ASCO 2012:
Lung Cancer Highlights

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## ASCO 2012: Lung Cancer Highlights

- Maintenance treatment for advanced NSCLC
- EGFR-TKIs for Treatment of molecularly selected NSCLC
- Treatment of *KRAS*-mutation positive NSCLC
- Immunotherapy for metastatic NSCLC
- New molecular targets for NSCLC

ASCO Annual '12 Meeting
June 1-5, 2012 | McCormick Place | Chicago, Illinois
Collaborating to Conquer Cancer

## Maintenance treatment for advanced NSCLC

- Continuation maintenance with:
  - Gemcitabine (previously reported)
  - Pemetrexed (ASCO 2012)

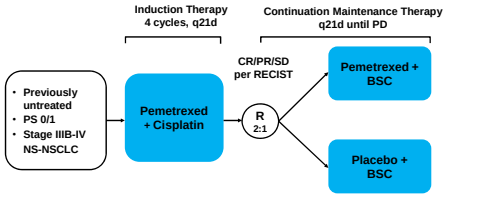
## Maintenance with gemcitabine following platinum+gemcitabine doublets

| | N | Platinum | Median OS (m) **Gemci *vs* Observation** | HR |
|---|---|---|---|---|
| Brodowicz [1] | 352 | cisplatin¶ | 13.0 *vs* 11.0 | NR |
| Perol [2] | 309 | cisplatin | 12.1 *vs* 10.7 | 0.86 |
| Belani [3] | 255 | carboplatin | 9.3 *vs* 8.0 | 0.97 |

Continuation maintenance therapy with single-agent gemcitabine in these trails (which were underpowered to detect OS difference) resulted in a 1.5 – 2.0 month improvement in median overall survival.

1 Brodowicz et al. Lung Cancer 2006; 52:155-163
2 Perol et al. ASCO 2010: abstract 7507
3 Belani et al. ASCO 2010: abstract 7506

## **PARAMOUNT**: Maintenance Pemetrexed following Pemetrexed + Cisplatin for Nonsquamous NSCLC

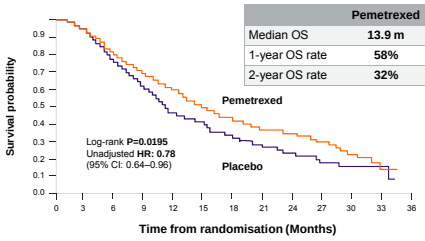



Significant improvement in 1[ary] endpoint PFS (HR 0.62) already previously published (Paz-Ares ea. *Lancet Oncology* 2012)

| | **Pemetrexed** (N 359) | **Placebo** (N 180) |
|---|---|---|
| Median # cycles | 4 | 4 |
| Mean # cycles | 8 | 5 |
| Pts receiving post-PD treat. | 64% | 72% |

Paz-Ares et al. LBA7507

## **PARAMOUNT**: Overall survival




| | **Pemetrexed** | Placebo |
|---|---|---|
| Median OS | **13.9 m** | **11.0 m** |
| 1-year OS rate | **58%** | **45%** |
| 2-year OS rate | **32%** | **21%** |

| | **HR for OS** (P value) |
|---|---|
| From randomization | **0.78** (P 0.0195) |
| From induction treatment | **0.78** (P 0.0191) |

Paz-Ares et al. LBA7507

## **PARAMOUNT**: possible drug-related CTCAEs

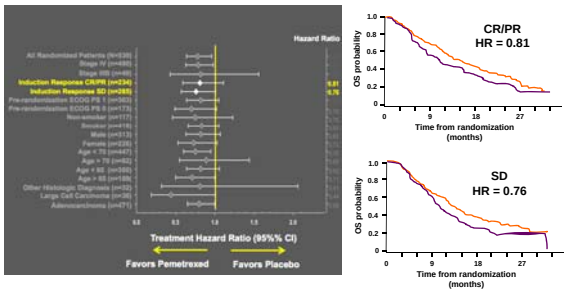
| | Pemetrexed (N=359) | | Placebo (N=180) | |
|---|---|---|---|---|
| | Grade 1/2 % | Grade 3/4 % | Grade 1/2 % | Grade 3/4 % |
| **Fatigue** * | **17.5** | **4.7** | **10.6** | **1.1** |
| Nausea | 13.4 | 0.6 | 2.2 | 0 |
| **Anemia** * | **11.7** | **6.4** | **4.4** | **0.6** |
| Vomiting | 7.5 | 0.3 | 1.1 | 0 |
| Mucositis/stomatitis | 5.8 | 0.6 | 2.2 | 0 |
| Neuropathy/sensory | 5.3 | 0.3 | 6.1 | 0.6 |
| Neutropenia * | **5.0** | **5.8** | **0.6** | **0** |
| Leukopenia | 2.8 | 2.2 | 0 | 0 |
| ALT (SGPT) | 2.5 | 0.3 | 0.6 | 0 |

Maintenance safety similar to known profile of single-agent pemetrexed

Toxicities of any grade, occurring in ≥5% of patients in either arm, are listed, along with some select toxicities.
*P<0.05 Fisher's exact test of Grade 3/4 toxicities.

Paz-Ares et al. LBA7507

## **PARAMOUNT**: Overall survival




OS results were consistent across all clinical subgroups subgroups.

Paz-Ares et al. LBA7507

## **PARAMOUNT:** Conclusions

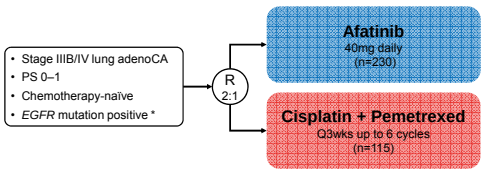
- These final results show that continuation pemetrexed following pemetrexed + cisplatin is:
  - feasible and well tolerated
  - does not affect the ability to administer 2nd-line treatment
  - results in a significant improvement in overall survival (improvement of in~3m median OS, and ~10% in 1yr OS)

Paz-Ares et al. LBA7507


## **EGFR-TKIs for Treatment of molecularly selected NSCLC**

- Afatinib in 1st line metastatic *EGFR* mut +
- Adjuvant erlotinib in resected *EGFR* mut +
- Erlotinib in 2nd line in metastatic *EGFR* wt

## **LUX-Lung 3**: afatinib vs cisplatin + pemetrexed as 1st-line treatment for *EGFR*-mutation+ NSCLC




**Primary endpoint:** PFS by independent review
Pre-planned subgroup analysis of patients with common mutations (Del19/L858R)

* Centralized Therascreen EGFR29* RGQ PCR testing: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

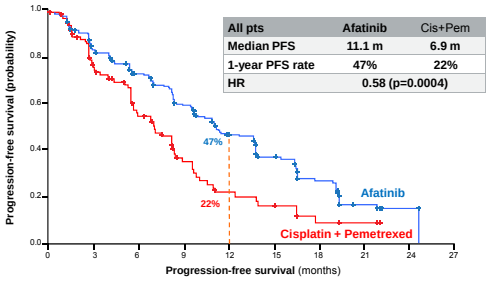
Yang et al. LBA7500

## **LUX-Lung 3**: demographics

| | | Afatinib (n=230) | Cis/Pem (n=115) | Total (n=345) |
|---|---|---|---|---|
| Gender | Male | 36 % | 33 % | 35 % |
| | Female | 64 % | 67 % | 65 % |
| Age, median (range) | | 62 yr (28–86) | 61 yr (31–83) | 61yr (28–86) |
| Race, | Caucasian | 27 % | 26 % | 26 % |
| | East Asian | 72 % | 72 % | 72 % |
| | Other | 1 % | 2 % | 2 % |
| Smoking status | Never smoked | 67 % | 70 % | 68 % |
| | Ex-smoker | 30 % | 28 % | 30 % |
| | Current smoker | 2 % | 2 % | 2 % |
| ECOG PS | 0 | 40 % | 36 % | 39 % |
| | 1 | 60 % | 64 % | 61 % |
| | 2 | 0 % | 1 % | <1 % |
| EGFR mutation | Del19 | 49 % | 49 % | 49 % |
| | L858R | 40 % | 41 % | 40 % |
| | Other | 11 % | 10 % | 11 % |

Yang et al. LBA7500

## **Lux-Lung 3**: progression-free survival

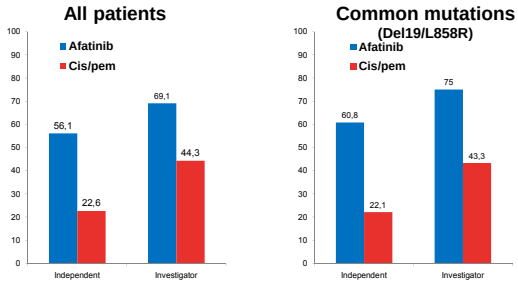



| All pts | Afatinib | Cis+Pem |
|---|---|---|
| Median PFS | 11.1 m | 6.9 m |
| 1-year PFS rate | 47% | 22% |
| HR | 0.58 (p=0.0004) | |

PFS results were consistent across relevant clinical subgroups (such as age, gender, ethnicity, mutation type and age).

Yang et al. LBA7500

## **Lux-Lung 3**: response rate




Median duration of response: 11.1m *vs* 5.5m (independent review)

Yang et al. LBA7500

## **Lux-Lung 3**: AE with >20% difference between arms

| | Afatinib | | Cisplatin + Pemetrexed | |
|---|---|---|---|---|
| | All grades (%) | Grade 3/4 (%) | All grades (%) | Grade 3/4 (%) |
| Diarrhea | 95.2 | 14.4 | 15.3 | 0 |
| Rash/acne | 89.1 | 16.2 | 6.3 | 0 |
| Stomatitis/mucositis | 72.1 | 8.7 | 15.3 | 0.9 |
| Paronychia | 56.8 | 11.4 | 0 | 0 |
| Dry skin | 29.3 | 0.4 | 1.8 | 0 |
| | | | | |
| Nausea | 17.9 | 0.9 | 65.8 | 3.6 |
| Decreased appetite | 20.5 | 3.1 | 53.2 | 2.7 |
| Fatigue | 17.5 | 1.3 | 46.8 | 12.6 |
| Vomiting | 17.0 | 3.1 | 42.3 | 2.7 |
| Neutropenia | 0.9 | 0.4 | 31.5 | 18.0 |
| Anemia | 3.1 | 0.4 | 27.9 | 6.3 |

Similar rates of drug-related AEs grade ≥3 (49% *vs* 48%) and SAEs (14% *vs* 14%).
Treatment duration (median): Afatinib 16 cycles (336 days) *vs* Cis/Pem 6 cycles

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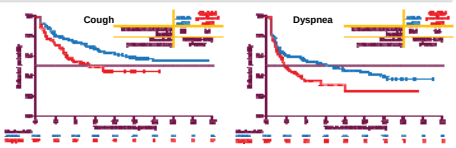
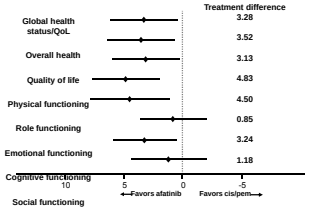
## **LUX-Lung 3**: patient reported outcomes

**Time to deterioration in lung cancer-related symptoms**




**Quality of life (EORTC QLQ C-30): Difference in mean scores**

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## **LUX-Lung 3**: conclusions

- Afatinib compared to Cisplatin + Pemetrexed results in:
  - Improved PFS (HR=0.58 all muts; HR=0.47 Del19+L858R muts)
  - Improved response rate and duration of response
  - Delay in worsening of lung cancer-related symptoms
  - Consistent efficacy in all relevant subgroups
  - Safety profile consistent with previous afatinib studies (Diarrhea and rash were the most frequent AEs)
- No overall survival data were presented

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## Phase III trials of 1st line EGFR-TKI *vs* chemo in *EGFR* mutation positive NSCLC

| Trial | N | Ethnicity | EGFR-TKI | Chemotherapy |
|---|---|---|---|---|
| IPASS (subgroup) | 261 | asian | Gefitinib | Cis + Doc (6x) |
| WJTOG3405 | 172 | asian | Gefitinib | Cis + Doc (6x) |
| NEJ002 | 228 | asian | Gefitinib | Carbo + Pacli (6x) |
| OPTIMAL | 165 | asian | Erlotinib | Carbo + Gemci (4x) |
| EURTAC | 174 | caucasian | Erlotinib | Cis/Carbo + Doc/Gemci (4x) |
| LUX-Lung 3 | 345 | mixed | Afatinib | Cis + Pem (6x) |

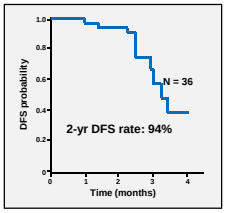
| Trial | *EGFR* mutations | RR (%) † | PFS (m) † | HR PFS † |
|---|---|---|---|---|
| IPASS (subgroup) | 19Del/L858R + other (8%) | 71 vs 47 | 9.6 vs 6.3 | 0.48 |
| WJTOG3405 | 19Del/L858R | 62 vs 3 | 9.2 vs 6.3 | 0.49 |
| NEJ002 | 19Del/L858R + other (6%) | 74 vs 31 | 10.8 vs 5.4 | 0.30 |
| OPTIMAL | 19Del/L858R | 83 vs 36 | 14.7 vs 4.6 | 0.16 |
| EURTAC | 19Del/L858R | 58 vs 15 | 9.7 vs 5.2 | 0.37 |
| Lux-Lung 3 *(common muts)* | 19Del/L858R + other (11%) *(only19Del/L858R)* | 56 vs 23 *(61 vs 22)* | 11.1 vs 6.9 *(13.6 vs 6.9)* | 0.58 *(0.47)* |

† different measurements of endpoint: timing and assessment of CT scans (independent vs investigator assessment) varies

## **SELECT study**: adjuvant EGFR-TKI in resected *EGFR* mutation positive NSCLC

- resected stage IA-IIIA NSCLC
- harboring activating EGFR mutations
- after completion of any standard adjuvant chemotherapy and/or radiotherapy

→ **Erlotinib** during 2 years




- 11 pts relapsed after stopping of erlotinib (range 2.5 – 24 months)
- In 6 of 8 rebiospy samples no EGFR-TKI resistance mechanism was found
- This phase II trial expanded to enroll 100 pts
- Needs confirmation in prospective phase III trial

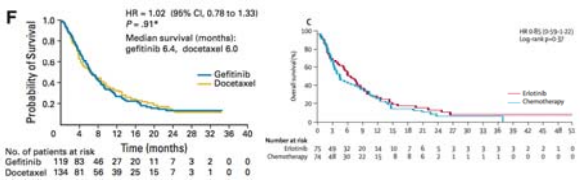
Neal et al. 7010

## Chemotherapy *vs* EGFR-TKI in previously treated unselected patients

| Study | Comparison | N | PFS | OS | Conclusion |
|---|---|---|---|---|---|
| INTEREST | Docetaxel vs. Gefitinib | 1466 | HR 1.04 | HR 1.02 | Non-inferiority demonstrated |
| V-15-32 | Docetaxel vs. Gefitinib | 489 | HR 0.9 | HR 1.12 | Not significantly different |
| ISTANA | Docetaxel vs. Gefitinib | 161 | HR 0.73 | HR 0.87 | Gefitinib better |
| TITAN | Docetaxel vs. Erlotinib | 421 | HR 1.19 | HR 0.96 | Not significantly different |
| HORG | Pemetexed vs. Erlotinib | 297 | 2.7 vs 3.6m | 8.9 v 7.9m | Not significantly different |

## **INTERST and TITAN**: overall survival in subgroup of patients with *EGFR* wild type NSCLC

**INTEREST trial** | **TITAN trial**




Douillard et al. *J Clin Oncol* 2009; *28*:744-752
Ciuleanu et al. *J Lancet Oncol* 2012; 13:300-308

## **TAILOR**: 2nd-line erlotinib *vs* docetaxel in *EGFR* wild-type advanced NSCLC

- Advanced/metastatic NSCLC
- Relapse or progression after platinum-based chemotherapy
- EGFR WT disease*
- ECOG PS 0–2

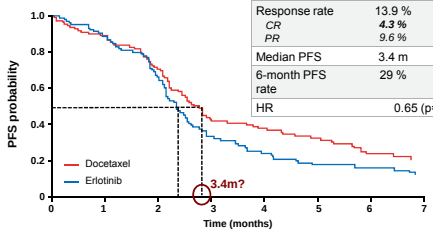
→ R → **Erlotinib** (n=108) / **Docetaxel** (n=110) → Cross-over not allowed

**Primary endpoint:** changed during trial and not yet reported

- 2007: designed as a biomarker-based study to test the interaction between EGFR-IHC, EGFR-FISH, *KRAS* mutation and treatment outcomes
- 2011: based in IDMC recommendation changed to a superiority trial of docetaxel over erlotinib for overall survival

Garassino et al. LBA7501

## **TAILOR**: response rate and PFS




| All pts | Docetaxel | Erlotinib |
|---|---|---|
| Response rate | 13.9 % | 2.2 % |
| *CR* | ***4.3 %*** | *0.0 %* |
| *PR* | *9.6 %* | *2.2 %* |
| Median PFS | 3.4 m | 2.4 m |
| 6-month PFS rate | 29 % | 17 % |
| HR | 0.65 (p=0.014) | |

| | Docetaxel | Erlotinib |
|---|---|---|
| **Men / Women(%)** | **66 / 34** | **71 / 29** |
| **Current or former smoker / never smoker (%)** | **72 / 28** | **82 / 18** |
| **Squamous / AdenoCA / Other (%)** | **21 / 76 / 4** | **28 / 63 / 8** |

Garassino et al. LBA7501

## **TAILOR**: conclusions

- In this academic multicenter trial of 2nd-line treatment of *EGFR* wild-type NSCLC, it is reported that docetaxel improves RR, DCR and PFS compared to erlotinib.
- However:
  - in this open label study there was no independent response evaluation
  - there is an imbalance in smoking status and histology (i.e. ~10% more (ex-)smokers and squamous CA in erlotinib arm)
- Thus the results of the OS analysis need to be awaited before any definitive conclusions can be drawn

Garassino et al. LBA7501


## Treatment of *KRAS*-mutation positive NSCLC

- *KRAS* as biomarker in resected NSCLC
- Selumetinib for metastatic *KRAS* mut +

## **LACE-bio study**: *KRAS* mutations in resected NSCLC

- Objectives:
  - assess predictive and prognostic effects of *KRAS* mutations in 4 LACE-Bio trials (1532 evaluable tumors)
  - determine wether *KRAS* mutations are associated with development of second primary cancers
- Results:
  - in the observation arm, *KRAS* mutations were found not to be prognostic for OS.
  - *KRAS* mutation status is not significantly predictive of survival benefit from adjuvant chemotherapy but codon 13 mutations appear to have worse outcome with chemotherapy (HR 0.89 in wt; HR 0.95 in codon 12 and HR 5.78 in codon 13 mutations)

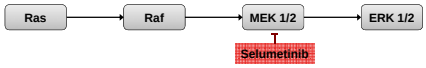
Shepherd et al. 7007

## **LACE-bio study**: *KRAS* mutations in resected NSCLC

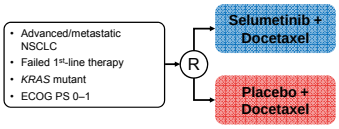
- Results:
  - In the observation arm there was an almost 3-fold increase in the rate of second primary cancers in KRAS-mutant NSCLC compared to KRAS wild-type.
  - In the adjuvant chemotherapy arm there was a 34% reduction of this rate in the KRAS-mutant cases compared to the wild-type.
- Conclusion:
  - **Treatment decision for adjuvant chemotherapy should not be based on KRAS mutation status**

Shepherd et al. 7007

## Docetaxel ± **Selumetinib** as 2nd-line treatment for advanced ***KRAS* mutant NSCLC**

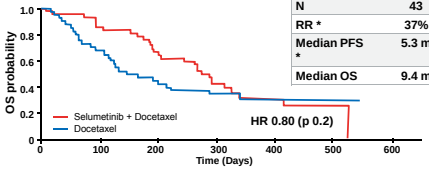



- Selumetinib is a potent and selective inhibitor of MEK ½.
- Selumetinib monotherapy has clinincal activity in pretreated NSCLC (but not superior to pemetrexed)
- The combination of selumitinib with docetaxel produced tumor regression in a preclinical *KRAS* mutant cancer model.




Janne et al. 7503

## Docetaxel ± **Selumetinib** as 2nd-line treatment for advanced ***KRAS* mutant NSCLC**




| | Selumetinib | Docetaxel |
|---|---|---|
| N | 43 | 40 |
| RR * | 37% | 0% |
| Median PFS * | 5.3 m | 2.1 m |
| Median OS | 9.4 m | 5.2 m |

* p< 0.05

**Conclusions:**

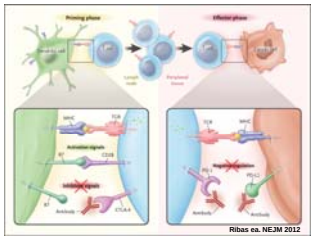
- This is the first prospective study to demonstrate a clinical benefit of a targeted therapy (selumetinib + docetaxel) for patients with *KRAS* mutant cancer of any type
- Further investigation of selumetinib + docetaxel in *KRAS* mutant NSCLC required

Janne et al. 7503


## Immunotherapy for metastatic NSCLC

- Anti-PD-1 in pretreated metastatic NSCLC
- Anti-CTLA-4 in chemonaive NSCLC

## Clinical activity of **anti-PD-1** in advanced NSCLC



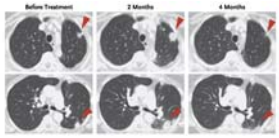

- Programmed death 1 (PD-1) is a key immune-checkpoint receptor expressed by activated T cells that mediates immunosuppression
- Expression of the PD-1 ligand (PD-L1) has been noted in NSCLC
- Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity

Brahmer et al. 7509

## Clinical activity of **anti-PD-1** in advanced NSCLC

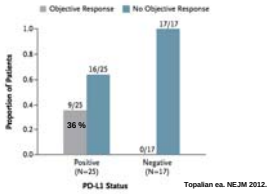
- BMS-936558: fully human PD-1 blocking Ab
- Phase I multi-dose regimen including NSCLC pts with progressive disease after 1-5 systemic therapies
- Clinical activity was observed at all dose levels:

| | 1 mg/kg | 3 mg/kg | 10 mg/kg |
|---|---|---|---|
| ORR | 6 % | 32 % | 18 % |
| PFS at 24 wks | 16 % | 41 % | 24 % |




Brahmer et al. 7509

## Clinical activity of **anti-PD-1** in advanced NSCLC

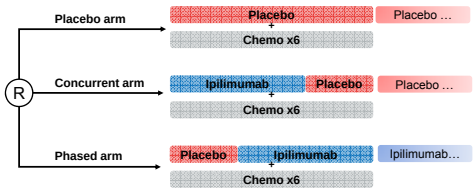



- BMS-936558 is well tolerated and has encouraging clinical activity in pts with heavily pretreated advanced NSCLC
- PD-L1 expression on tumor cells in pretreatment tumor samples is associated with an objective response, suggesting that PD-L1 expression in tumors is a candidate molecular marker

Brahmer et al. 7509

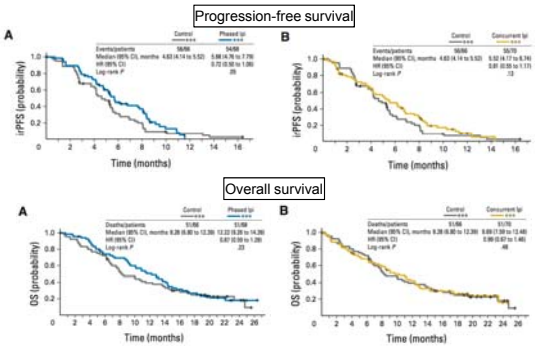
## **Ipilimumab** in Combination With Paclitaxel and Carboplatin As First-Line Treatment in advanced NSCLC

- Ipilimumab: fully human monoclonal Ab blocking the binding of CTLA-4 to its ligands




Lynch et al. *J Clin Oncol* 2012; 30:2046-2054

## **Ipilimumab** in Combination With Paclitaxel and Carboplatin As First-Line Treatment in advanced NSCLC

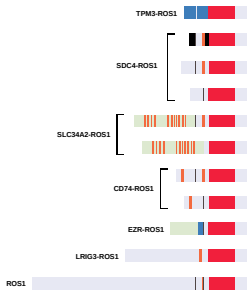



Lynch et al. *J Clin Oncol* 2012; 30:2046-2054


## New molecular targets for NSCLC

- Crizotinib for *ROS1* gene rearrangement
- KIF5B-RET rearrangements in NSCLC
- Therapeutic molecular targets in squamous cell carcinoma

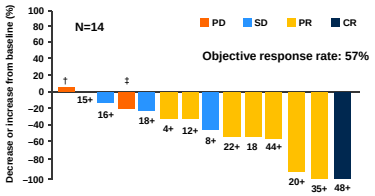
## *ROS1* rearrangements in NSCLC




- ROS1 is receptor tyrosine kinase of the insulin receptor family
- *ROS1* gene fusions are potential driver mutations and are present in ~1% of NSCLC cases
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

## **Crizotinib** in advanced NSCLC harboring ***ROS1* gene rearrangement**

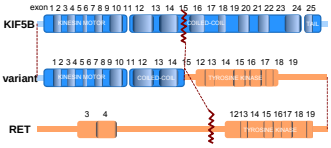


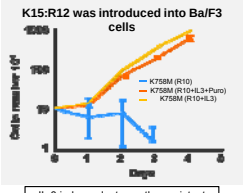

- Crizotinib demonstrates marked antitumour activity in patients with advanced NSCLC with *ROS1* gene rearrangement
- This study represents the first clinical validation of ROS as a therapeutic target in cancer

Shaw et al., 7509

## *KIF5B-RET* rearrangements in NSCLC

Using next-generation sequencing a novel gene fusion joining exons 1–15 of *KIF5B* to exons 12–20 of *RET* (K15:R12) was identified in a Caucasian never smoker




IL-3 independent growth consistent with **oncogenic transformation**.

- **KIF5B-RET** was found to be **oncogenic** .
- KIF5B-RET cells were **sensitive to the RET-inhibitors** (sunitinib, sorafenib and vandetinib)
- Four unique KIF5B-RET variants were found (K15:R12, K16:R12, K22:R12 and K15:R1) in 11/643 additional tumours.

Capelletti et al. 7510

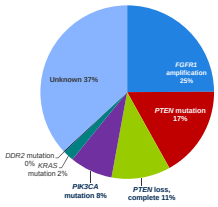
## **The Cancer Genome Atlas**: genetics of squamous cell lung carcinomas

- Squamous NSCLC show:
  - high somatic mutation rates (mean 228 non-silent mutations/tumor)
  - near universal *TP53* mutation
  - **potential therapeutic targets in 75% of pts**

| Gene | Event type | Frequency (%) |
|---|---|---|
| *CDKN2A* | Deletion/mutation/methylation | 72 |
| *PI3KCA* | Mutation | 16 |
| *PTEN* | Mutation/Detection | 15 |
| *FGFR1* | Amplification | 15 |
| *EGFR* | Amplification | 9 |
| *PDGFRA* | Amplification/Mutation | 9 |
| *CCND1* | Amplification | 8 |
| *DDR2* | Mutation | 4 |
| *BRAF* | Mutation | 4 |
| *ERBB2* | Amplification | 4 |
| *FGFR2* | Mutation | 3 |

Govindan et al. 7006

## **Multiplex testing for driver mutations in squamous cell carcinomas of the lung**




| Target | N | Frequency | 95% CI |
|---|---|---|---|
| *FGFR1* amplification | 13/52 | 25% | 15–38% |
| *PTEN* mutation | 3/18 | 17% | 5–37% |
| *PTEN* loss, complete | 3/27 | 11% | 3–26% |
| *PIK3CA* mutation | 4/52 | 8% | 2–17% |
| *KRAS* mutation | 1/52 | 2% | 1–9% |
| *DDR2* mutation | 0/18 | 0% | 0–15% |

**Conclusions:**

- "drugable" driver mutations were detected in 63% tumors from 52 pts with squamous cell NSCLC

Capelletti et al. 7505

## FGFR1 amplification in squamous cell lung cancers

| Abstract | No of cases | Histology subtype | Disease stage(s) | Technique | Definition of amplification | % amplified | % polysomy (if available) |
|---|---|---|---|---|---|---|---|
| 7041 | **101** | **Squamous** | I–IV | FISH | Median of 6 or more gene copies | **6.9** | 43/94 |
| 7061 | **447** | **Squamous** | I–IV | FISH | Mean of 6 or more gene copies | **8.3** | - |
| 7063 | **119** | **Squamous** | I–IV | Quantitative PCR | Predicted CNV of ≥2 in ≥1 exon | **24.4** | - |
| 7545 | **177** | **Squamous** | I–IV | FISH | Copy number >2 and <9 (low); >9 (high) | **25.2** | - |

CNV, copy number variation

Martinez et al. 7041
Toschi et al. 7061
Cote et al. 7063
Wei et al. 7545