Latest update of targeted therapy for Lung Cancer with rare actionable mutations

James Chih-Hsin Yang M.D., Ph.D.

楊志新教授

Professor and Director, Graduate Institute of Oncology, NTU

台灣大學醫學院腫瘤醫學研究所所長

Director, Department of Oncology, National Taiwan University Hospital

台大醫院腫瘤醫學部主任

2017 May
NSCLC Treatment Map

Small cell
Lung cancer

台大醫院 NTUH

Squamous cell carcinoma
(non-adenocarcinoma)

Driver mut-
Or no TT*

Adenocarcinoma
(Non-SCC)

Other drivers#

PD L1>50%?

Molecular diagnosis

Driver mut+

platinum +
gem/taxane/vn

+necitumumab

Pembrolizumab

platinum + pem

+ pembrolizumab

EGFR mut

ALK fusion

afatinib, erlotinib,
gefitinib

+bevacizumab

alectinib

nivolumab, atezolizumab
or pembrolizumab(PDL1+)

platinum + pem
or paclitaxel/car/bev

T790M-

platinum + pem+/maint
or paclitaxel/car/bev

pem maintenance

afatinib
erlotinib?

docetaxel

+ramucirumab
or Nintedanib(fast PD)

nivolumab, atezolizumab
or pembrolizumab(PDL1+)

T790M+

T790M-

osimertinib

ceritinib
alectinib

+ramucirumab
or Nintedanib(fast PD)

Docetaxel

other not used agents or clinical trials

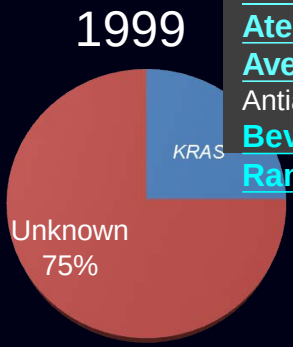
#cMET exon14 skip, RET fusion, ROS1 fusion, TRK fusion etc.

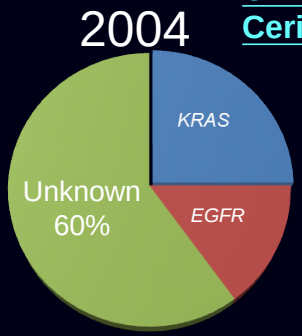
K-ras, N-ras, HER2, EGFRexon20 ins, etc.

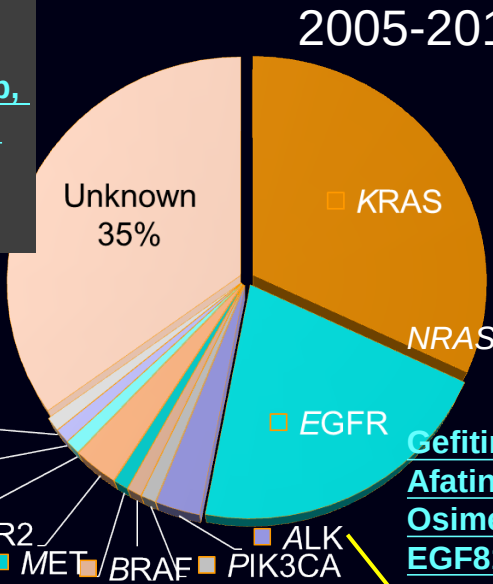
Corresponding targeted therapy, chemotherapy, immunotherapy

Unique Feature of Lung Adenocarcinoma: Single Driver Oncogenes

HSP90 client oncoprotein
AUY922
PD1/PD-L1 expression
Pembrolizumab, Nivolumab, Ateolizumab, Durvalumab, Avelumab etc.
Antiangiogenesis
Bevacizumab, Nintedanib
Ramucimumab







Vandetanib?
XL184?
Sunitinib?

Crizotinib
Ceritinib, Lorlatinib
Selumetinib?

Afatinib?
Dacomitinib?

INC280
MSC2156119j
LY2801653
Crizotinib

Dabrafenib, Vemurafenib
Regorafenib, Selumetinib, Trametinib

MK2206?
BKM120?

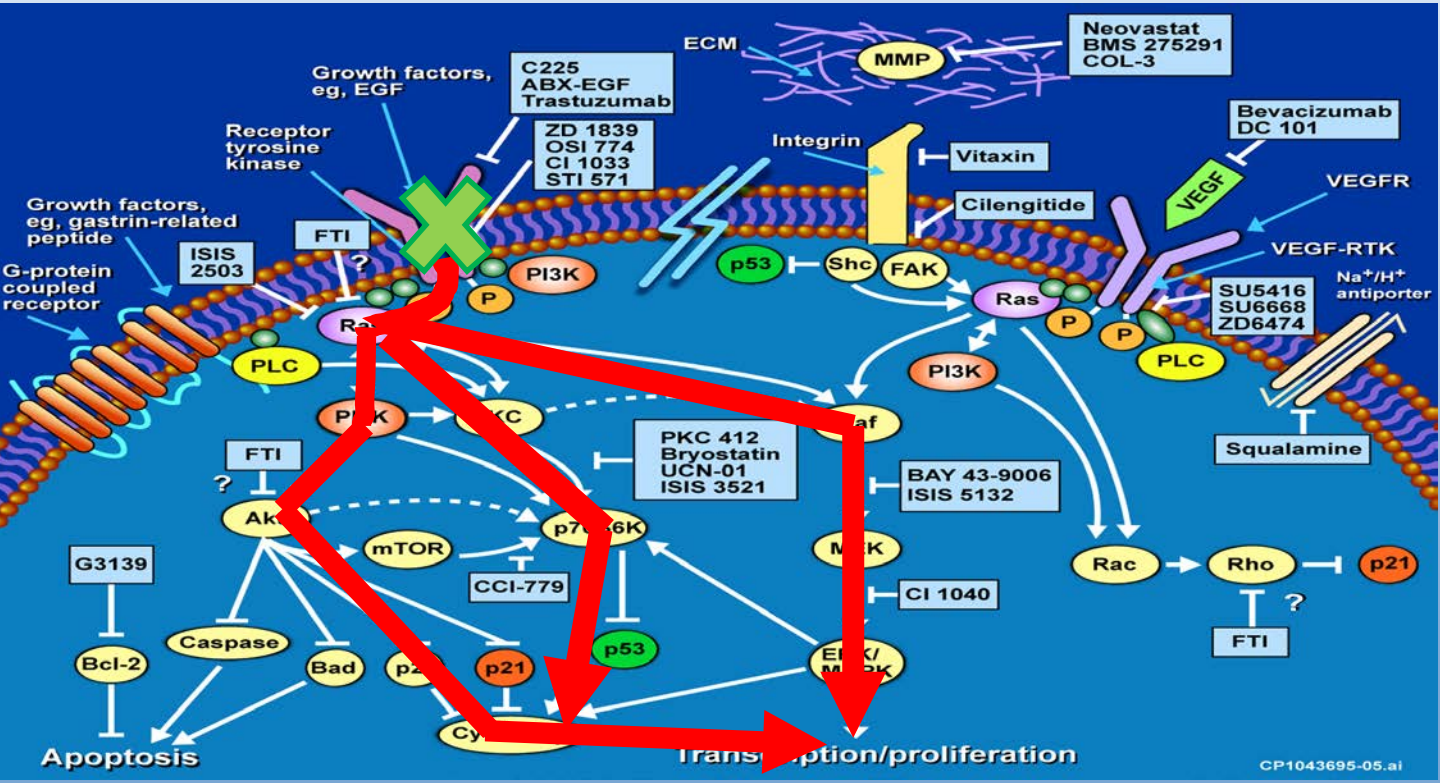
Crizotinib, Ceritinib, Alectinib, Brigatinib
Lorlatinib

Selumetinib
Trametinib

Gefitinib,Erlotinib
Afatinib, Dacomitinib
Osimertinib, Olmutinib
EGF816

Modified from Kris M et al. IASLC 2012 Targeted Therapies

Actionable Mutations (Driver Mutations?)



Driver mutation

- Single pathway control cell growth and death
- Oncogene addiction
- Mutually exclusive with other driver mutant genes

Proof of concept in human trials:

- Inhibitor resulted in high response and disease control
- Durable response if alternative pathways relatively inactive

Actionable
is it a driver mutation gene?

- Not true driver mutations:

PI3K, assisting driving

- Not sure about being a driver mutation

AKT, MEK mutations

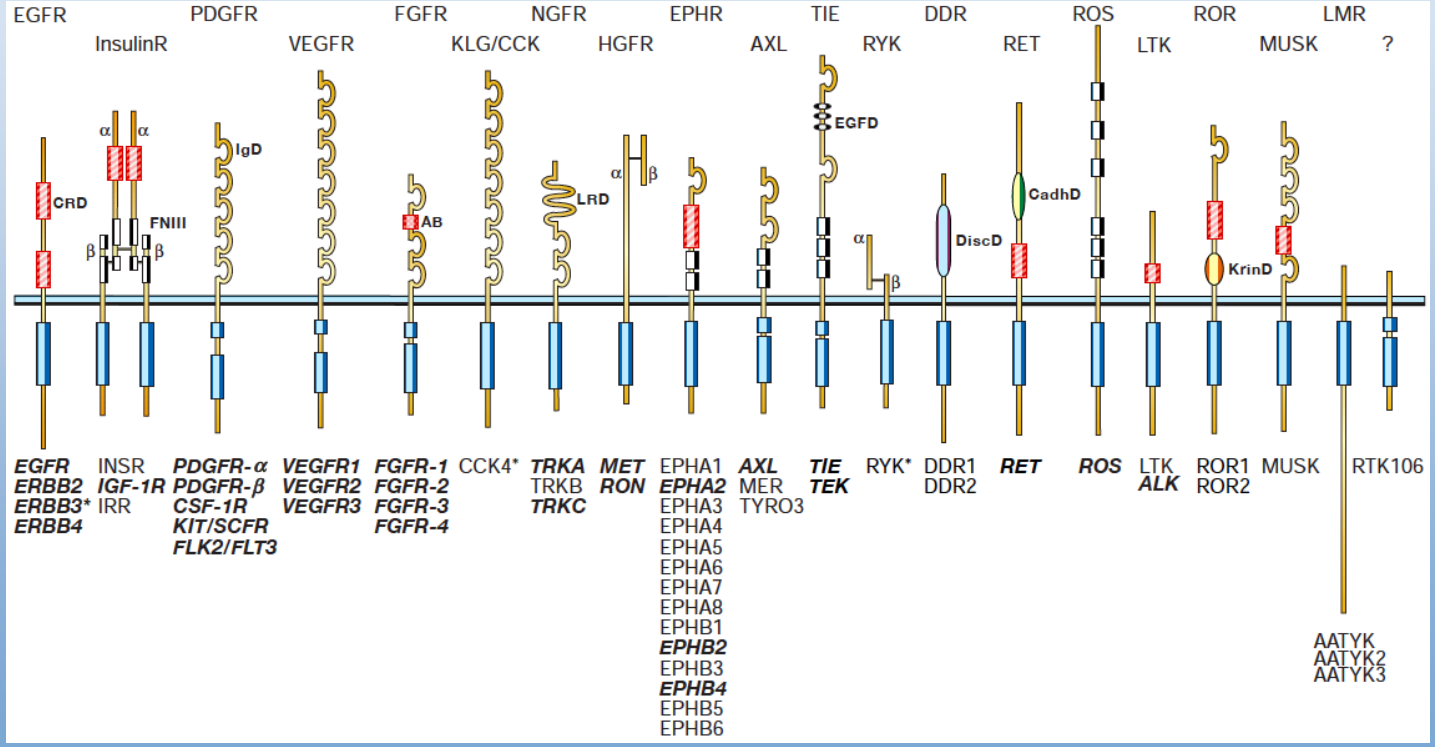
Not targetable yet:

K-ras, HER2, EGFR insertion 20

- Not targetable and not a full driver:

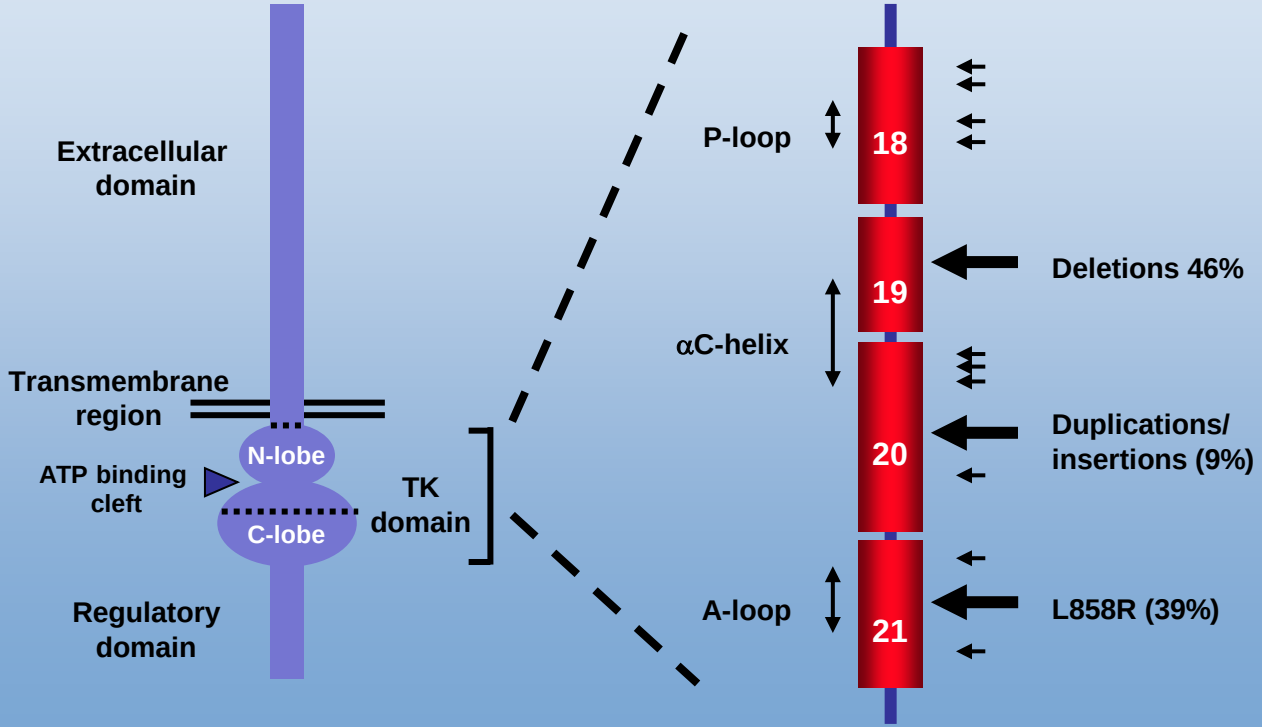
P53, RB loss, PTEN loss, etc.

Human Receptor Tyrosine Kinases



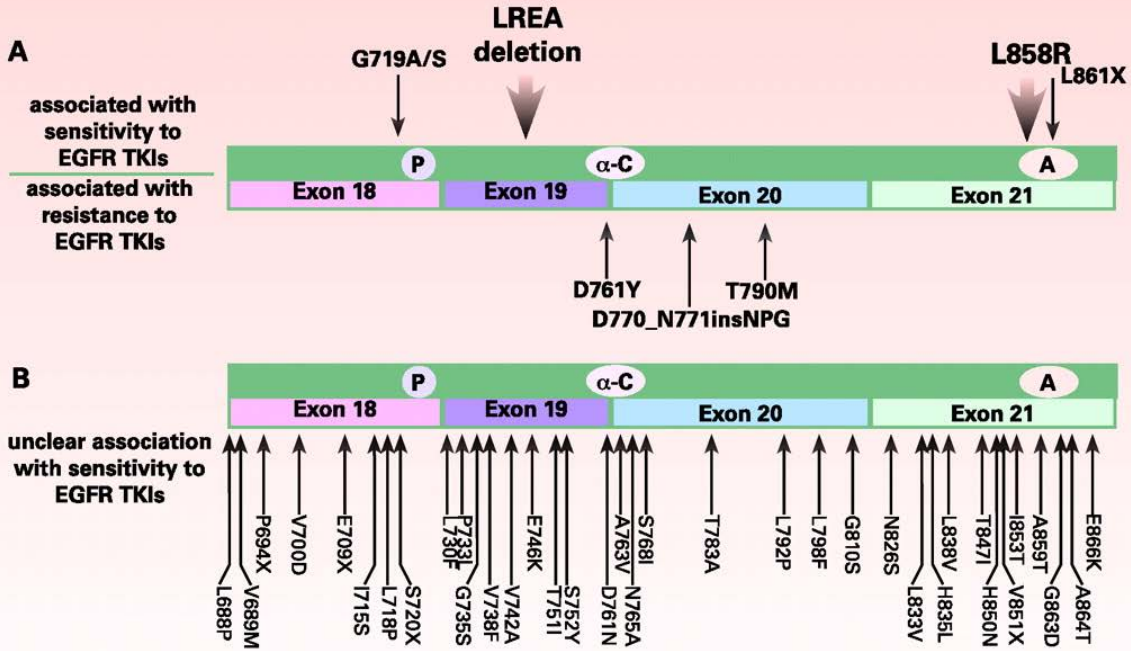
Blume-Jensen P, Hunter T. *Nature 2001: 411: 355-365*

Distribution of mutations in the TK domain of EGFR: meta-analysis of five studies (n=1256)



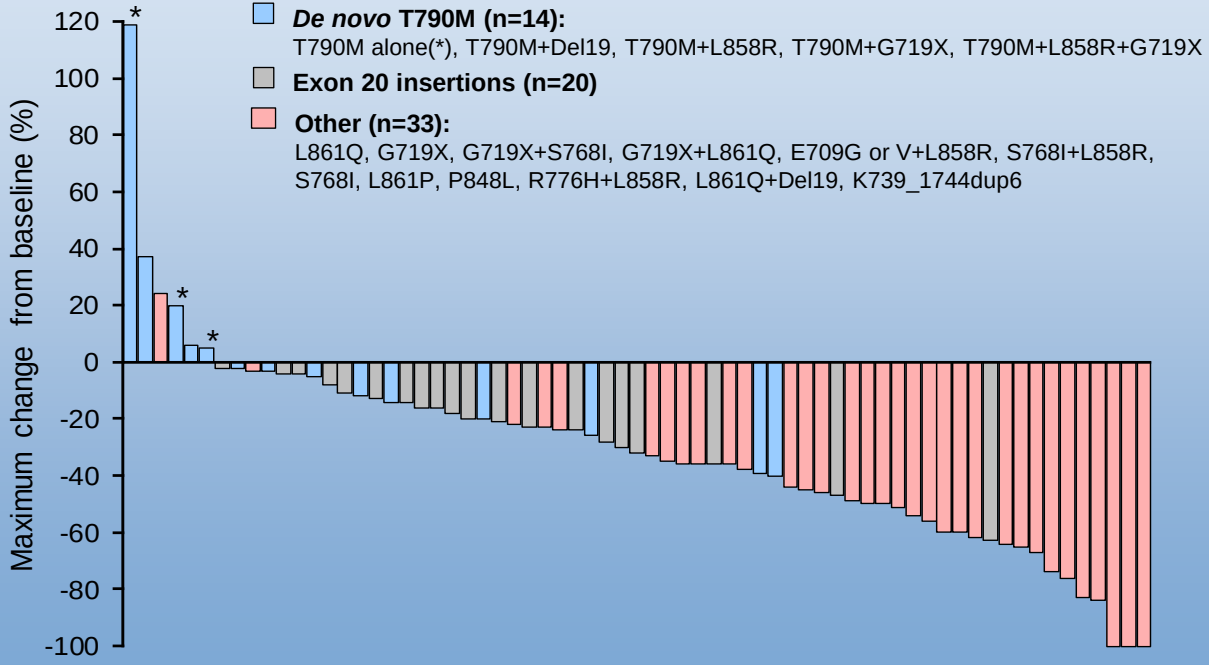
TK: tyrosine kinase; EGFR; epidermal growth factor receptor

Gregory J. Riely, Katerina A. Politi, Vincent A. Miller and William Pao. CCR 2006



Tumour shrinkage in patients with uncommon mutations

Independent review (n=67†)



†8 patients were not included due to insufficient data

Yang JC et al. Lancet Oncology 2015

Activity of afatinib in specific uncommon EGFR mutations

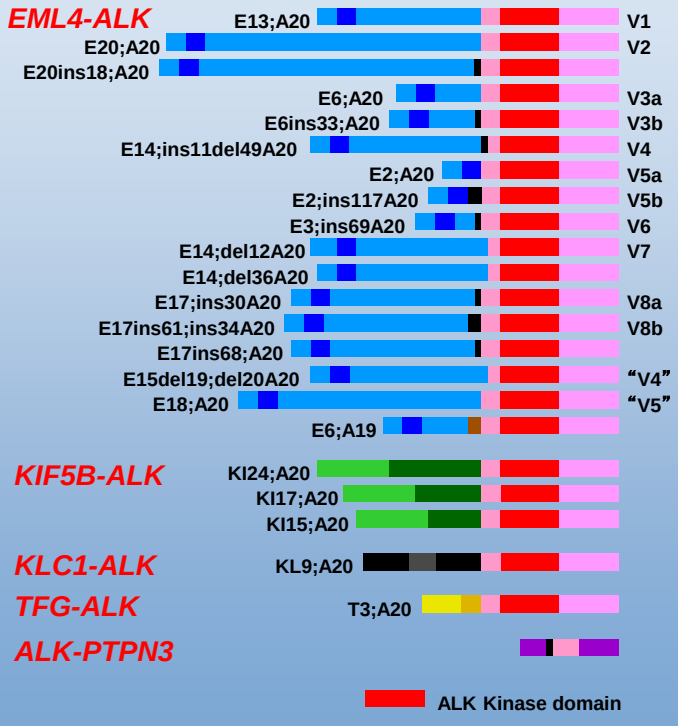
Genotypes		ORR, n (%)	PFS (months), median (95% CI)	OS (months), median (95% CI)
G719X (n=18)	G719X (n=8) G719X+T790M (n=1) G719X+S768I (n=5) G719X+L861Q (n=3) G719X+T790M+L858R (n=1)	14 (78)	13.8 (6.8–NE)	26.9 (16.4–NE)
L861Q (n=16)	L861Q (n=12) L861Q+G719X (n=3) L861Q+Del19 (n=1)	9 (56)	8.2 (4.5–16.6)	16.9 (15.3–22.0)
S768I (n=8)	S768I (n=1) S768I + G719X (n=5) S768I +L858R (n=2)	8 (100)	14.7 (2.6–NE)	NE (3.4–NE)

Note: A patient may be presented in more than one category

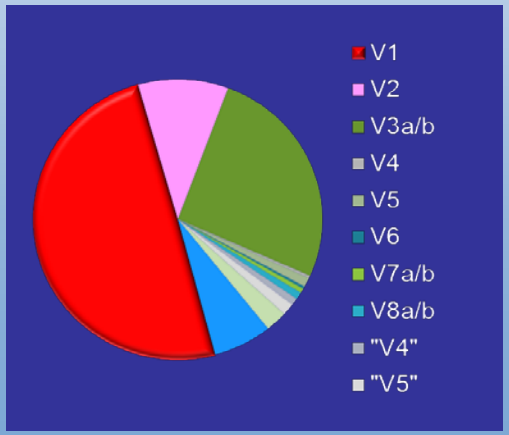
NE = not estimable

Yang JC et al. Lancet Oncology 2015

EML4-ALK fusion variants in NSCLC



- Several *EML4-ALK* fusion variants have been identified in NSCLC that demonstrate gain-of-function properties
- ALK tyrosine kinase activity is required for transforming activity
- Evidence shows ALK inhibitors lead to tumor shrinkage in vivo, and suggests oncogene addiction, and the potential target for therapeutic intervention



Ou et al., *Oncologis*t 2012; 2012;17:1351-75

Published fusion partners in *ALK*-rearranged NSCLC

Number	Fusion partner	Reference
1	EML4	Seto, *Nature* 2007; Rihova, *Cell* 2007
2	KIF5B	Takeuchi, *Clin Cancer Res* 2009
3	TFG	Rihova, *Cell* 2007
4	KCL1	Togashi, *PLoS* 2012
5	STRN	Majewski, *J Path* 2013
6	TPR	Choi, *J Thorac Oncol* 2014
7	HIP1	Fang, *J Thorac Oncol* 2014; Hong *J Thoracic Oncol* 2014
8	SOCS5	Drilon, *Clin Cancer Res* 2014
9	CLIP4	Drilon, *Clin Cancer Res* 2014
10	BRIC6	Shan, *J Thoracic Oncol* 2015
11	DCTN1	Iyevleva, *Cancer Lett* 2015
12	SQSTM1	Iyevleva, *Cancer Lett* 2015
13	EIF2AK	Ali, *Oncologist* 2016
14	PPM1B	Ali, *Oncologist* 2016
15	PRKAR1A	Ali, *Oncologist* 2016

ALK kinase domain mutations – drug efficacy-

	1st gen	2nd gen			3rd gen
	Crizotinib	**Alectinib**	**Brigatinib**	**Ceritinib**	**Lorlatinib**
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res [4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens [1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

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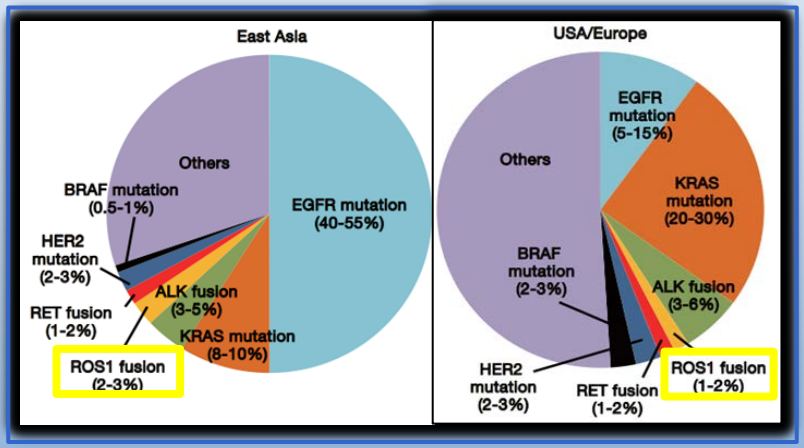
1. Shaw NEJM 2016
2. Toyokawa JTO 2015
3. Katayama STM 2012
4. Katayama CCR 2014
5. Ou Lung Cancer 2015
6. Ceccon MCR 2014
7. Friboulet Cancer Discov 2014
8. Kodityal Lung Cancer 2016
9. Zou Cancer Cell 2015
10. Bayliss Cel Mol Lif Sci 2015

Courtesy- Dr. Christine Lovly

ROS1 fusions

- The ROS1 oncogene encodes an orphan tyrosine kinase related to *ALK* and insulin-receptor family members[1]
- ROS1 rearrangements have been identified in a number of different tumor types
  - ROS1 fusion events activate growth and survival signalling pathways common to other receptor tyrosine kinases[2]
- Approximately 1–3% of NSCLCs involve ROS1 rearrangements[3-6]
- Crizotinib has shown antitumor activity in ROS1-positive NSCLC[7]



Kohno T et al 2015.[6]

1. Acquaviva J et al. Biochim Biophys Acta 2009;1795:37–52
2. Davies KD et al. Clin Cancer Res 2013;19:4040–5
3. Chen YF et al. J Thorac Oncol 2014;9:1171-9
4. Bergethon, K et al. J Clin Oncol 2012;30:863-70
5. Davies K et al. 2012;18:4750-9
6. Kohno T et al. Transl Lung Cancer Res. 2015 Apr; 4(2): 156–64
7.. Shaw AT et al. N Engl J Med 2014;371:1963–71

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; ROS1, c-Ros oncogene.

Fusion partners and fusion variants in *ROS1*+ NSCLC

#	Fusion partner	Chromosomal breakpoint	Reference	Total
1	CD74	C6;R32	Li, 2007	1
		C6;R34	Rikova, 2007	2
2	SLC34A2	S4;R32	Rikova, 2007	3
		S4;R34	Rikova, 2007	4
		S13del2046; R32	Takeuchi, 2012	5
		S13del2046; R34	Takeuchi, 2012	6
3	SDC4	S2;R32	Takeuchi, 2012	7
		S2;R34	Takeuchi, 2012	8
4	GOPC	F3;R36	Rimkunas, 2012	9
		F7;R35	Suehara, 2012	10
5	ERZ	E10;R34	Takeuchi, 2012	11
		E10;R35	Zheng 2014	12
6	TPM3	T8;R35	Takeuchi, 2012	13
7	LRIG3	L16; R35	Takeuchi, 2012	14
8	CCDC6	C6;R34	Seo, 2012	15
9	CLTC	C31; C35	TCGA, Nature 2014	16
10	KRELR2	Not reported	Govindan, 2012	17
11	LIMA1	L10;R35	Shaw, 2014	18
12	MSN	M8; R34	Shaw, 2014	19
13	TMEM106B	T3;R35	Ou, 2015	20
14	TPD52L1	T3; R34	Zhu, 2016	21

Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small cell lung cancer

Study Design (NCT01945021)

Key entry criteria:

- ROS1-positive by central RT-PCR testing[a]
- Negative for translocation or inversion events involving the ALK gene by a validated ALK assay[b]
- Locally-advanced or metastatic NSCLC
- ≤3 lines of prior systemic chemotherapy
- ECOG PS 0 or 1
- Measurable disease
- Stable treated brain metastases allowed

→ **Crizotinib 250 mg BID PO, continuous dosing (N=127)** →

Endpoints

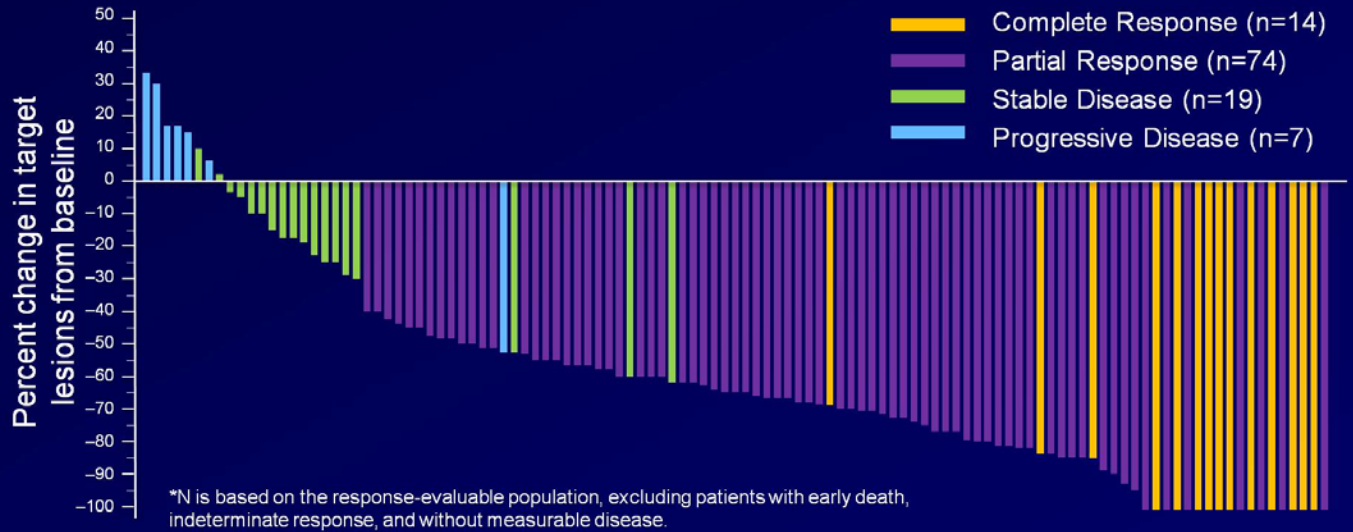
- Primary
  - ORR (RECIST 1.1, by IRR)
- Secondary
  - Duration of response
  - Time to response
  - Disease control rate
  - PFS
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30)

[a]ROS1 status determined using a validated Amoy RT-PCR assay.
[b]ALK status determined using by a validated ALK assay (such as Abbott Vysis ALK FISH test, Ventana ALK IHC test, or Amoy ALK RT-PCR test).
ALK, anaplastic lymphoma kinase; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Score; EORTC, European Organisation for the Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire C30; FISH, fluorescence in situ hybridization; IRR, independent radiology review; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ROS1, c-ros oncogene 1; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcription polymerase chain reaction.

Goto K. et al. ASCO 2016 abstract 9022

Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small cell lung cancer

IRR-assessed Best Percent Change from Baseline in Target Lesion Size*



*N is based on the response-evaluable population, excluding patients with early death, indeterminate response, and without measurable disease.

IRR, independent radiology review.

Goto K. et al. ASCO 2016 abstract 9022

RET rearrangement in Lung Cancer & other solid tumors

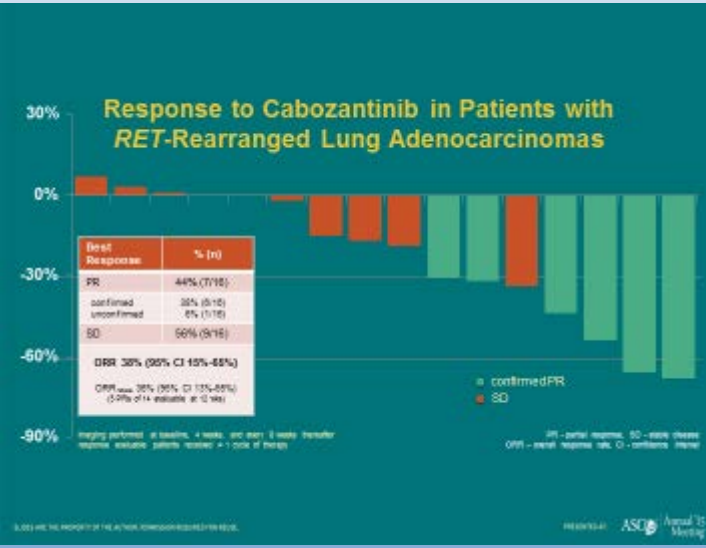
RET+ Lung Cancer	*RET*+ *Solid tumors*
KIF5B-RET	*KTN1-RET (thyroid)*
*CCDC6-RET**	*CCDC6-RET* (colon, thyroid)
*NCOA4-RET**	*NCOA4-RET* (colon, thyroid))
TRIM33-RET	*TRIM33-RET* (thyroid)
**same chromosome (10) as RET*	*TRIM24-RET* (thyroid)
Santoro *Eur J Endocrin* 2006; 155: 645-653 Gainor & Shaw Oncologist 2013; 18: 865-875 Stransky *Nat Commun* 2014 Sep 10;5:4846	*TRIM27-RET* (thyroid)
	PRKARIA-RET (thyroid)
	RAB61P2-RET (thyroid)
	GLOGA5-RET (thyroid)
	PCm1-RET (thyroid)
	TBL1XR1`-RET (thyroid)
	SPECC1l-RET (thyroid)
	AKAP13-RET (thyroid)
	FKBP15-RET (thyroid)
	ERC1-RET (breast)

RET inhibitors

Compound	Tradename	Manufacturer	IC_{50} (nM) In vitro kinase	IC_{50} (nM) Cellular kinase	IC50 (nM) In vitro kinase RET V804M	Other targets
Regorafenib (1)	Stivarga	Bayer	1.5	~10	NR	VEGFR1-3, BRAF, c-kit, PDGF-β
Levantinib (2)	Lenvima	Eisai	1.5	48	NR	VEGFR1-3, FGFR1-3, c-kit, PDGFR
Alectinib (7)	Alecensa	Roche/Chugai	4.8	?	53 V804L (32)	ALK (1.9 nM)
Cabozantinib (3)	Cometriq	Exelixis	5.2	27-85	4094	VEGFR2, MET
Ponatinib (4)	Iclusig	ARIAD	7	0.7-11	12	Bcr-abl, FGFR1-4
Sunitinib (4)	Sutent	Pfizer	30	40-164	55	VEGFR, PDGFR, c-kit, Flt-3
Sorafenib (5)	Nexaavar	Bayer	47	~20-50	12	RAF, VEGFR2-3, PDGFR, c-kit, Flt-3
Vandetanib (6)	Capresia	AstraZeneca	100	NR	> 10,000	VEGFR, EGFR

1. Wilheim, 2011; 2. Oamoto, 2013; 3. Bentzein 2013; 4. Mologni, 2013; 5. Carlomagno 2006; 6. Carlomagno 2002.
7. Kodama et al, Mol Cancer Ther 2014

Cabozantinib in RET fusion

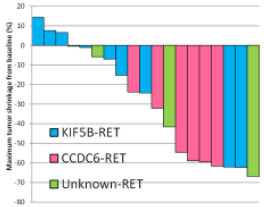


Vandetanib in RET fusions NSCLC

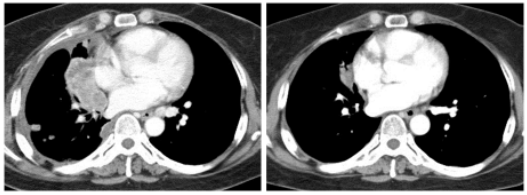
Primary analysis in 17 eligible patients

- The ORR was 53% (90% CI, 31 to 74) of which 9 partial responses met the primary endpoint.

Response to vandetanib in RET-rearranged NSCLC (n = 19: ITT population)



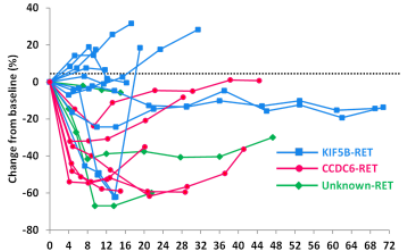
Effect of vandetanib treatment



Baseline | After 20 Weeks

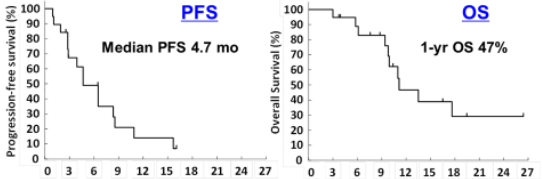
- This patient with CCDC6-RET NSCLC had a partial response with a 62% reduction in tumor burden.

Changes of target tumor burden over time (n = 19; weeks)



- The median DOR was 5.6 months (range, 1.5 to 9.1).
- On May 2016, 2 responders are ongoing over 1 years.

Kaplan-Meier plots (n = 19; months)



LURET study, ASCO 2016

Levantinib in RET fusion NSCLC

台大醫院 NTUH

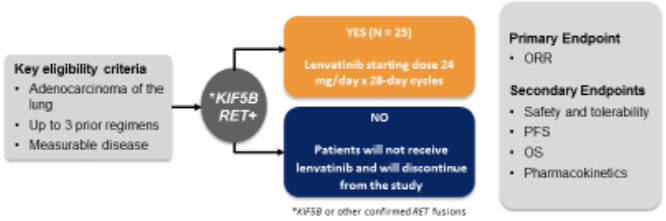
PHASE 2 STUDY OF LENVATINIB IN PATIENTS WITH *RET* FUSION–POSITIVE ADENOCARCINOMA OF THE LUNG

Vamsidhar Velcheti,[1] Toyoaki Hida,[2] Karen L. Reckamp,[3] James C. Yang,[4] Hiroshi Nokihara,[5] Pallavi Sachdev,[5] Kevie Feit,[5] Tomoki Kubota,[7] Takuya Nakada,[7] Corina E. Dutcus,[8] Min Ren,[6] Tomohide Tamura[9]

[1]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Aichi Cancer Center Hospital, Nagoya, Japan; [3]City of Hope Hospital, Duarte, CA, USA; [4]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei City, Taiwan; [5]National Cancer Center Hospital, Tokyo, Japan; [6]Eisai Inc., Woodcliff Lake, NJ, USA; [7]Eisai Co., Ltd., Tokyo, Japan; [8]St Luke's International Hospital, Tokyo, Japan.

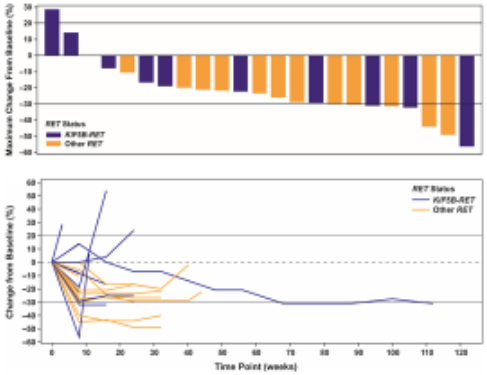
esmo.org

Study Design



Maximum Percentage Change From Baseline in Sum of Target Lesion Diameters

- The majority of patients showed a decrease in tumor burden from baseline



ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Efficacy Outcomes Overall and by *RET* Fusion

- Of note, 9 (36%) patients received > 2 prior anticancer regiments
- Partial responses and stable disease were demonstrated in both patients with *KIF5B-RET* and other *RET* fusions
- Objective response rate was similar between the *KIF5B-RET* and other *RET* fusion groups
- Lenvatinib showed similar efficacy in patients with and without prior RET-targeted therapy (see Table 3 in the poster)

	KIF5B-RET (n = 13)	Other *RET* (n = 12)	Total (n = 25)
Best overall response, n (%)			
Partial response, n (%)	2 (15.4)	2 (16.7)	4 (16.0)
Stable disease, n (%)	6 (46.2)	9 (75.0)	15 (60.0)
Progressive disease, n (%)	3 (23.1)	0	3 (12.0)
Not evaluable, n (%)	1 (7.7)	1 (8.3)	2 (8.0)
Unknown, n (%)	1 (7.7)	0	1 (4.0)
Objective response rate, n (%)	2 (15.4)	2 (16.7)	4 (16.0)
Median PFS, months (95% CI)	3.6 (1.0–NE)	9.1 (2.3–10.2)	7.3 (3.6–10.2)
Median OS, months (95% CI)	11.4 (4.2–NE)	NE (4.3–NE)	NE (5.8–NE)
Disease control rate, n (%)	8 (61.5)	11 (91.7)	19 (76.0)
Clinical benefit rate, n (%)	4 (30.8)	8 (66.7)	12 (48.0)

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Targeting RET in patients with RET-rearranged lung cancers: results from a global registry

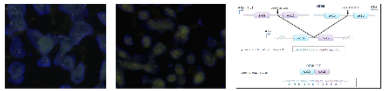
Gautschi O, Wolf J, Milia J, Filleron T, Carbone D, Camidge R, Shih J, Awad M, Cabillic F, Peled N, Van Den Heuvel M, Owen D, Kris M, Janne P, Besse B, Cho B, Karp D, Rosell R, Mazieres J, Drilon A, on behalf of the GLORY investigators. Coordinating centers: University Hospital Toulouse, France; Cantonal Hospital Lucerne, Switzerland; MSKCC New York, USA.

ABSTRACT

Background: Alongside prospective clinical trials for patients (pts) with non-small cell lung cancers (NSCLC) driven by rare genomic alterations, registries can provide complementary information on response to targeted therapies. We present the results of a global registry of RET-rearranged NSCLC, providing the largest data set on outcomes with RET-directed therapy so far. **Methods:** Pts were identified by a global, multicenter network of thoracic oncologists. IRB approval was obtained according to local requirements. Eligibility included a diagnosis of NSCLC harboring a RET fusion by FISH, RT-PCR or NGS. Anonymized data (age, gender, smoking, histology, stage, systemic therapy, survival) were collected centrally and evaluated by an independent statistician. In an analysis of pts treated off-protocol with multikinase inhibitors known to target RET, the primary endpoint was best objective response (RECIST). **Results:** 132 pts with RET-rearranged NSCLC from the USA, Asia, and Europe were registered. Median age at diagnosis was 61 years (range: 28-89), 52% were female, 62% were never-smokers, 97% had adenocarcinoma, and 91% had stage IIIB/IV disease. 41 pts (31%) received RET inhibitor therapy off-protocol: cabozantinib (14), vandetanib (11), sunitinib (10), sorafenib (2), alectinib (1), lenvatinib (1), nintedanib (1), and ponatinib (1). Most pts received a RET inhibitor in the third-line setting (range: 1st-8th line). Median PFS was 2.9 months (95%CI: 1.3-5.6), OS 6.8 months (95%CI: 3.9-14.3); median duration of therapy 2.2 months (range: 0.5-12.2). 8 pts remain on treatment. In 35 pts with serial imaging evaluated by RECIST, ORR was 23% (1 CR, 7 PR, 12 SD, 14 PD, 1 not measurable) and DCR 57%. Individual ORR (DCR) for cabozantinib and vandetanib was 31% (62%) and 18% (46%), respectively. No unexpected adverse effects were reported. **Conclusions:** RET inhibitors are active in a proportion of pts with RET-rearranged NSCLC. Consistent with results from an ongoing phase II trial of cabozantinib (Drilon, ASCO 2015), this proportion is lower than that observed with targeted therapy for EGFR-mutant and ALK-rearranged NSCLC. New therapeutic approaches and an improved understanding of tumor biology and response are needed.

AIMS & METHODS

This registry was opened to collect information about individual patients with RET-rearranged NSCLC of all stages. Investigators have to obtain consent and can use FISH, RT-PCR or NGS. Data are anonymized, collected in a central database, and evaluated by an independent statistician. Patients treated with tyrosine kinase inhibitors (TKI) known to target RET are eligible only if treated outside of a clinical protocol. Response to TKI was assessed locally by RECIST1.1.



Panel 1: Lung adenocarcinoma with rearrangement of KIF5B and RET by FISH (left and middle). Matched NGS result of the same tumor, confirming the KIF5B-RET fusion (right).

Images: J. Diebold (Lucerne) and F. Leenders (Cologne)

RESULTS

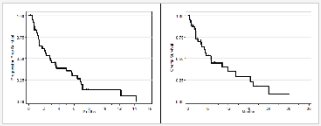
Characteristics	All	With RET inhibitor	P-value*
Eligible Patients	132 (100%)	41 (31%)	
Age [years] median (range) below 70 70 and older	61 (28 – 89) 102 (77%) 30 (23%)	58 (29 – 83) 34 (83%) 7 (17%)	 NS
Gender female male	69 (52%) 63 (48%)	23 (56%) 18 (44%)	NS
Smoking status (n=131) never former current	81 (62%) 37 (28%) 13 (10%)	26 (65%) 8 (20%) 6 (15%)	NS
Histology Adenocarcinoma NSCLC NOS Squamous	128 (97%) 3 (2%) 1 (1%)	40 (98%) 1 (2%) 0	NS
UICC stage (n=129) I-II III IV	12 (9%) 23 (18%) 94 (73%)	0 6 (15%) 33 (85%)	0.027
Concomitant driver EGFR mutation KRAS mutation MET amplification	3 (2%) 2 (2%) 1 (1%)	0 1 (2%) 1 (2%)	NS

Panel 2: Patients included in the registry at the first data cutoff in December 2015. NS = not significant by chi2 or Fishers exact test for subgroup "with RET inhibitor" versus "others"

RET inhibitor	Patients	IC50 for RET	Further targets
Cabozantinib	14 (34%)	4 nM	VEGFR2, MET, KIT, AXL
Vandetanib	11 (27%)	130 nM	VEGFR2
Sunitinib	10 (24%)	224 nM	VEGFR2, PDGFRß, KIT
Sorafenib	2 (5%)	50 nM	RAF1, BRAF, VEGFR2, PDGFR
Alectinib	1 (2%)	5 nM	ALK
Lenvatinib	1 (2%)	35 nM	VEGFR1-3
Nintedanib	1 (2%)	36 nM	VEGFR1-3, PDGFR1-3, FGFR1-3
Ponatinib	1 (2%)	25 nM	ABL, PDGFRa VEGFR2, FGFR1

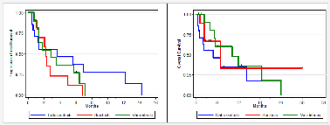
Inhibitor	CR	PR	SD	PD	NE	Missing	Total
Cabozantinib	1	3	4	5	0	1	14
Vandetanib	0	2	3	6	0	0	11
Sunitinib	0	2	3	3	1	1	10
Sorafenib	0	0	2	0	0	0	2
Alectinib	0	0	0	0	0	1	1
Lenvatinib	0	0	0	0	0	1	1
Nintedanib	0	0	0	0	0	1	1
Ponatinib	0	0	0	0	0	1	1

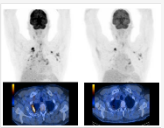
Panel 3: Inhibitors with known target effect for RET kinase used in the registry (top). Best response for individual RET inhibitors in patients with evaluable disease according to RECIST (bottom). NE = not evaluable.



Best RECIST response (N=35)	Progression free survival (N=41)	Overall survival (n=41)
CR = 1 (3%) PR = 7 (20%) SD = 12 (34%) PD = 14 (40%) NT = 1 (3%) ORR = 23% DCR = 57%	Median 2.9 months [95%CI= 1.3;5.6] 33 events (81%)	Median 6.8 months [95%CI=3.9;14.3] 24 events (59%)

Panel 4 : Kaplan Meier survival curves for all 41 patients with RET inhibitor therapy (top). RECIST response, PFS and OS from the start of first RET inhibitor (bottom). NE = not evaluable.





Panel 5: Survival curves for the 35 patients treated with cabozantinib, vandetanib or sunitinib (top). PET/CT of a patient at baseline (bottom left) and after 2 weeks of vandetanib (bottom right). Images: K. Strobel (Lucerne).

SUMMARY

1. This is the largest database of patients with RET-rearranged NSCLC.
2. Consistent with previous reports, tumor remissions were observed with cabozantinib, vandetanib and sunitinib.
3. The registry remains open for follow up, and inclusion of further patients with RET-targeted therapy.

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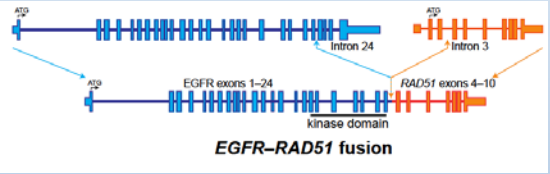
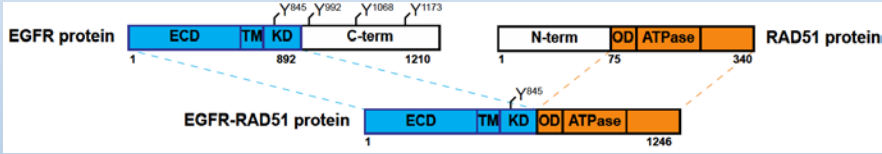
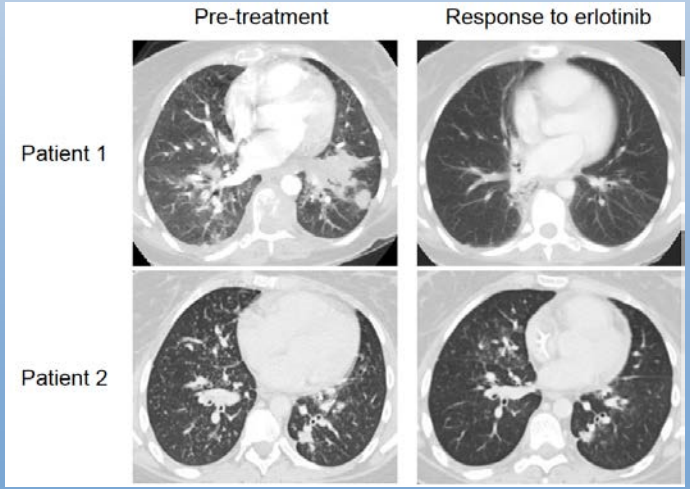
ASCO 2016 abstract 9014
Presenting author: oliver.gautschi@luks.ch

Rare EGFR Fusion



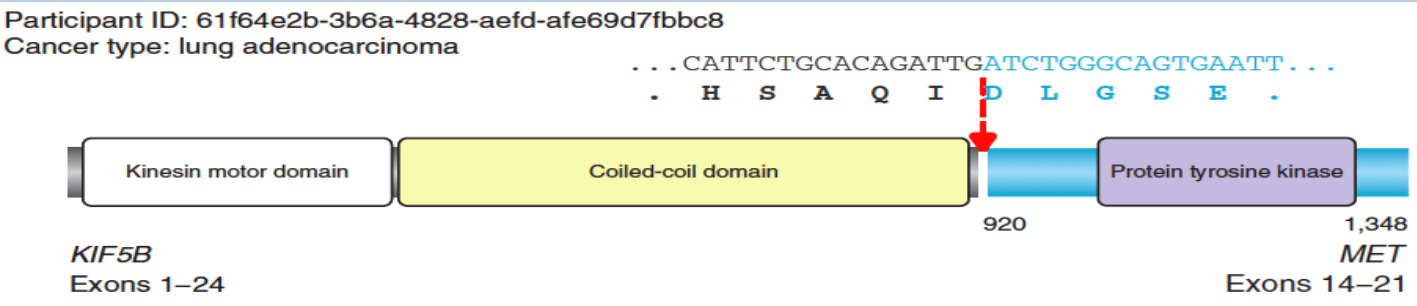




Konduri et al, *Cancer Discov. 2016 Jun;6(6):601-11.*

MET & *AXL* rearrangement in Lung Cancer

MET+ Lung Cancer	*AXL*+ Lung Cancer
KIF5B-MET	*AXL-MBIP*



Stransky *Nat Commun* 2014 Sep 10;5:4846

Seo *Genome Res* 2012; 22: 2109-2119

Summary of actionable RTK fusion partners identified in lung cancer

RTK	ALK	ROS1	MET	RET	NTRK1	NTRK2	EGFR	ERBB 4	FGFR 1	FGFR2	FGFR3	PDGFR-a	AXL
Fusion partners	EML4 KIF5B TFG KLC1 HIP1 TRP STRN SOCS5 CLIP4 BRIC6 DCTN1 SQSTM1 EIF2AK PPM1B PRKAR1A	GOCP (FIG) KIF5B CD74 CCDC6 SLC34A2 TPM3 ERZ LRIG3 KDELR2 LIMA1 MSN TMEM106B TPD52L1	KIF5B	NCOA4 KIF5B CCDC6 TRIM33	MPRIP CD74 RFWD2	TRIM24	CD74	ERZ	BAG4	KIAA1967	TACC3	SCAF11	MBIP

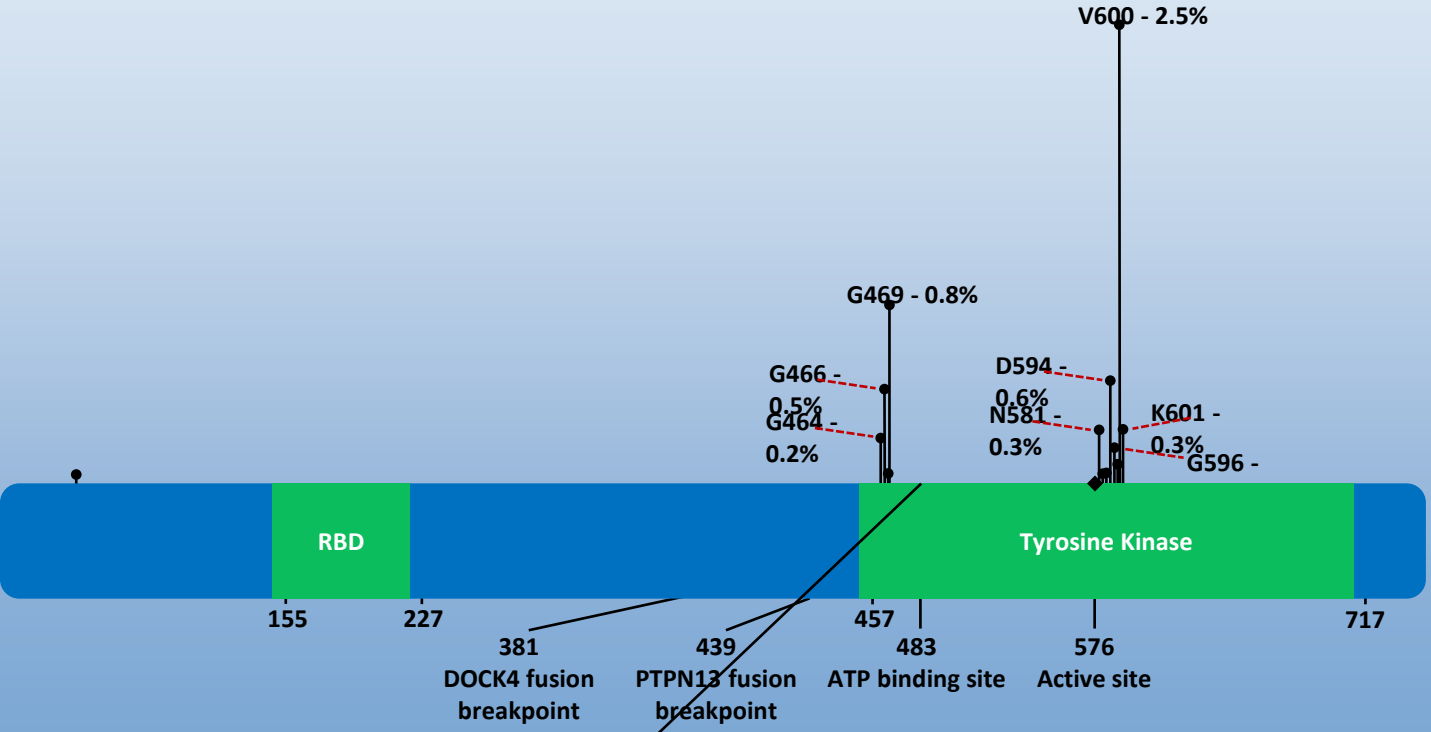
13 RTK fusions

36 different RTK fusion partners

KIF5B-, CCDC6- are recurring fusion partners, More to be discovered?

BRAF fusions in NSCLC

BRAF alteration frequency in 2179 lung adenocarcinoma cases



- Of the total 6.1% of adenocarcinoma case with *BRAF* alterations, G469x, D594x, G466x all were at 8+%.
- Focal *BRAF* amplifications defined as occuring on a <20 MB segment were at 8%.
- Two *BRAF* fusions were identified in this series with breakpoints between intron 9 and 10.

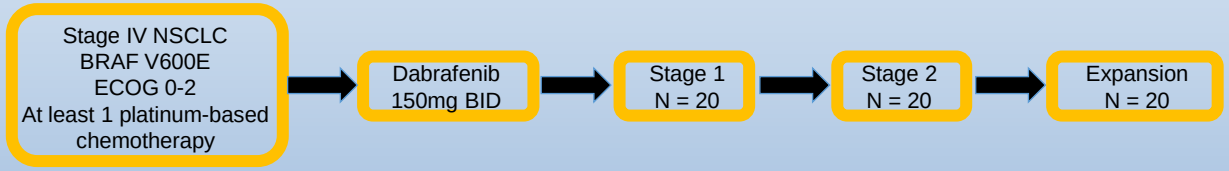
BRAF alterations in 3300 lung cases (%)

BRAF alteration	Adenocarcinoma (N=2179)	Non-small cell lung carcinoma (N=535)	Squamous cell carcinoma (SCC) (N=385)	Small cell lung carcinoma (SCLC) (N=201)
V600	2.5	0.4	0	0
G469	0.8	1.3	0.3	0
G466	0.5	0.6	0	0
D594	0.6	0	0	0
G464	0.2	0.4	0.3	0
N581	0.3	0	0	0
K601	0.3	0	0	0
G596	0.1	0.4	0	0
Other short variants	0.3	0	0	0
Amplification	0.5	0.2	0	0
BRAF fusion	0.1	0	0	0
TOTAL	6.1%	3.2%	0.8%	0

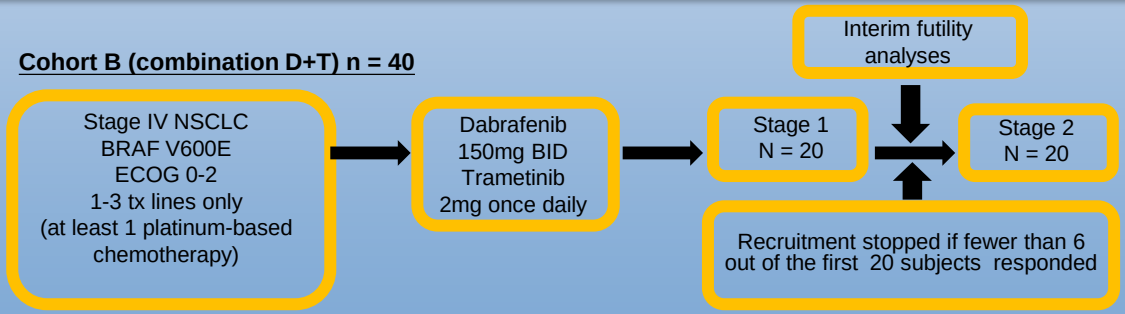
- From right to left, small cell lung cancer did not harbor *BRAF* alterations.
- Squamous cell carcinoma harbored 0.8% *BRAF* alterations none of which were *BRAF* V600E.
- Of the 3.2% of NSCLC NOS cases with *BRAF* alterations, 85% were non V600E *BRAF*.
- Of the 6.1% of adenocarcinoma case with *BRAF* alterations, >50% were non V600E *BRAF.*

BRF113928: Study Design

Cohort A (monotherapy) n = 60



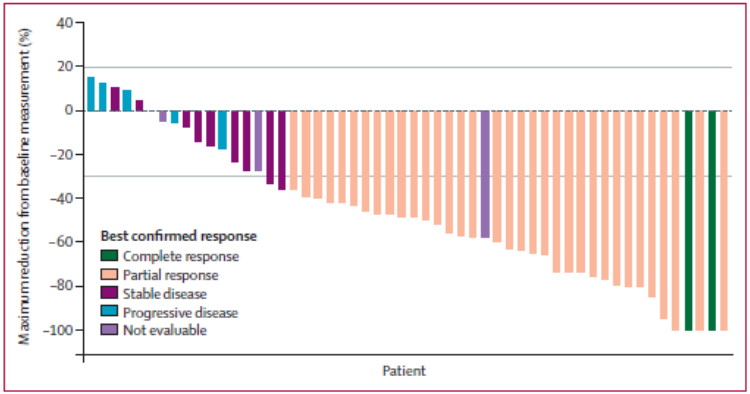
Cohort B (combination D+T) n = 40



Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

www.thelancet.com/oncology **Vol 17 July 2016**



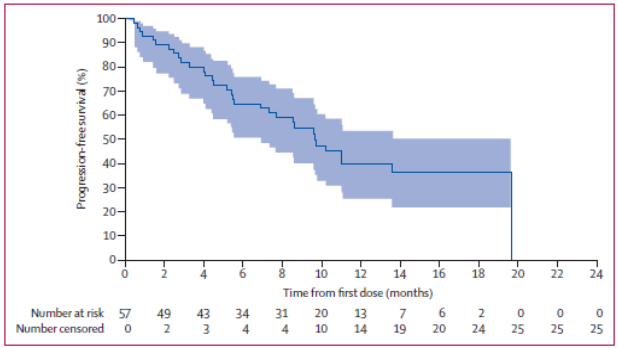


Figure 3: **Kaplan-Meier curve of investigator-assessed progression-free survival in patients receiving second-line or later treatment**
Shaded area represents 95% CI. Number of patients censored represent cumulative totals.

N=57, RR: 63.2%, DCR: 78.9%, PFS: 9.7M,

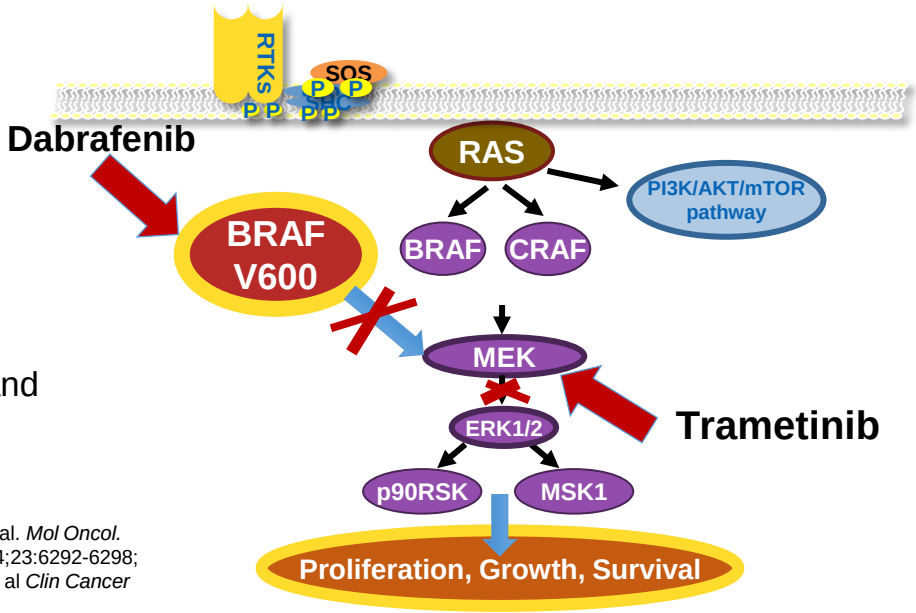
Dabrafenib single agent : RR: 33%, PFS: 5.5M

Planchard D. et. al. Lancet Oncol, 17 (2016), pp. 642–650

Dabrafenib Inhibits BRAF V600 Kinase and Trametinib Inhibits Downstream MEK Signaling

Dabrafenib mode of action
- Reversible, small molecule
- BRAF inhibitor
- ATP competitive
- BRAF V600E: IC_{50} 0.65 nM

Trametinib mode of action
- Reversible, small molecule
- MEK1 and MEK2 allosteric inhibitor
- MEK1 and MEK2: IC_{50} 0.7 and 0.9 nM



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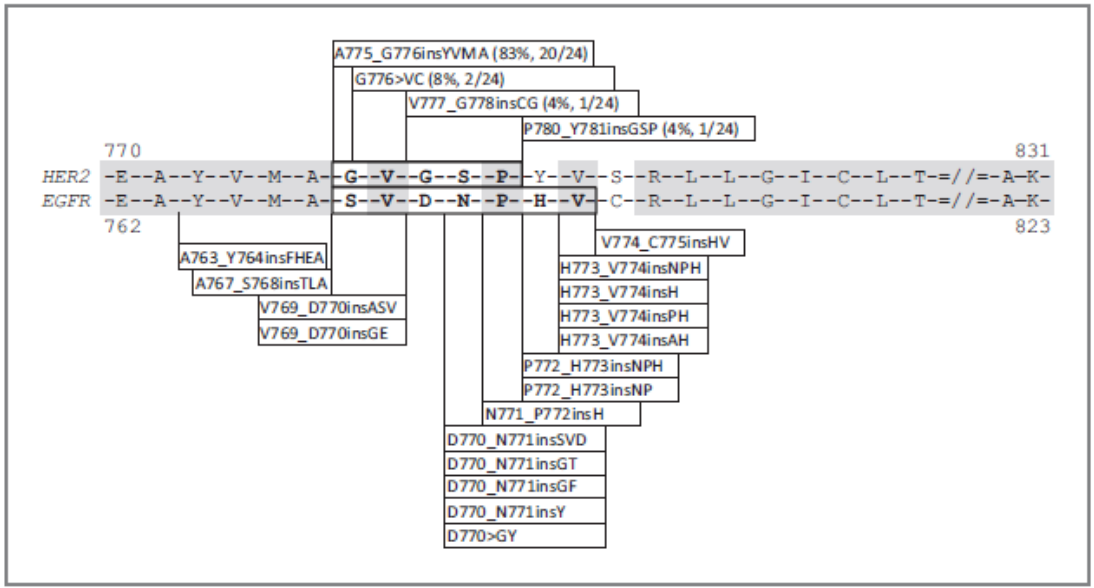
Published OnlineFirst July 3, 2012; DOI: 10.1158/1078-0432.CCR-12-0512

Clinical Cancer Research

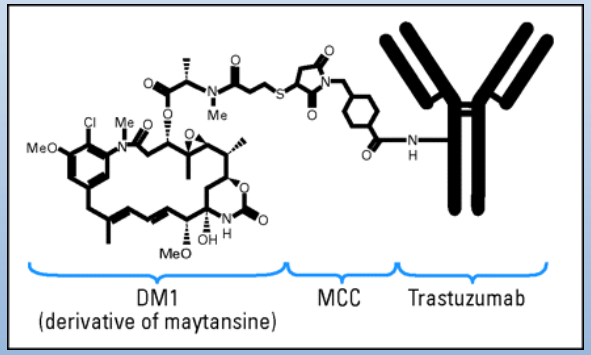
Human Cancer Biology

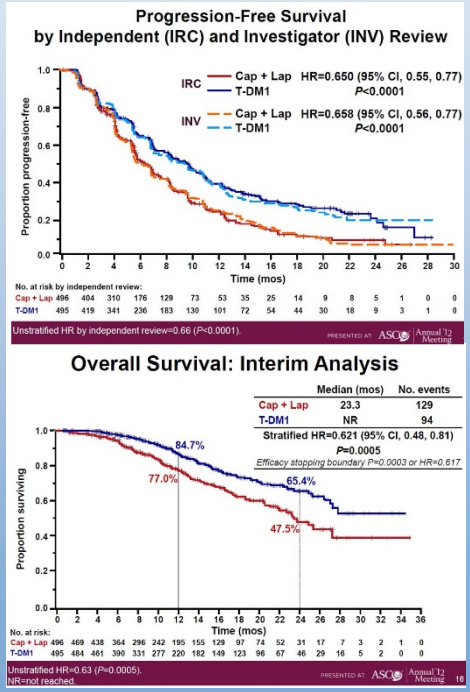
Prevalence, Clinicopathologic Associations, and Molecular Spectrum of *ERBB2* (*HER2*) Tyrosine Kinase Mutations in Lung Adenocarcinomas

Maria E. Arcila[1], Jamie E. Chaft[2], Khedoudja Nafa[1], Sinchita Roy-Chowdhuri[1], Christopher Lau[1], Michael Zaidinski[1], Paul K. Paik[2], Maureen F. Zakowski[1], Mark G. Kris[2], and Marc Ladanyi[1]



Immunotoxin: T-DM1 EMILIA





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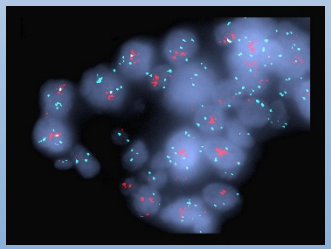
Methods of direct *MET* oncogene activation

Methods of direct MET activation

- *Amplification*
- *Point mutation*
- *Protein overexpression*
- *Rearrangement*



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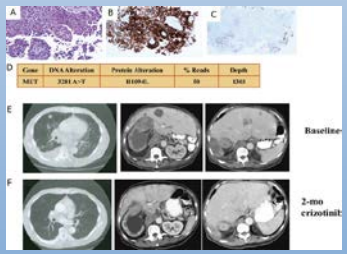

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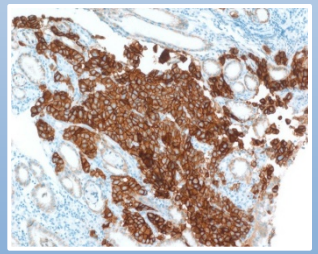
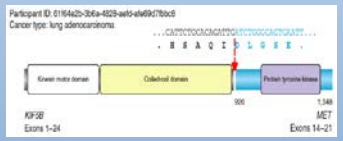


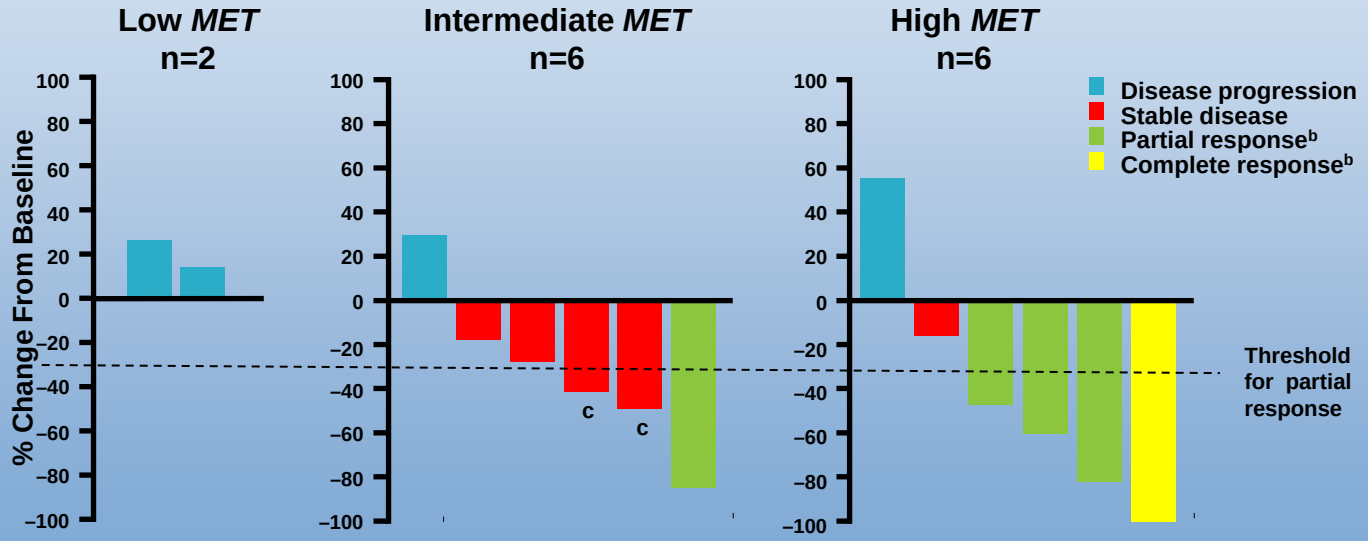
Jeeyun Lee, MD
Samsung Medical Center
Personal communication



Stransky et al *Nat Commun* 2014 Sep 10;5:4846

Efficacy of crizotinib in patients with advanced MET-amplified NSCLC

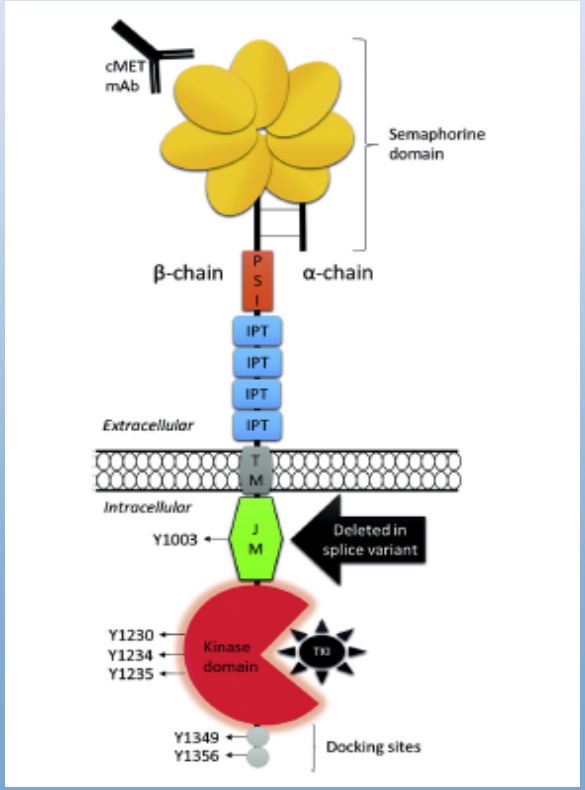
Best percent change from baseline in target tumor lesions[a] by patient



[a]Confirmed objective responses.
[b]Based on investigator assessment.
[c]Two patients in the intermediate *MET* group had an unconfirmed PR that was not confirmed in a second assessment.

Camidge DR et al. ASCO 2014 abstract 8001

NSCLC
cMET skipping exon 14 mutation



Nele Van Der Steen et al. JTO 2016;11(9):1423-1432

NSCLC
cMET skipping exon 14 mutation

Nele Van Der Steen et al. JTO 2016;11(9):1423-1432

Table 1. Overview cMET Exon 14 Skipping Patients Who Received Anti-cMET Therapy: An Overview of the Characteristics of the Patients Described Thus Far Who Presented with cMET Exon 14 Skipping and Were Treated with cMET Small Molecule Inhibitors

Age	Sex	Smoker	Cancer Type	Previous Treatments	cMET ex14 Splice Mutation	Other Genetic Information	cMET Inhibitor	Response	Ref
84	Female	Never	Stage III histiocytic sarcoma	None	c2888-5_2944del62	*TP53* pR175H *ZMYM3* c3008-1G>A	Crizotinib	-60% progression after 11 mo	7
82	Female	25 PY	Stage IV large cell lung cancer	Resection	c3028G>C	*TP53* pN30fs*14	Capmatinib	-53%	7
66	Female	4 PY	Stage I squamous carcinoma lung	Resection Gemcitabine + carboplatin Palliative radiotherapy Paclitaxel + carboplatin CHK1 inhibitor	c3028+1G>T	NA	Capmatinib	-61%	7
80	Female	Never	Stage Ia lung adenocarcinoma	Docetaxel Pemetrexed Radiotherapy	c3028G>C	*cMET* amplification	Cabozantinib	Stable disease	6
78	Male	Yes	Stage IV adenocarcinoma lung	Carboplatin + pemetrexed + bevacizumab Pemetrexed + bevacizumab Albumin-bound paclitaxel	c3024_3028delAGAAGGT ATATT	*CDKN2A* deletion *CDKN2B* deletion	Crizotinib	-30%	6
65	Male	Yes	Stage IV adenocarcinoma lung	Cisplatin + pemetrexed + bevacizumab Pemetrexed + bevacizumab Gemcitabine	c3028+1G>T	*EGFR* WT *ALK* WT	Crizotinib	-31%	6
90	Female	Never	Metastatic adenocarcinoma lung	Pemetrexed Gemcitabine	c3028G>T	*CDK4* amplification *MDM2* amplification	Crizotinib	-47%	6
64	Female	Never	Metastatic poorly differentiated adenocarcinoma	Chemotherapy (not specified)	c3028G>A	*EGFR, KRAS, BRAF, ALK, ROS1* WT cMET amplification	Crizotinib	Ongoing response at 8 mo	74
71	Male	15 PY	Metastatic lung adenocarcinoma	Radiotherapy (3000 cGy) Carboplatin + pemetrexed	c3082G>C	No *cMET* amplification	Crizotinib	Ongoing response at 6 mo	75
86	Male	Never	Metastatic lung adenocarcinoma	Radiotherapy Pemetrexed	c2887-18_2887-7del12	NA	Crizotinib	Response, but discontinued because of pneumonitis	76
61	Male	Never	Sarcomatoid NSCLC	Radiotherapy Carboplatin + paclitaxel + bevacizumab	c2888-5_2890TTAAGATC>A c3028+2T>G c3280C>T	NA	Crizotinib	Partial response Progression after 5 mo	77

cMet, mesenchymal-epithelial transition factor; Ref, reference; *cMet*, MMNG HOS Transforming gene; *TP53*, tumor protein p53 gene; *ZMYM3*, zinc finger *MYM*-containing 3 gene; PY, pack-years; NA, not applicable; *CDKN2A*, cyclin-dependent kinase inhibitor 2A gene; *CDKN2B*, cyclin-dependent kinase inhibitor 2B gene; *EGFR*, epidermal growth factor receptor gene; WT, wild type; *ALK*, anaplastic lymphoma receptor tyrosine kinase gene; *CDK4*, cyclin-dependent kinase 4 gene; *MDM2*, MDM2 proto-oncogene, E3 ubiquitin protein ligase gene; *KRAS*, Kirsten rat sarcoma viral oncogene homolog gene; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase gene; NSCLS, non-small cell lung cancer.

Looking for Needle in the hay

台大醫院 NTUH

Patients with driver mutations current challenges

- Detection of driver mutations : NGS
- Detection and quantitation of T790M: plasma test
- Selection of TKIs 1st line vs. 2nd line
- CNS metastasis
- Poor performance patients
- Selecting patients for combination therapy (bevacizumab, chemotherapy other targeted therapy)

Service

Resear

Teaching

總結

In conclusion

Presented by: 楊志新 James Chih-Hsin Yang