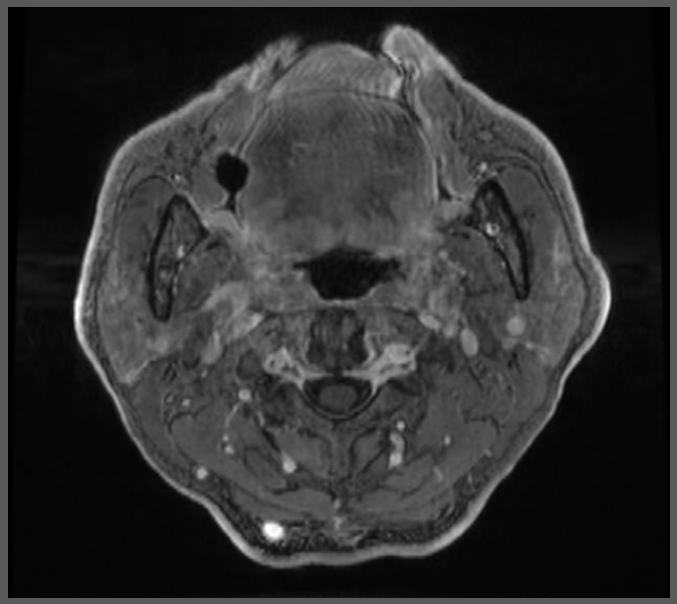
FIGURE 3. Kaplan–Meier plots of PFS (A) and OS (B) in patients with low and high nuclear TS expression (H-score) (n = 60).

Nicolson, Marianne C., et al. Journal of Thoracic Oncology 8.7 (2013): 930-939.

M/61, never smoker







M/61

- ✓ Never smoker
- ✓ ECOG 0
- ✓ Lung cancer, cT2bN1M1b, stage IV (2012.10)
  multiple bone metastasis
- ✓ Polycythemia Vera (JAK-2 mutation : V617F Heterozygote)

- ✓ TBLB at LLL mass
  : Adenocarcinoma, poorly differentiated.

  EGFR mutation (PNA real time PCR): L858R or L861Q m+
  KRAS mutation: wild
  ALK IHC: -

M/61

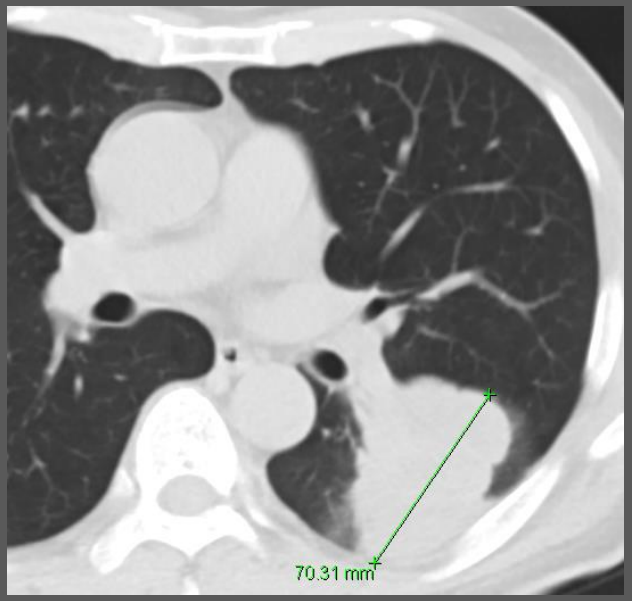
- ✓ Never smoker
- ✓ ECOG 0
- ✓ Lung cancer, cT2bN1M1b, stage IV (2012.10)
  multiple bone metastasis
- ✓ Polycythemia Vera (JAK-2 mutation : V617F Heterozygote)

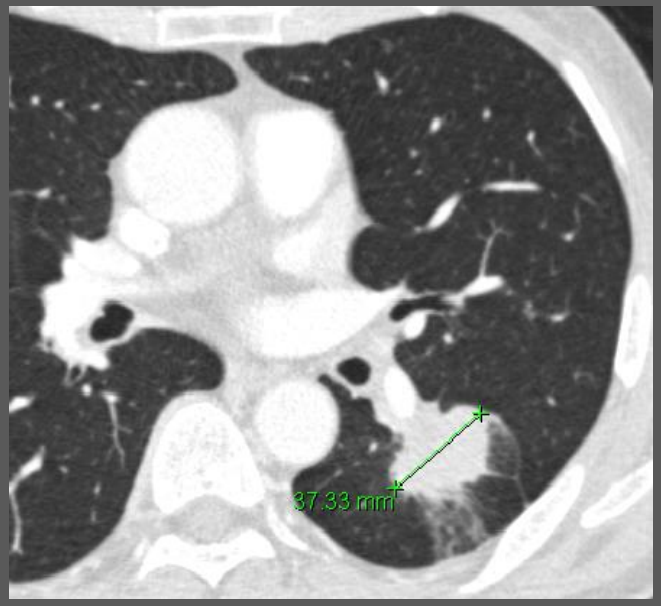
- ✓ s/p 1st line 4th Paclitaxel/Cisplatin CTx (2013.01)
  → PD (newly developed brain metastasis)
  s/p 2nd line Gefitinib CTx (2013.2 – 현재)

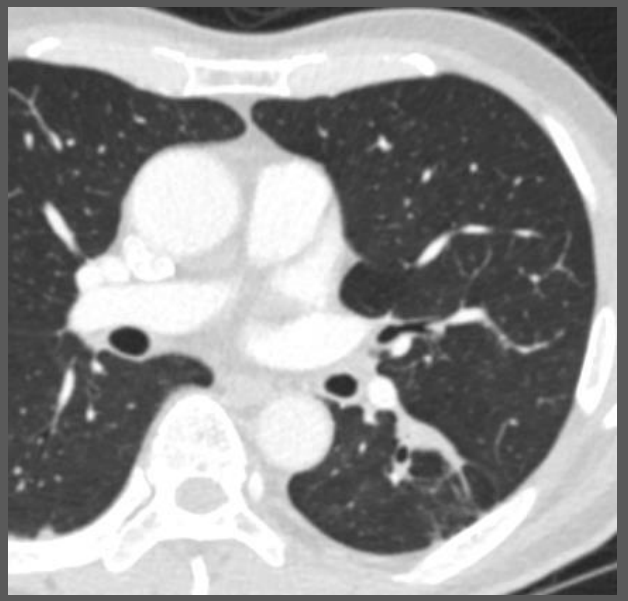
Baseline

s/p 4th Paclitaxel/Cisplatin

on gefitinib







2012.10

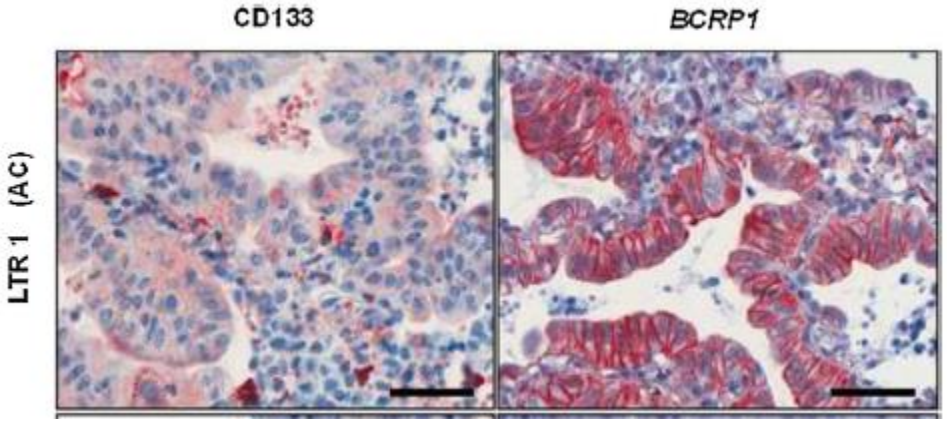
2013.02

2017.05

The gefitinib long-term responder (LTR)—A cancer stem-like cell story? Insights from molecular analyses of German long-term responders treated in the IRESSA expanded access program (EAP)

Sandra Gottschling[a,*], Esther Herpel[b], Wilfried E.E. Eberhardt[c], David F. Heigener[d], Jürgen R. Fischer[e], Claus-Henning Köhne[f], Cornelius Kortsik[g], Thomas Kuhnt[h], Thomas Muley[i], Michael Meister[i], Helge G. Bischoff[a], Peter Klein[j], Ines Moldenhauer[k], Philipp A. Schnabel[b], Michael Thomas[a], Roland Penzel[b]

- ✓ German patients with advanced NSCLC who experienced ≥3 year response to gefitinib.
- ✓ Antigens characterizing cancer stem-like cells might identify a fraction of long-term responders.



Gottschling, Sandra, et al. Lung Cancer 77.1 (2012): 183-191.

Impact of *TP53* Mutations on Outcome in *EGFR*-Mutated Patients Treated with First-Line Tyrosine Kinase Inhibitors

Matteo Canale[1], Elisabetta Petracci[2], Angelo Delmonte[3], Elisa Chiadini[1], Claudio Dazzi[4], Maximilian Papi[5], Laura Capelli[1], Claudia Casanova[4], Nicoletta De Luigi[3], Marita Mariotti[3], Alessandro Gamboni[6], Rita Chiari[7], Chiara Bennati[7], Daniele Calistri[1], Vienna Ludovini[7], Lucio Crinò[7], Dino Amadori[3], and Paola Ulivi[1]

- ✓ between 2012 and 2015
- ✓ 136 EGFR m+ NSCLC treated with TKI as 1st line therapy
- ✓ retrospective study
- ✓ TP53 mutations were observed in 37 (30.1%)

Table 1. Clinicopathologic characteristics of patients ($n = 136$)

	n **(%)**
Gender	
Female	102 (75.0)
Male	34 (25.0)
Age at start of first-line of therapy, years	
Mean ± sd	70.4 ± 10.7
Smoking status	
Never smoker	62 (59.0)
Former smoker	28 (26.7)
Current smoker	15 (14.3)
Missing	31
Histology	
ADC	134 (98.5)
Poorly differentiated carcinoma	2 (1.5)
EGFR Mutation	
Exon 18 point mutation	6 (4.4)
Exon 19 deletion	74[a] (54.4)
Exon 21 point mutation	56 (41.2)
L858R	49 (36.0)
L861Q	7 (5.1)
Type of first-line therapy	
Gefitinib	104 (76.5)
Erlotinib	27 (19.8)
Afatinib	3 (2.2)
Dacomitinib	2 (1.5)
Therapy response	
CR	4 (3.0)
PR	71 (52.6)
SD	37 (27.4)
PD	23 (17.0)
Missing	1
TP53 status	
Wt	86 (69.9)[b]
Mutated	37 (30.1)[b]
Exon 5	10 (27.0)[c]
Exon 6	6 (16.2)[c]
Exon 7	9 (24.3)[c]
Exon 8	12 (32.4)[c]

Table 2. Response to TKIs in *EGFR*-mutated NSCLC patients

Response	Overall ($n = 136$)	Exon 19 deletion ($n = 74$)	Exon 21 L858R ($n = 49$)	Exon 21 L861Q and exon 18 mutations ($n = 13$)	*P*
Best response					
CR	4	3	1	—	
PR	71	48	21	2	
SD	37	17	15	5	
PD	22	6	11	5	
Missing	2	—	1	1	
ORR	56.0%	68.9%	45.8%	16.7%	<0.001
DCR	83.6%	91.9%	77.1%	58.3%	0.001
Duration of response					
Non responders or responders for <3 months	25	7 (9.5%)	13 (27.1%)	5 (41.7%)	0.008
Short-term responders	50	28 (37.8%)	20 (41.7%)	2 (16.6%)	
Long-term responders	59	39 (52.7%)	15 (31.2%)	5 (41.7%)	

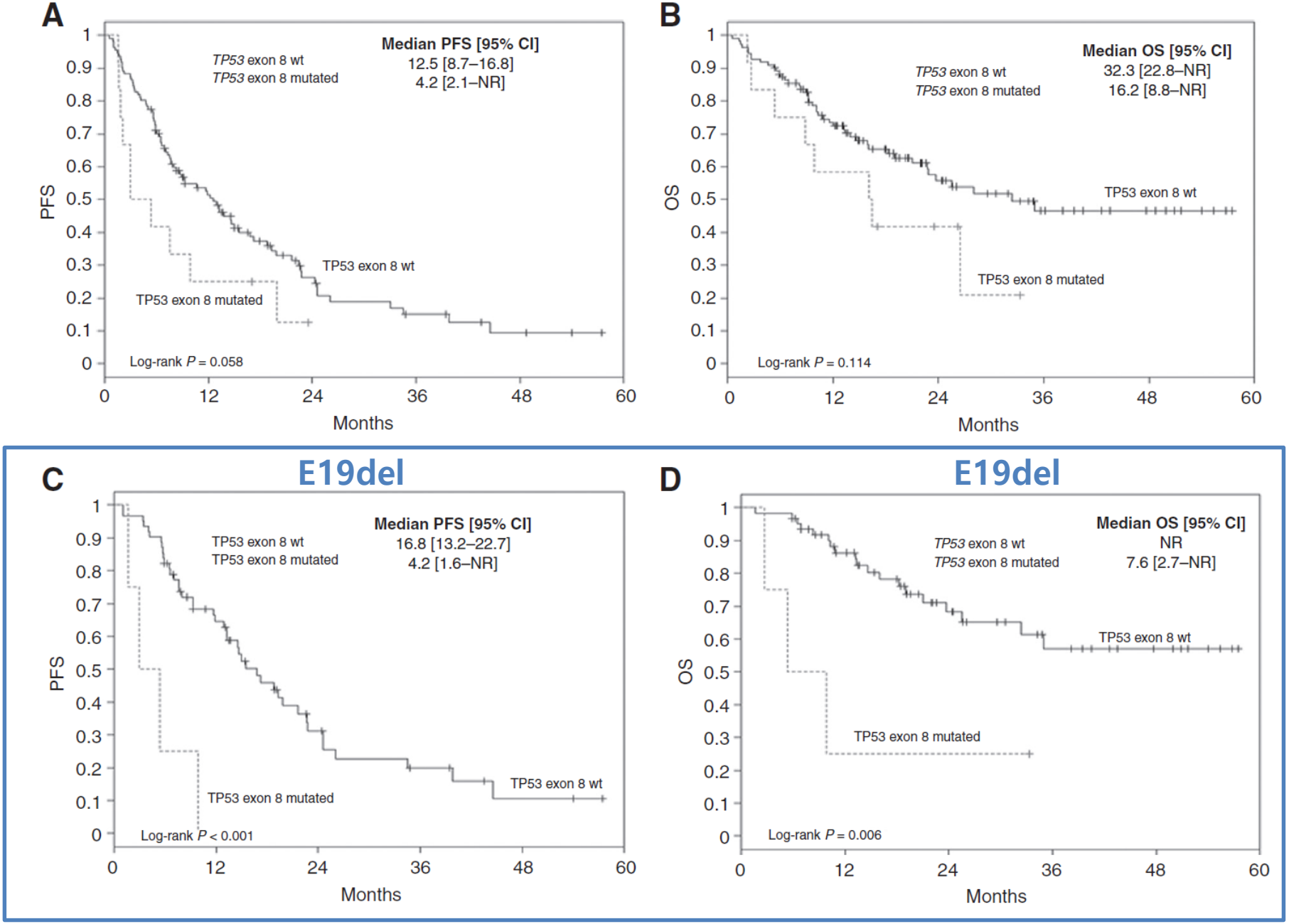
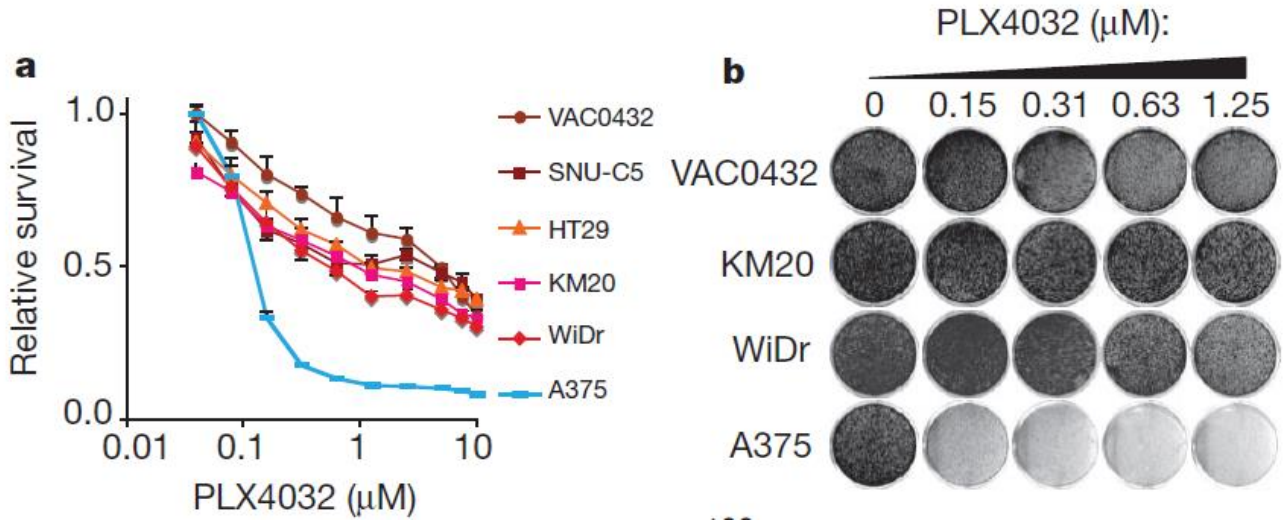


Figure 2.

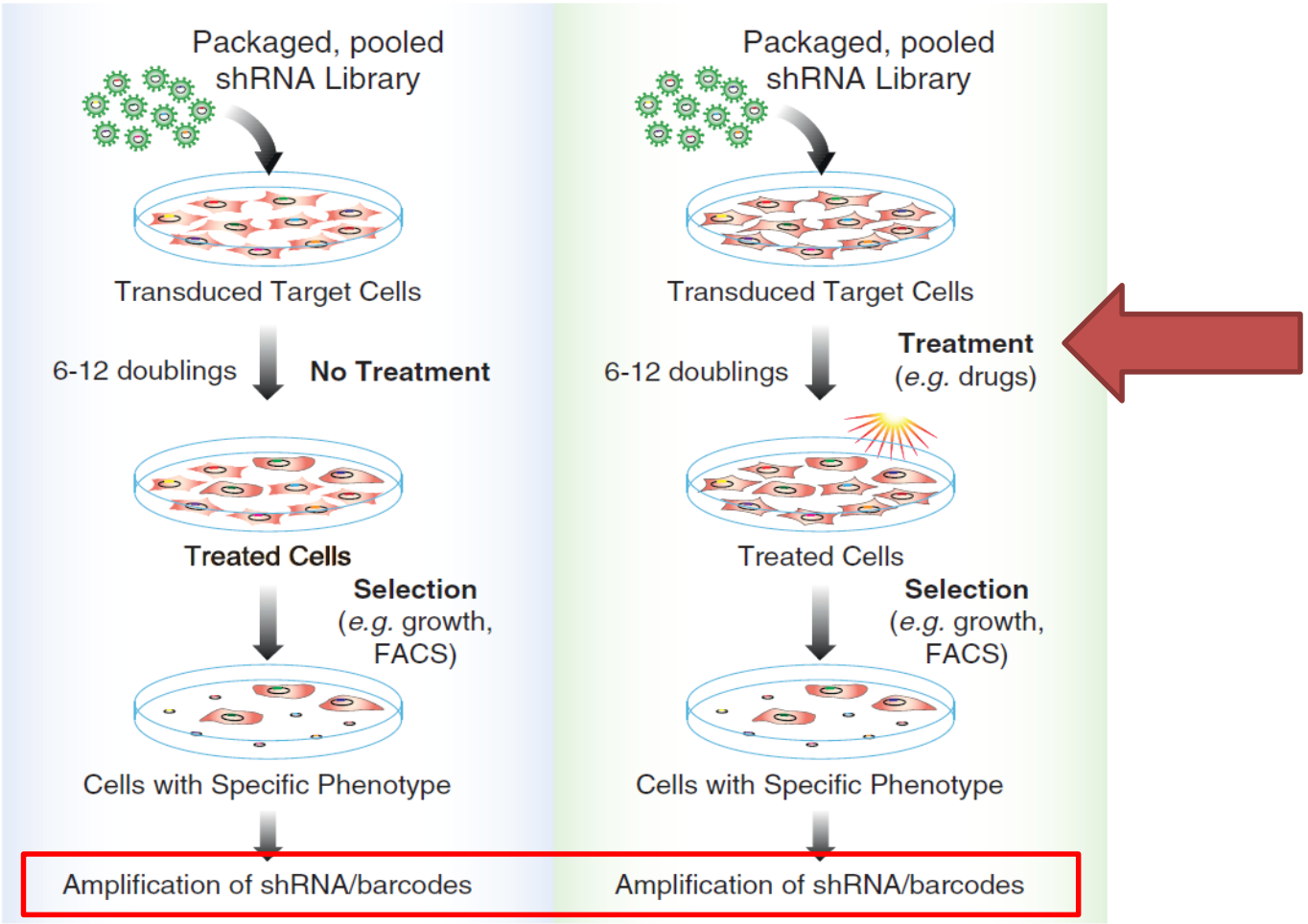
PFS (**A**) and OS (**B**) of patients with *TP53* exon 8–mutated patients compared with *TP53* exon 8 wt patients; PFS (**C**) and OS of *TP53* exon 8–mutated patients compared with *TP53* exon 8 wt patients in the subgroup of *EGFR* exon 19–deleted patients (**D**). NR, not reached.

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prahallad[1]*, Chong Sun[1]*, Sidong Huang[1]*, Federica Di Nicolantonio[2,3]*, Ramon Salazar[4], Davide Zecchin[2], Roderick L. Beijersbergen[1], Alberto Bardelli[2,3] & René Bernards[1]



Use of RNAi screens to uncover resistance mechanisms in cancer cells and identify synthetic lethal interactions



Drug Discovery Today: Technologies

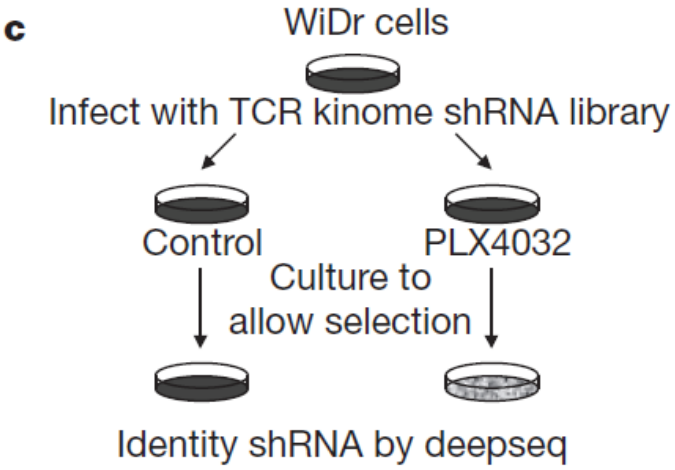
Dropout viability screening process using pooled shRNA library

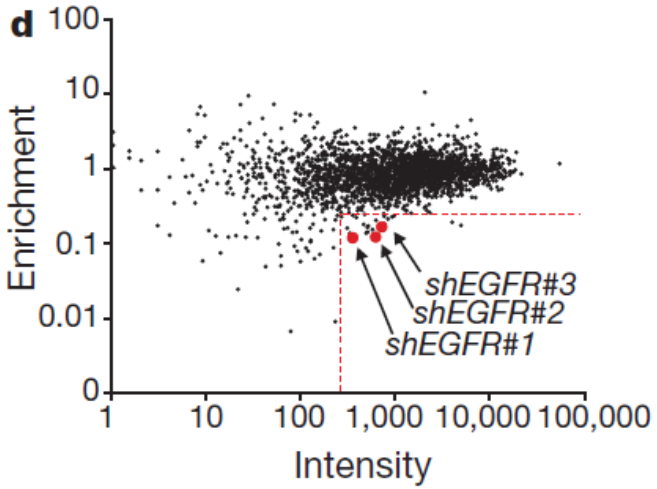
Diehl, Paul, Donato Tedesco, and Alex Chenchik. Drug Discovery Today: Technologies 11 (2014): 11-18.

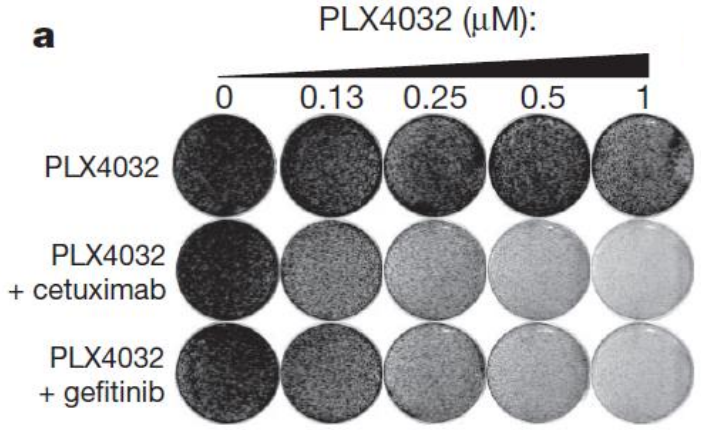
colsums total reads		6986728	6890019	7306969	7204529	Relative abundance ratio	sequence
tag		PLX	PLX replicate	Untreated	Untreated_replicate	PLX/UT	
TRCN0000021477	**ALPK1**	144	113	848	723	0.171025053	GCCCAGGTGAAGGAACATTTA
TRCN0000009939	**BTK**	107	128	780	691	0.167238063	GCGGAAGGGTGATGAATATTT
TRCN0000038671	**CSNK1G2**	326	433	2335	1750	0.194688133	CGCCTAGGAAAGAATCTCTAT
TRCN0000009953	**DGKG**	76	98	513	667	0.154196265	GGCCAACAGCGCAGATACTAA
TRCN0000000651	**DYRK2**	123	40	475	473	0.179170225	GCAGGGTAGAAGCGGTATTAA
TRCN0000121206	**EGFR**	29	41	310	455	0.095675	GCCAAGCCAAATGGCATCTTT
TRCN0000039633	**EGFR**	98	78	779	606	0.1329003	GCTGAGAATGTGGAATACCTA
TRCN0000121068	**EGFR**	66	182	807	646	0.179210448	GCCACAAAGCAGTGAATTTAT
TRCN0000039881	**ERBB2**	163	97	634	795	0.189780194	CAGTGCCAATATCCAGGAGTT
TRCN0000001786	**MAK**	93	183	903	674	0.183625364	GATCCACTTAGCACCTCTCAA
TRCN0000001471	**NEK3**	826	910	4855	5464	0.175914511	GCAGTCCCATAGAACAGAAAT
TRCN0000001314	**NPR2**	63	79	449	595	0.14220807	GCCTTTCTCCACAACAGCATT
TRCN0000006244	**PCTK2**	62	70	621	383	0.137776453	GCCATGAAACATGTGTACTTT
TRCN0000037587	**PI4K2B**	84	126	912	1128	0.107719313	GCTGCAATTGATAATGGTCTA
TRCN0000010407	**PIK3CA**	96	78	556	499	0.172414295	AATGAAAGCTCACTCTGGATT
TRCN0000033287	**PIK3R1**	563	360	4211	4142	0.115383151	CCTCAATGTCACACTAGCCTA
TRCN0000002004	**PRKACB**	18	70	331	344	0.136876438	GCCAACTGACTTAACAACATT
TRCN0000003116	**PRKCB**	48	47	447	325	0.128819981	CTATCCCAAGTCTATGTCCAA
TRCN0000001066	**RAF1**	728	808	4345	3962	0.19349512	CGGAGATGTTGCAGTAAAGAT
TRCN0000007149	**SCYL2**	84	13	319	312	0.159948199	GCCACCAACTACTATGACCAA
TRCN0000001622	**STK4**	89	75	540	495	0.165654177	AGTTGAGTGATAGCTGGGAAA
TRCN0000001602	**TIE1**	75	74	513	761	0.12213051	CAGCACTCACACCACTAACAT

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prahallad[1]*, Chong Sun[1]*, Sidong Huang[1]*, Federica Di Nicolantonio[2,3]*, Ramon Salazar[4], Davide Zecchin[2], Roderick L. Beijersbergen[1], Alberto Bardelli[2,3] & René Bernards[1]







CANCER TREATMENT

- Types of Cancer Treatment +
- Side Effects
- Clinical Trials Information +
- A to Z List of Cancer Drugs +
- Complementary & Alternative Medicine (CAM) +
- Questions to Ask about Your Treatment
- Research

Exceptional Responders Initiative: Questions and Answers

1. What is the purpose of the Exceptional Responders Initiative?

The National Cancer Institute (NCI) has embarked on the Exceptional Responders Initiative (ERI) to understand the molecular underpinnings of exceptional responses to treatment, primarily via chemotherapy, in cancer patients. Exceptional responders are patients who have a unique response to treatments that are not effective for most other patients. For this initiative, exceptional responders will be identified among patients enrolled in early-phase clinical trials in which fewer than 10% of the patients responded to the treatments being studied; patients who were treated with drugs not found to be generally effective for their disease; patients who were treated in later-phase clinical trials of single agents or combinations; and even patients who were treated with established therapies. In this pilot study, malignant tissue (and normal tissue, when possible) and clinical data will be obtained from a group of exceptional responders and analyzed in detail. The goal is to determine whether certain molecular features of the malignant tissue can predict responses to the same or similar drugs. The study also has an optional survey of complementary and alternative medicines, lifestyle changes, and additional medical conditions and their medications that may help to clarify the exceptional response.

2. What are the eligibility requirements for this study?

Exceptional responders are patients who meet the following criteria:

BIOMARKERS

Exceptional responders—discovering predictive biomarkers

Naoko Takebe, Lisa McShane and Barbara Conley

Modern genomics technologies enable the identification of genetic alterations, even those present at a low frequency, and can contribute to unveiling the mechanistic rationale behind the unexpected clinical response of 'exceptional responders'. This approach will drive the identification of molecular biomarkers that can be integrated into clinical trials and predict response to a specific therapy.

Takebe, N. *et al. Nat. Rev. Clin. Oncol.* **12**, 132–134 (2015); published online 17 February 2015; doi:10.1038/nrclinonc.2015.19

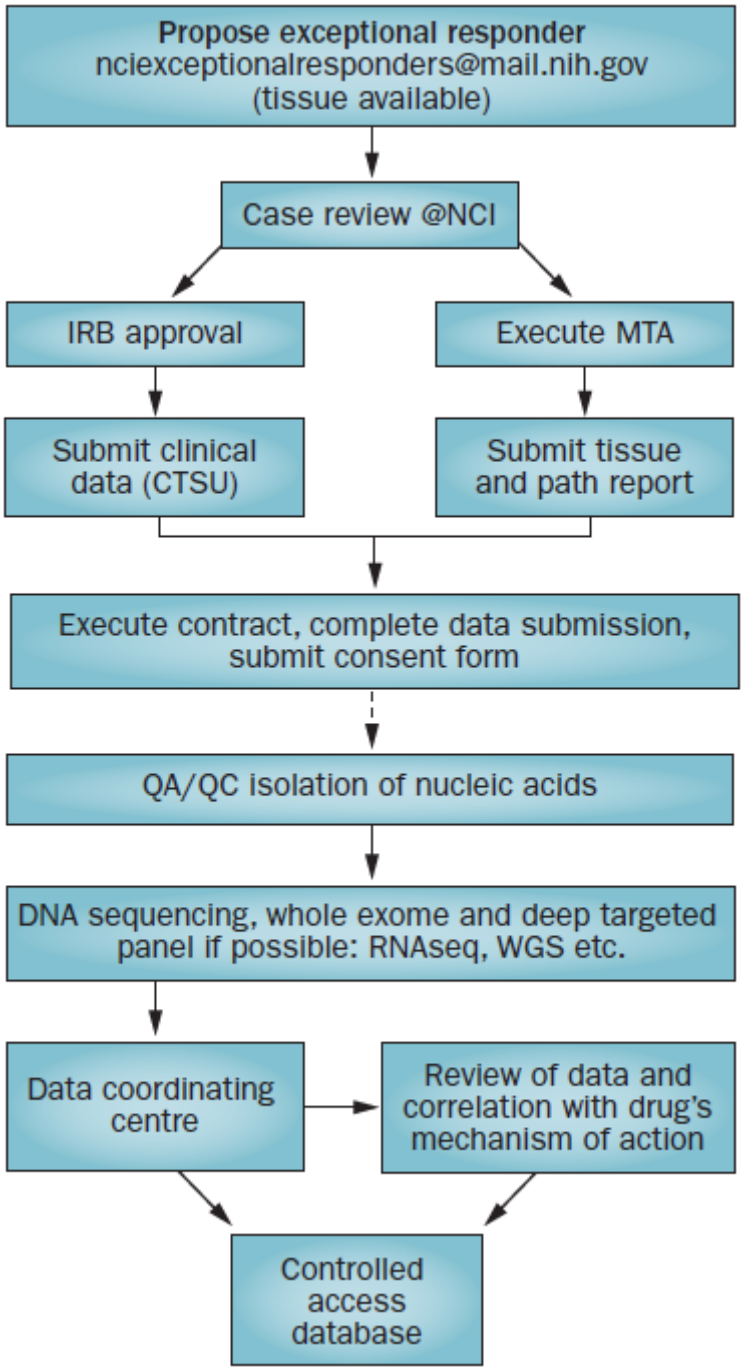


Figure 1 | Algorithm of the NCI Exceptional Responders Initiative.

Molecular Profiling in Tissue Samples From Patients With Cancer Who Are Exceptional Responders to Treatment

This study is currently recruiting participants.

See Contacts and Locations

Verified July 2017 by National Cancer Institute (NCI)

Sponsor:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:
NCT02243592

First received: September 16, 2014
Last updated: July 6, 2017
Last verified: July 2017
History of Changes

- ✓ Loss-of-function mutations in the *TSC1* and *NF2* genes in bladder cancer patient with long term everolimus response
- ✓ L1237F mutation in the RAD50 protein in patients with metastatic small-cell cancer of unknown origin received a combination of AZD7762, a CHK1/2 inhibitor, and irinotecan, a topoisomerase I inhibitor.
- ✓ IGF-1R–IRS-1 signalling axis in remarkable responder who received treatment with an IGF-1R monoclonal antibody for stage IV ALK-positive lung adenocarcinoma.

> “Cancer is heterogeneous and the discovery ... of predictive biomarkers is key to the success of personalized medicine”

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Cancer Researchers Report Progress in Studying Exceptional Responders

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July 6, 2017, by NCI Staff

- ✓ *RAD50* mutation in bladder cancer patient
- ✓ metastatic breast cancer who had a complete response to docetaxel, carboplatin, and trastuzumab
  : “This woman had a perfect storm of DNA repair mutations”
- ✓ Can immune system be play a role in some patients’ unusual responses?
- ✓ Based on their early results, the researchers estimate that between 10% and 20% of tumors from exceptional responder cases have unusually high numbers of genetic mutations.

Lessons in cancer's exceptional responders

- ✓ Discover a new "biomarker," or suspected link, to the disease, while simultaneously identifying a possible appropriate drug for patients with any type of cancer who have that mutation.

- ✓ Hundreds of drugs have been abandoned over the years after failing clinical trials, although many had their own exceptional responders.

- ✓ Some of those drugs could be resurrected, and newer ones could be saved, if the genetic links are established.