Pedro Solivan, MD

Other Targeted Agents in NSCLC

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers Bureau: BMS, BI, Janssen

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

RET, PI3CK, HER-2 and KRAS

The Medical Educator Consortium

7th Annual Puerto Rico Winter Cancer Symposium

RET Fusion

- Patients: AdenoCA and adenoSCC carcinoma, never or former smokers, poor differentiation ?, earlier LN metastases
- Frequency:
  - 1.4% in all,
  - 5.6 % in “triple negative”(EGFR, ALK, KRAS)
  - 6.3% in non smokers negative for EGFR, KRAS, ALK, HER2, BRAF, and ROS1
  - 16% in non smokers negative for EGFR, KRAS, ALK, ROS1, NRAS, BRAF, HER2, PIK3CA, MEK1, and AKT
- Biology: 4-5 variants have been identified in NSCLC so far
  - Clinical significance is unknown.
  - KIF5B-, CCDC6-, NCOA4-. TRIM33

RET Rearrangements

- intact tyrosine kinase domain fused to an upstream gene partner
  - most common: *KIF5B*
  - others: *CCDC6, NCOA4, TRIM33, KIAA1468*
- result in ligand-independent dimerization and downstream growth pathway activation
- oncogenic *in vitro* and *in vivo*

Drilon AD, et al, Cancer Discov 2013;3:630-5, Kohno T, et al, Nat Med 2012;18:375-7, Saito M, et al, Carcinogenesis 2014;35:2452-6
Suehara Y, et al, Nat Med 2012;18:6599-608, Lipson D, et al, Nat Med 2012;18:382-40, Takeuchi K, et al, Nat Med 2012;18:378-81

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Methods of RET Detection

- RT-PCR
  - Cons: False negatives; 3 variants have been described in a matter of 12 months. Has to be multiplexed, i.e probes to all known variants. Unknown variants will not be detected.
- FISH break apart
  - Cons: if inversion involves a small locus it could be false negative; can not distinguish variants; cut off is 15% of nuclei with split signal; not widely available; low through output
- IHC
  - Current IHC antibodies do not correlate with RET fusion

Cabozantinib

- oral multi-tyrosine kinase inhibitor with potent activity against RET
  - inhibits growth of *RET*-rearranged lung cancers *in vitro* and *in vivo*
  - FDA-approved for progressive metastatic medullary thyroid cancers
- minimal activity in unselected non-small cell lung cancers
  - phase II randomized discontinuation trial
  - 60 patients with advanced NSCLCs
  - ORR 10%, median PFS 4 months

Kinase	IC_{50} (nM)
VEGFR2	0.035
MET	1.3
RET	5.2
KIT	4.6
AXL	7.0
FLT3	11.3
TIE2	14.3

ORR – overall response rate, PFS – progression-free survival, NSCLCs – non-small cell lung cancers

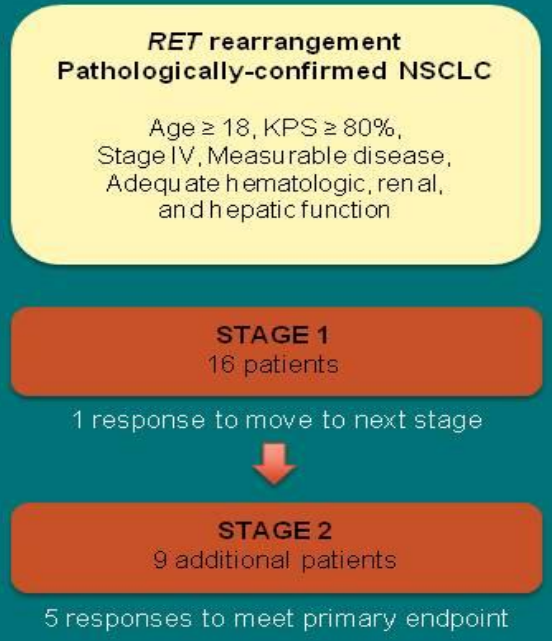
Yakes FM, et al, Mol Cancer Ther 2011;10:2298-308, Kodama T, et al, Mol Cancer Ther 2014;13:2910-8, Hellerstedt BA, et al, J Clin Oncol 2012;(suppl; abstr 7514)

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Study Design

- Phase II, open-label, single-center trial
  - cabozantinib, 60 mg daily, 28-day cycles
  - status: 20 patients treated, 18 of which were evaluable for response → stage I of Simon two-stage design completed (n=16) and reported here
- Objectives
  - Primary: overall response rate (ORR, RECIST v1.1)
  - Secondary: ORR at 12 weeks, progression-free survival (PFS), overall survival (OS), toxicity
- Identification of *RET* rearrangements
  - FISH: cutoff for positive test was 10% of cells with split green (5') and red (3') signals, or single red signals
  - next-generation sequencing



RECIST: Response Evaluation Criteria in Solid Tumors, Eisenhauer EA, et al, Eur J Cancer 2009;45:228-47

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Patients

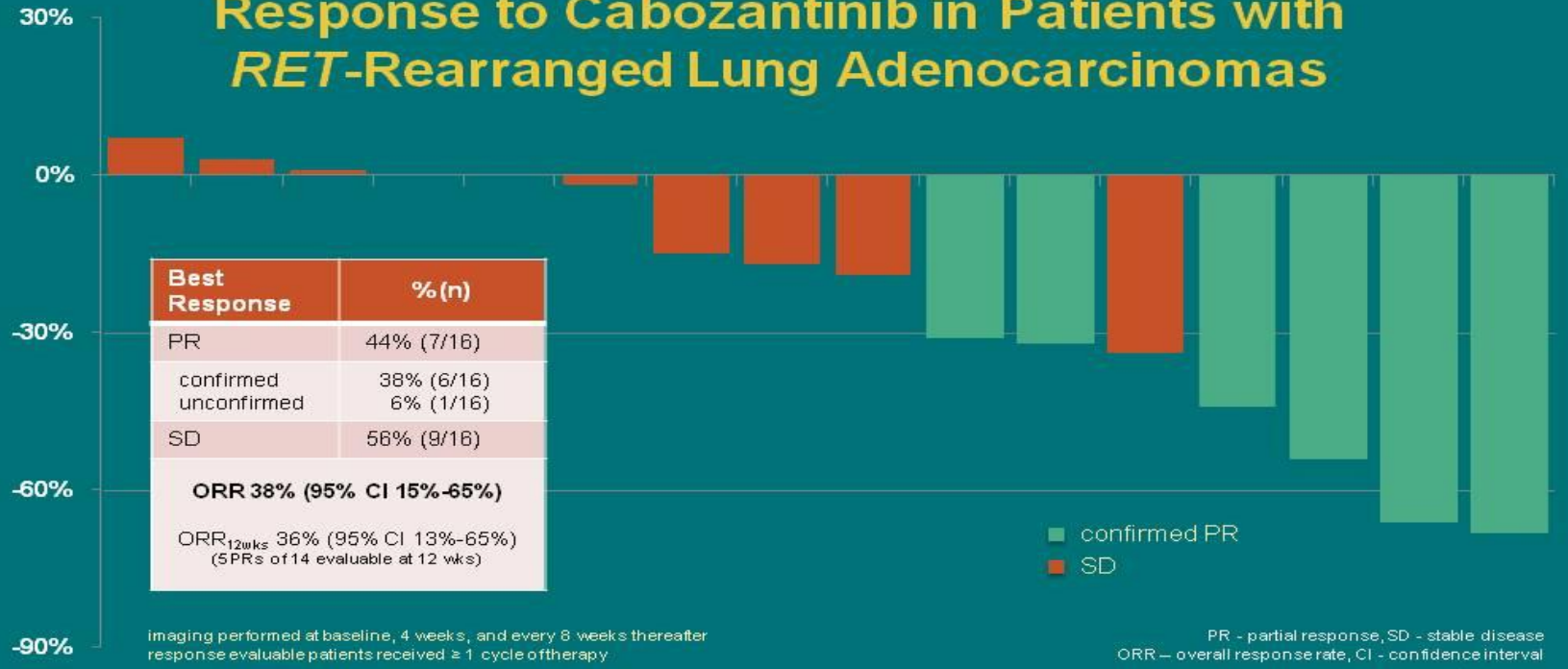
Patient Characteristics (Stage 1, n=16)		
Age	median 59 (range 38-80 years)	
Sex	Male Female	38% (n=6) 62% (n=10)
Race	Caucasian Asian African American	69% (n=11) 25% (n=4) 6% (n=1)
Cigarette smoking history	Never smoker >0-15 pack years >15 pack years	75% (n=12) 19% (n=3, range 1-7 pack years) 6% (n=1, 55 pack years)
Lines of prior chemotherapy	0 1 ≥ 2	25% (n=4) 44% (n=7) 31% (n=5)
Prior bevacizumab	Yes No	50% (n=8) 50% (n=8)
Histology	Adenocarcinoma	100% (n=16)
Fusion type	*KIF5B-RET* *CLIP1-RET* *TRIM33-RET* FISH Positive	50% (n=8) 6% (n=1) 6% (n=1) 38% (n=6)

never smoker: <100 lifetime cigarettes

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Response to Cabozantinib in Patients with *RET*-Rearranged Lung Adenocarcinomas



Best Response	%(n)
PR	44% (7/16)
confirmed	38% (6/16)
unconfirmed	6% (1/16)
SD	56% (9/16)

ORR 38% (95% CI 15%-65%)

ORR_{12wks} 36% (95% CI 13%-65%)
(5 PRs of 14 evaluable at 12 wks)

imaging performed at baseline, 4 weeks, and every 8 weeks thereafter
response evaluable patients received ≥ 1 cycle of therapy

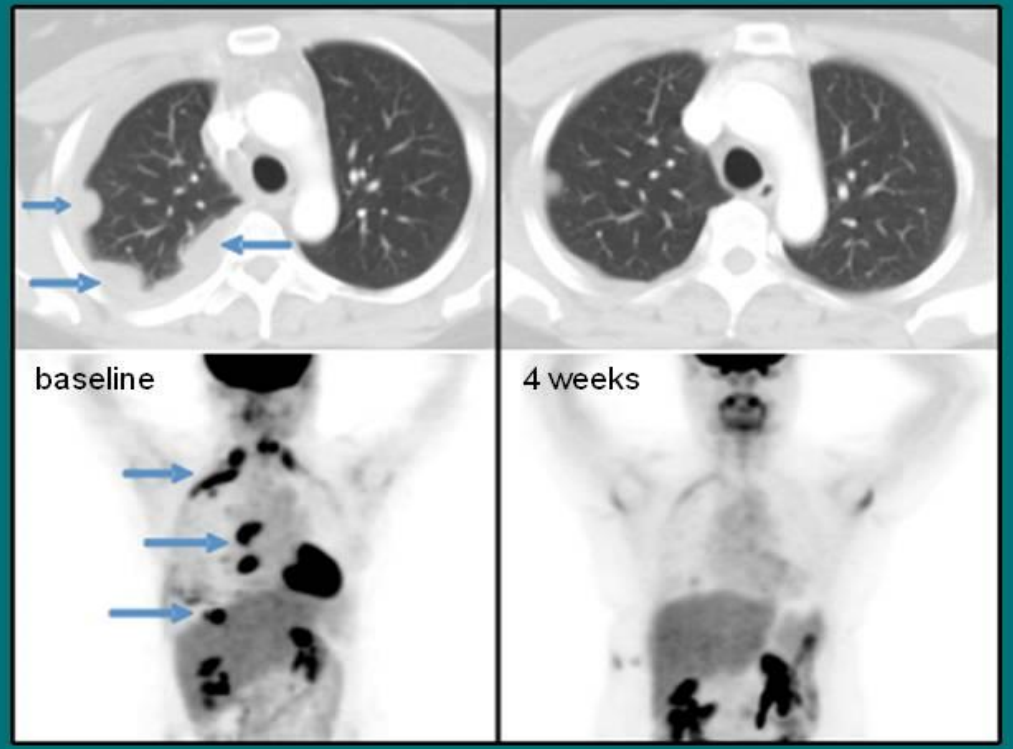
PR - partial response, SD - stable disease
ORR – overall response rate, CI - confidence interval

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Response to Cabozantinib

- 46-year-old female never smoker with *CLIP1-RET*-rearranged lung adenocarcinoma
- received cabozantinib as first-line therapy
- confirmed partial response lasting 19 months

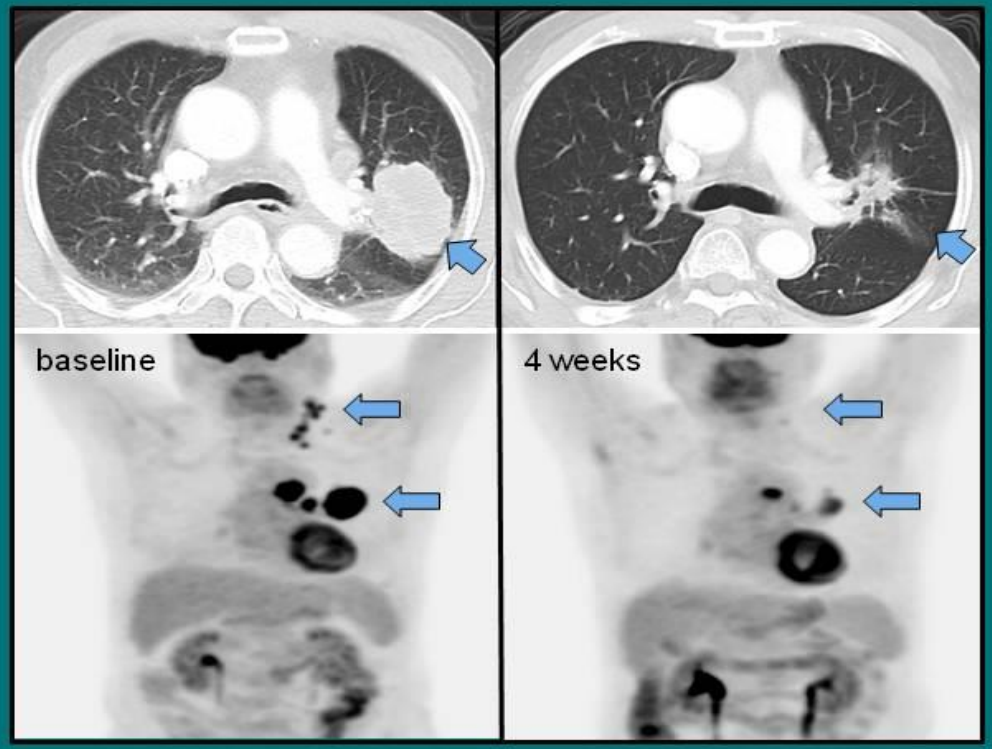


SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Response to Cabozantinib

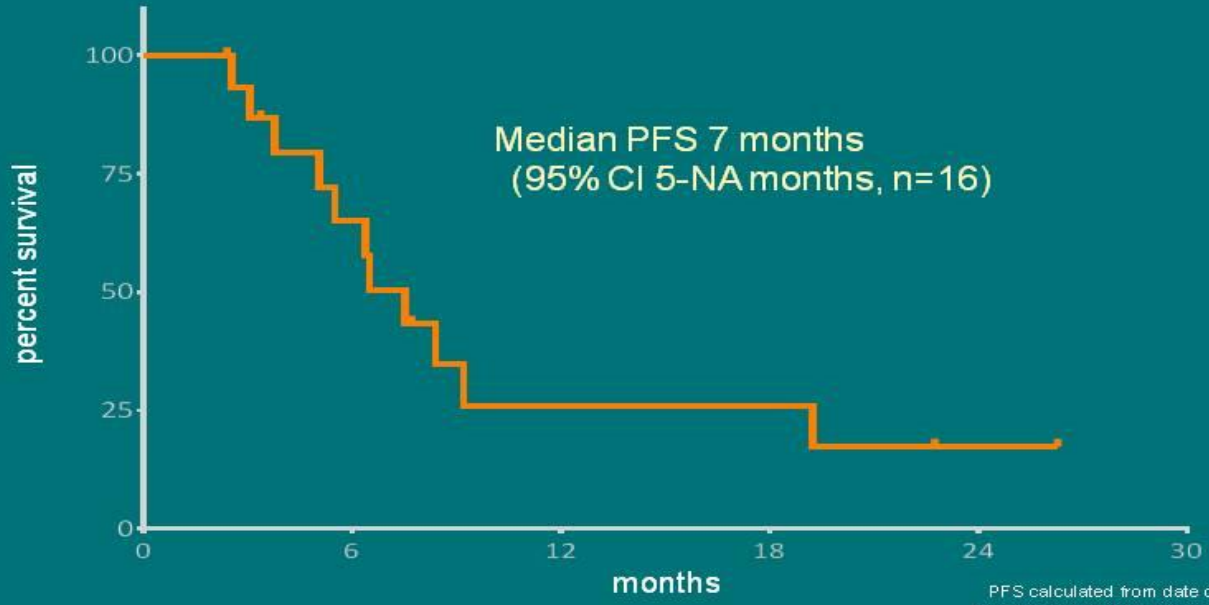
- 80-year-old male never smoker with *KIF5B-RET*-rearranged lung adenocarcinoma
- received cabozantinib after progression on chemotherapy (carboplatin and pemetrexed followed by maintenance pemetrexed)
- confirmed partial response lasting 5 ½ months



SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Progression-Free Survival (PFS)



PFS calculated from date of initiation of cabozantinib to radiololgic progression or death, NA– not applicable

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Overall Survival (OS)

OS calculated from date of initiation of cabozantinib to death, NA – not applicable

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Toxicity

Most common drug-related adverse events

Adverse Event (Stage I, n=16)	Grade 1 % (n)	Grade 2 % (n)	Grade 3 % (n)	All grades % (n)
ALT increased	88% (14)	6% (1)		94% (15)
AST increased	69% (11)		6% (1)	75% (12)
Diarrhea	44% (7)	19% (3)		63% (10)
Fatigue	38% (6)	19% (3)	6% (1)	63% (10)
Mucositis oral	38% (6)	6% (1)	6% (1)	50% (8)
Skin and hair hypopigmentation		44% (7)		44% (7)
Palmar-plantar erythrodysesthesia	31% (5)	6% (1)	6% (1)	44% (7)
Lipase increased	25% (4)	6% (1)	13% (2)	44% (7)
Platelet count decreased	25% (4)		19% (3)	44% (7)
Serum amylase increased	31% (5)	6% (1)		38% (6)
Nausea	31% (5)			31% (5)
Vomiting	31% (5)			31% (5)
Dysgeusia	31% (5)			31% (5)
Anorexia	6% (1)	19% (3)		25% (4)
Hypophosphatemia		19% (3)	6% (1)	25% (4)
Hypertension		13% (2)	6% (1)	19% (3)
Proteinuria		19% (3)		19% (3)
Hypothyroidism		13% (2)		13% (2)

graded using CTCAE (Common Toxicity Criteria for Adverse Events) version 4.0

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

Toxicity

- dose modifications
  - the majority of patients required at least one dose reduction during the course of therapy

number of cabozantinib dose reductions (from 60 mg daily)	%(n)
1 (to 40 mg daily)	50% (8/16)
2 (to 20 mg daily)	19% (3/16)

- other
  - 1 patient discontinued therapy secondary to a grade 3 retroperitoneal hemorrhage
  - 1 death unrelated to drug: grade 5 respiratory failure (post-thoracentesis)

reasons for dose reduction: fatigue, nausea, vomiting, diarrhea, transaminitis, mucositis, palmar-plantar erythrodysesthesia, elevated lipase, thrombocytopenia, proteinuria

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

Summary

- Cabozantinib is active in patients with *RET*-rearranged lung adenocarcinomas.
  - stage 1 completed
    - ORR 38% (95% CI 15%-65%)
    - Median PFS 7 months (95% CI 5-NA months)
    - Median OS 10 months (95% CI 8-NA months)
  - stage 2 currently accruing
- Drug-related adverse events were mostly grade 1 or 2 but were frequent.
  - at a starting dose of 60 mg daily, most patients required a dose reduction
  - clinical benefit can be maintained despite dose reduction
- This phase II trial has met its primary endpoint.
  - sufficient total responses (minimum of 5 at any stage surpassed) to meet primary endpoint
  - a larger, confirmatory trial is warranted

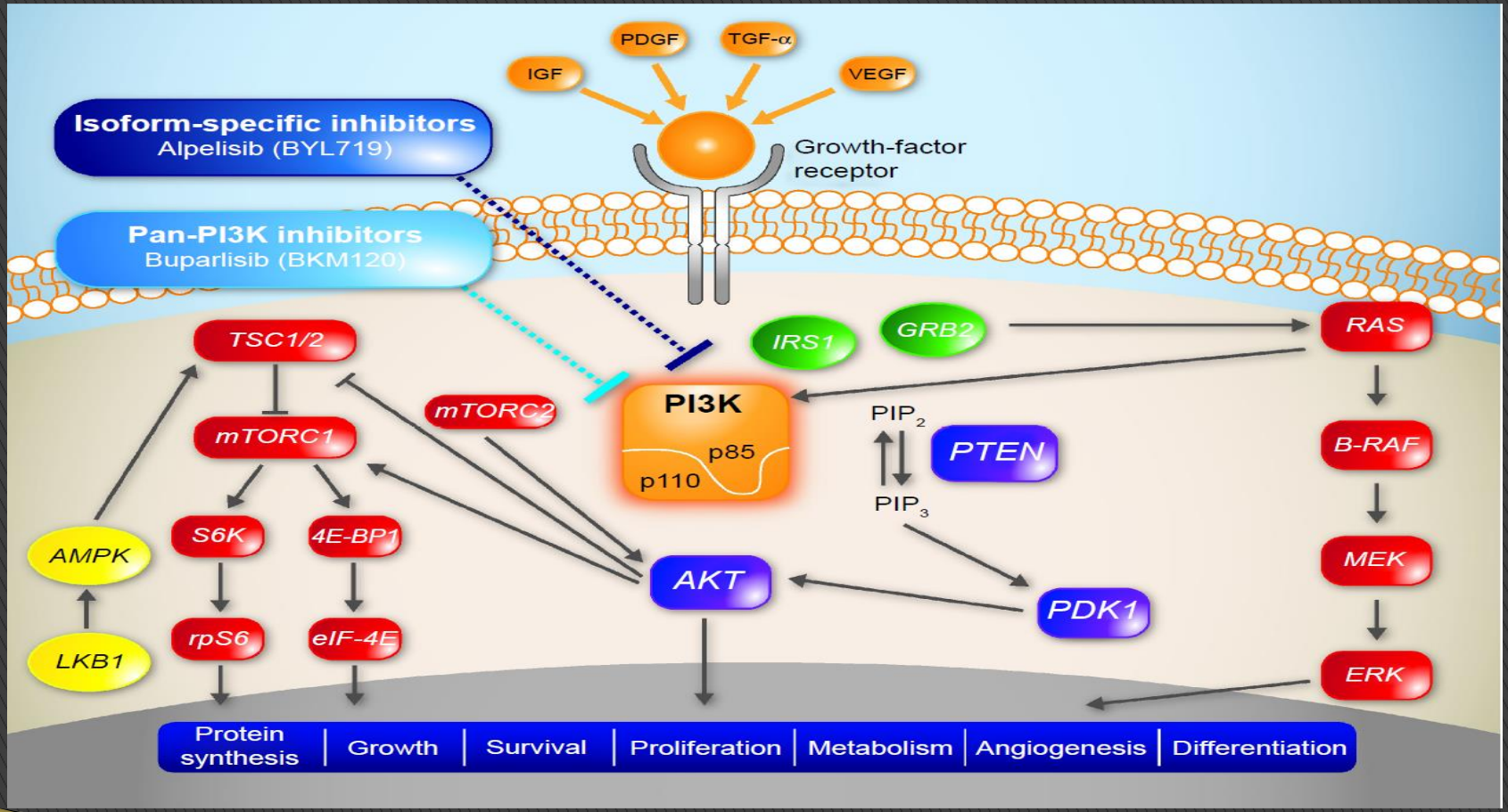
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

RET Fusion Gene Agents

- Sunitinib, Sorafenib, Vandetanib, Carbozatinib, Ponatinib, and Lenvatinib all have potential for activity
- All active in KIF5B-RET–transformed cell lines
- Last 4 are in formal clinical trials

PI3K pathway

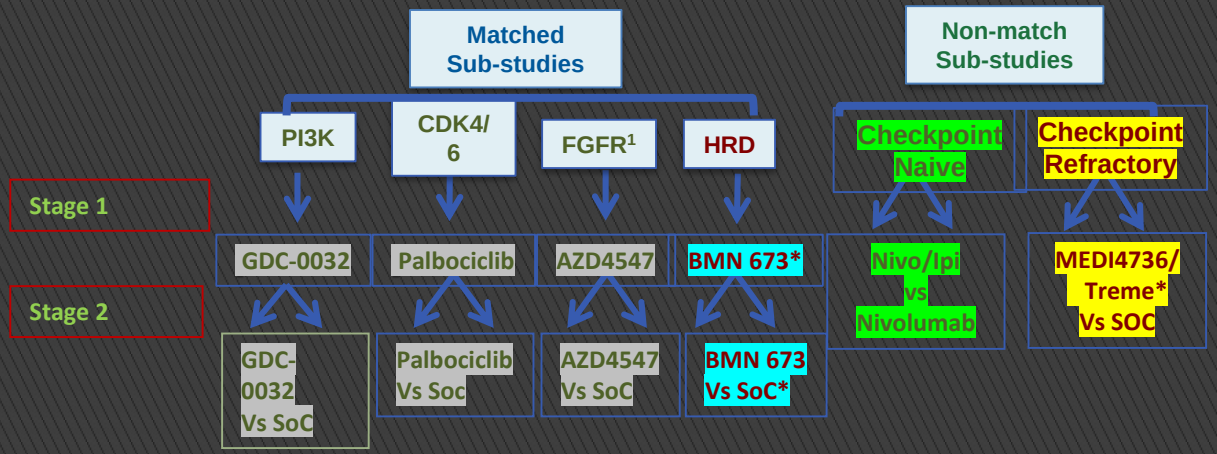

PDGF
TGF-α
IGF
VEGF
Isoform-specific inhibitors
Alpelisib (BYL719)
Growth-factor receptor
Pan-PI3K inhibitors
Buparlisib (BKM120)
TSC1/2
IRS1
GRB2
RAS
mTORC2
PI3K
p85
p110
PIP2
PIP3
PTEN
mTORC1
B-RAF
AMPK
S6K
4E-BP1
AKT
PDK1
MEK
LKB1
rpS6
eIF-4E
ERK
Protein synthesis
Growth
Survival
Proliferation
Metabolism
Angiogenesis
Differentiation

PI3K pathway clinical trials

Drug	Target(s)	Clinicaltrials.gov #
BKM120	PIK3CA	NCT01297491 (phase 2)
carboplatin + paclitaxel + BKM120	PIK3CA	NCT01723800 (phase 1)
GDC0032	PIK3CA	pending

- Overlap with FGFR1 amplification, NFE2L2/KEAP1 mutations complicates clinical validation

Updated Lung-MAP Trial Schema (2016 with Revs # 3 & 4)

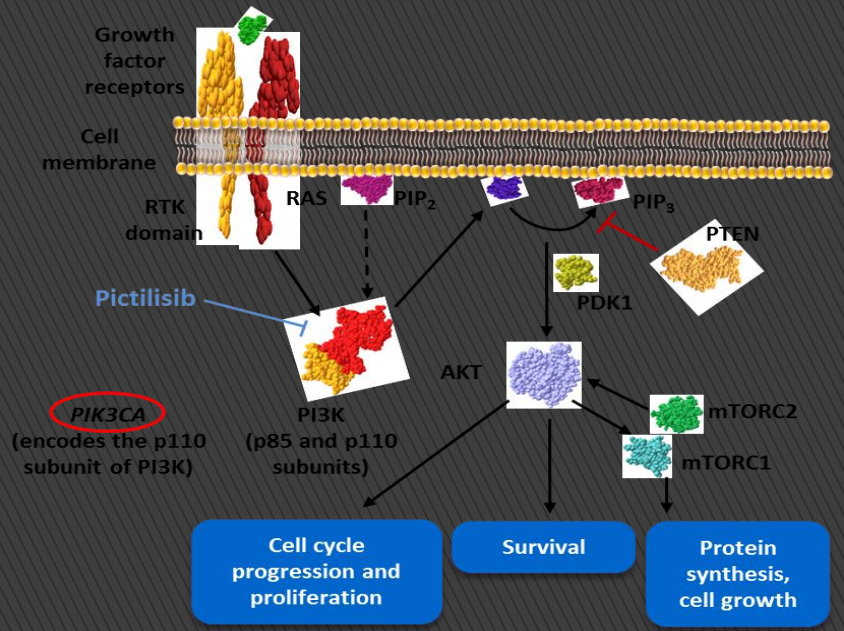


- **Lung-MAP amended to 2nd line therapy & beyond to accommodate Nivolumab approval**
- **Pre-screening added back**
- **Eligibility criteria broadened; *Sub-studies in development**

CDK, cyclin D-dependent kinase; FGFR, fibroblast growth factor receptor; HRD, Homologous Recombination Defects; Ipi, ipilimumab; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SoC, standard-of-care

1. Lung-MAP. Available at: http://www.lung-map.org/healthcare-providers. Accessed February, 2016

Pictilisib (GDC-0941)

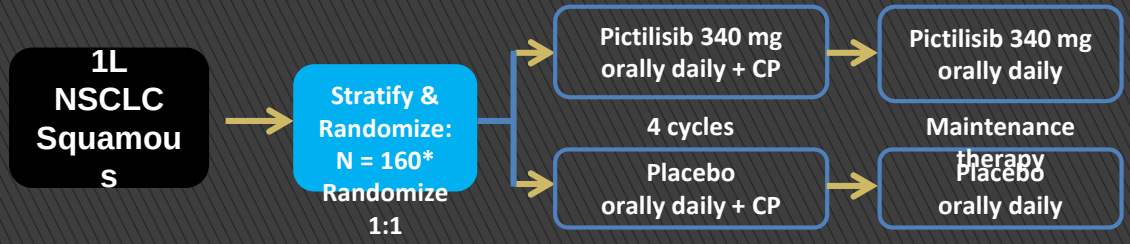


- PI3K has been implicated in the development of several cancers[1] including NSCLC
- Pictilisib (GDC-0941) is a potent and selective orally available pan-PI3K inhibitor that has been shown to potentiate the activity of taxanes and platinum agents in preclinical NSCLC models[2,3]
- FIGARO is the first randomized phase II trial of a PI3K inhibitor in combination with chemotherapy in first-line squamous NSCLC

PI3K, phosphatidylinositol 3-kinase;
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit.

1. Wong KK, *et al. Curr Opin Genet Devel* 2010; **20:**87;
2. Spoerke JM, *et al. Clin Cancer Res* 2012; **18:**6771–6783;
3. Folkes AJ, *et al. J Med Chem* 2008; **51:**5522–5532.
Figure is adapted from Baselga J, *et al.* ASCO 2015: Poster TPS629.

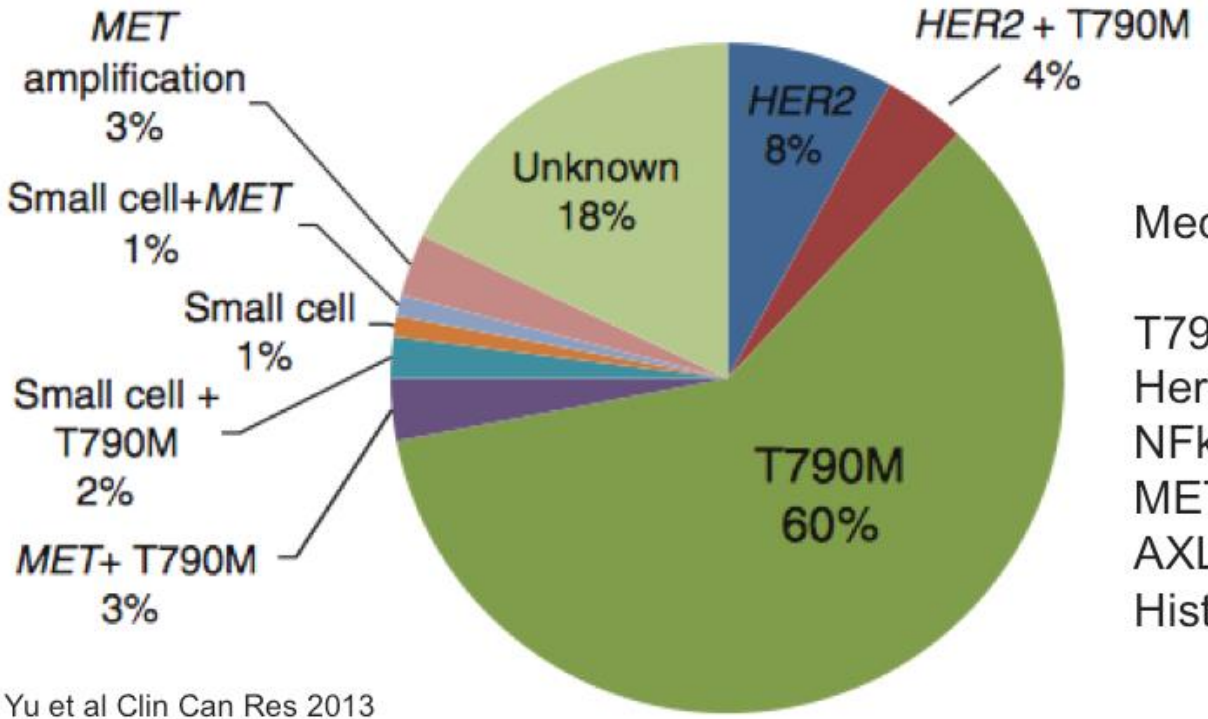
FIGARO study design: squamous NSCLC



- In this first randomized phase II trial of a PI3K inhibitor in first-line squamous NSCLC, combining pictilisib with chemotherapy resulted in:
  - Minimal PFS improvement
  - No OS benefit
  - Additional toxicity – AE-related discontinuations and deaths were higher in the pictilisib arm than the placebo arm
- In the *PIK3CA* amplification subpopulation, no clear benefit in PFS was observed
- Overall, the safety profile observed was consistent with those previously seen in other pictilisib trials

HER 2 Insertions

- **Patients*:*** Adenocarcinomas, never smokers
- **Frequency:** Incidence 2.8-4.2%
- **Biology:**
  - In-frame insertions into exon 20. Transgenic mouse models confirm oncogenicity
- **Therapy:**
  - Drugs of interest: neratinib, afatinib, dacomitinib
    - Preclinical models show synergy with mTOR inhibitors.
    - Clinical trial of neratinib + temsirolimus ongoing, several PR are reported
    - Both afatinib and dacomitinib have case reports of responses



Yu et al Clin Can Res 2013

Mechanisms of Resistance:

T790M 60%
Her2 Amplification
NFkB Upregulation
MET Amplification
AXL Upregulation
Histologic Transformation

Agents for Her-2 Inhibition

Afatinib

3 pts non-smokers stage IV with HER2 mutations with ORR in all cases.

Neratinib

(irreversible pan *ERBB inhibitor)*

phase II trial in pts with NSCLC who progressed following erlotinib or gefitinib. 3 subgroups, EGFR mutant, with EGFR and EGFR TKI naive were compared with ORR of 3.4%, 0% and 0%. Only pts with G719X mutation at exon 18 of EGFR-(+) refractory to reversible TKIs, benefited from neratinib.

PF00299804 (dacomitinib)

Irreversible TKI targeting *ERBB family members EGFR, HER2 and HER4. In the HER2-mutant reveal a 14% (3 /22) PR and 27% SD (6 /22).*

Other molecules: Heat shock protein 90 (Hsp90)

HER2 in Lung Cancers
Agents Targeting HER2

Amplification and Protein Expression

- Trastuzumab
- Pertuzumab
- Lapatinib
- Ado-Trastuzumab Emtansine

Trials of Investigational Agents

Targeting HER2 Mutations

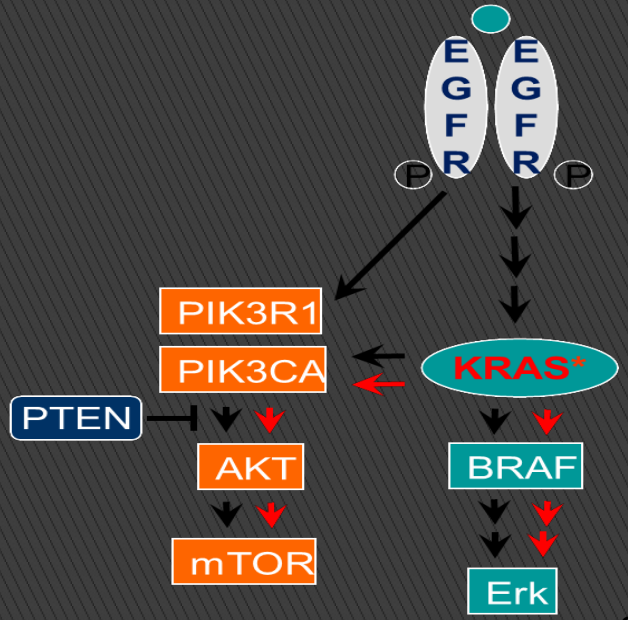
- Dacomitinib
- Afatinib
- Neratinib
- Neratinib + Temsirolimus

HER-2 Inhibition

- Her2-targeted therapies, such as trastuzumab, have been insufficiently powered to determine whether patients with NSCLC with Her2 gene amplification (rather than overexpression by IHC) may benefit.
  It is unclear whether agents targeting Her2 might prove successful either with Her2 amplification or Her2 gene mutations.
- The frequency of Her2 mutations in NSCLC may be too low to justify a prospective clinical trial.
- The frequency of Her2 amplification (2-23%) in NSCLC and the use of FISH might justify a study of trastuzumab monotherapy.
- The most promising Her2-targeted strategy will likely prove to be combinatorial approaches using an EGFR tyrosine kinase inhibitor together with Her2 dimerization inhibitors.

Kirsten ras oncogene homolog from the mammalian ras gene family (KRAS)

- proto-oncogene -> central regulator of growth factor receptor tyrosine kinase signaling cascades
- important downstream component of the epidermal growth factor receptor (EGFR) signaling pathway
- **germline KRAS mutations** are associated with **cardio-facio-cutaneous syndrome** and **Noonan syndrome**
- **oncogenic somatic KRAS** mutations are frequently identified in leukemia, colorectal and pancreatic cancers and in **lung adenocarcinoma**
- KRAS and EGFR activating mutations have been described to be usually mutually exclusive



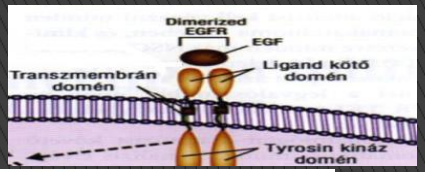
KRAS mutation in NSCLC

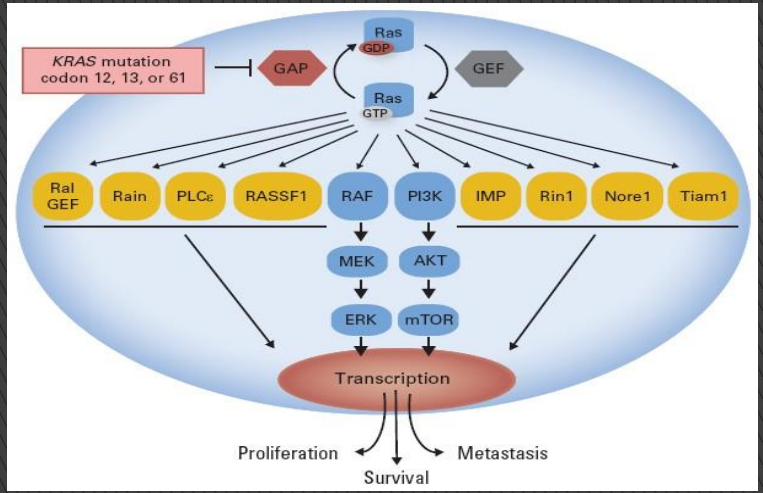
Courtesy of G. Ostoros

Oncogenic KRAS mutations

- The KRAS oncogene in certain malignant tumors is present in one third of cases
- KRAS mutations in codon 12, 13 or 61
- KRAS mutation in CRC is a negative prognostic factor
- Prognostic and predictive role in lung adenocarcinoma is the most intensively studied question

	EGFR	KRAS
Lung adenocarcinoma	8-20%	15-25%
Colorectal cancer	~40% (amplif.)	35-45%





Roberts, Stinchcombe JCO 2013

The most frequent oncogenic subtype mutations of KRAS in lung adenocarcinoma

Nucleotid change	Amino acid change Mutation		
GGT>TGT	Glycin	Cystein	G**12**C
GGT>GTT	Glycin	Valin	G**12**V
GGT>GAT	Glycin	Aspartat	G**12**D
GGT>GCT	Glycin	Alanin	G**12**A
GGT>AGT	Glycin	Serin	G**12**S
GGT>CGT	Glycin	Arginin	G1**2**R
GGC>GAC	Glycin	Aspartat	G**13**D

sign

Dogan S et al, Clin Cancer Res. 2012

Incidence of KRAS mutation/smoking habits

MEDICAL UNIVERSITY OF VIENNA

Incidence of KRAS mutation in smokers and in non-smokers					
Study	No. of smokers	No. of non-smokers	KRAS mutation in smokers	KRAS mutation in non-smokers	P-value
Nelson	180	16	44 (24%)	0	0,028
Marchetti	35	35	12 (34%)	0	0,00016
De Gregorio	160	23	47 (29%)	0	0,0013
Gealy	32	23	8 (25%)	2 (9%)	0,18
Westra	84	27	36 (31%)	2 (7%)	0,017
Ahrendt	92	14	40 (43%)	0	0,0014
All	583	138	177 (30%)	4 (2,9%)	<0,001

Incidence of KRAS mutation in smoker adenocarcinoma patients: 24-43% Strong correlation with number of cigarettes during lifetime and with pack-year

Ahrendt et al. Cancer 2001 Mitsudomi t al. Int J Clin Oncol 2006 Kosaka at al. Cancer Res 2004

KRAS mutation in NSCLC

- 7th Annual Puerto Rico Winter Cancer Symposium

Comparison of KRAS and EGFR mutations in lung cancer

	KRAS	*EGFR*
Discovery of mutation	1982	2004
Biochemical function	Small GTP-binding protein	Receptor tyrosine kinase
Common mutation	Missense mutation at codons 12, 13 or 61	Exon 19 deletion, missense mutation at codon 858 (L858R) in tyrosine kinase domain
Allele-specific imbalance	Present (uniparental disomy common)	Present (copy number gain common)
Mutation in tumors other than lung cancer	Common (pancreas, colon, bile duct, etc.)	Absent[a]
Smoking status	Smokers	Non-smokers
Ethnicity	Caucasians>East Asians	East Asians>Caucasians
Sex	Male>female	Female>male
Histology	Adenocarcinoma (mucinous BAC[b])	Adenocarcinoma (non-mucinous BAC[b])
Prognostic impact	Poorer	Better
Response rate for EGFR-TKI therapy	0%	70–80%

Suda et al. Cancer Metastasis Rev, 2010

No response to EGFR-TKI treatment in KRAS mutant lung adenocarcinoma

MEDICAL UNIVERSITY OF VIENNA

	Agent	n	Responses
Pao 2005	Gefitinib/Erlotinib	9	0
Tsao 2006	Erlotinib	20	1
Fujimoto 2006	Gefitinib	6	0
van Zandwijk 2006	Gefitinib	3	0
Han 2006	Gefitinib	9	0
Hirsch 2006	Gefitinib	6	0
Miller 2006	Erlotinib	19	0
Giaccone 2006	Erlotinib	10	0
Jackman 2007	Erlotinib	6	0
Douillard 2007	Gefitinib	20	0
Total		108	1 (< 1%)

Courtesy of G. Ostoros

Summary & Take home messages

- Mainly in adenocarcinoma
- 30% in Caucasian patients
- < 10% in Asian patients
- Typically related to smoking habits
- Rare in never smokers
- Prognostic and predictive value is debated
- KRAS mutation is heterogenous
- Different KRAS mutation subtypes could be prognostic

The end

- Thanks