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

Maintenance treatment for advanced NSCLC

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

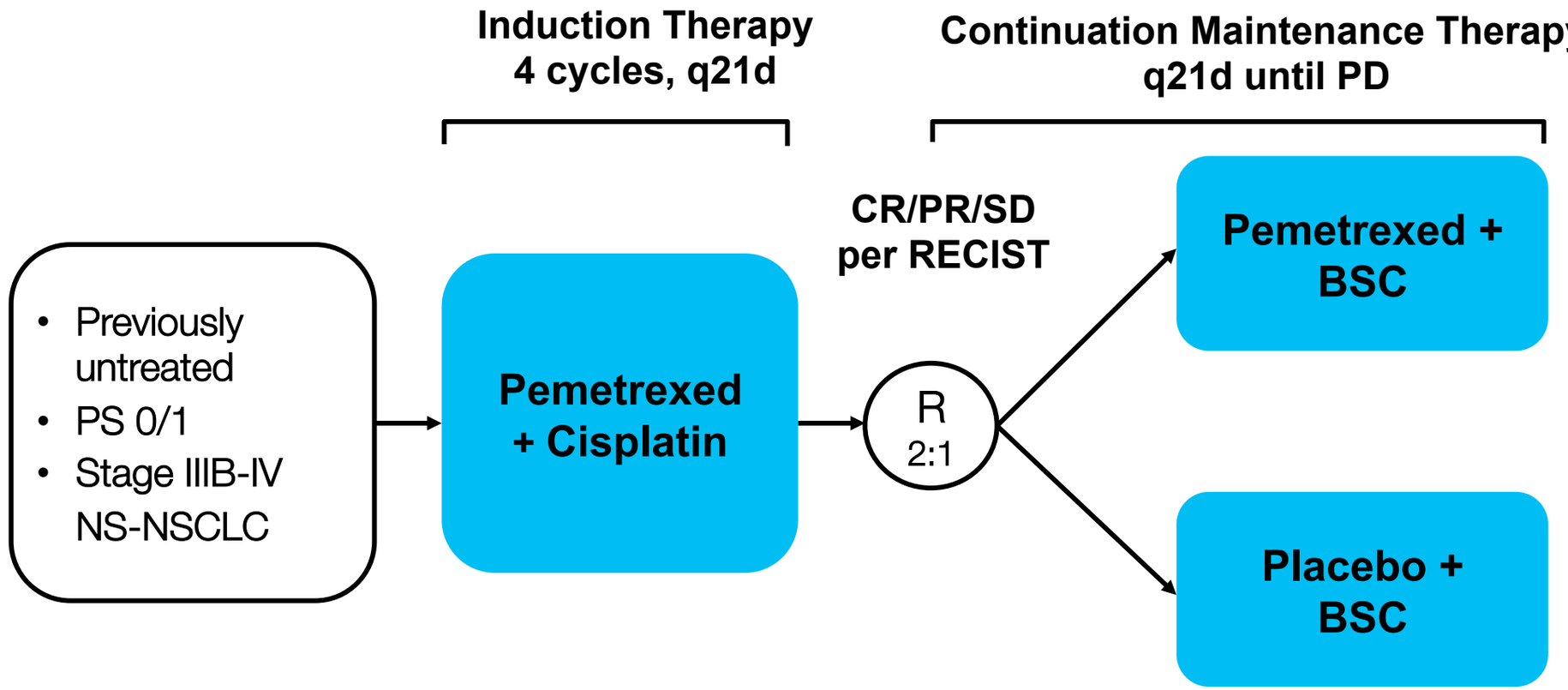
Maintenance with gemcitabine following platinum +gemcitabine doublets

	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

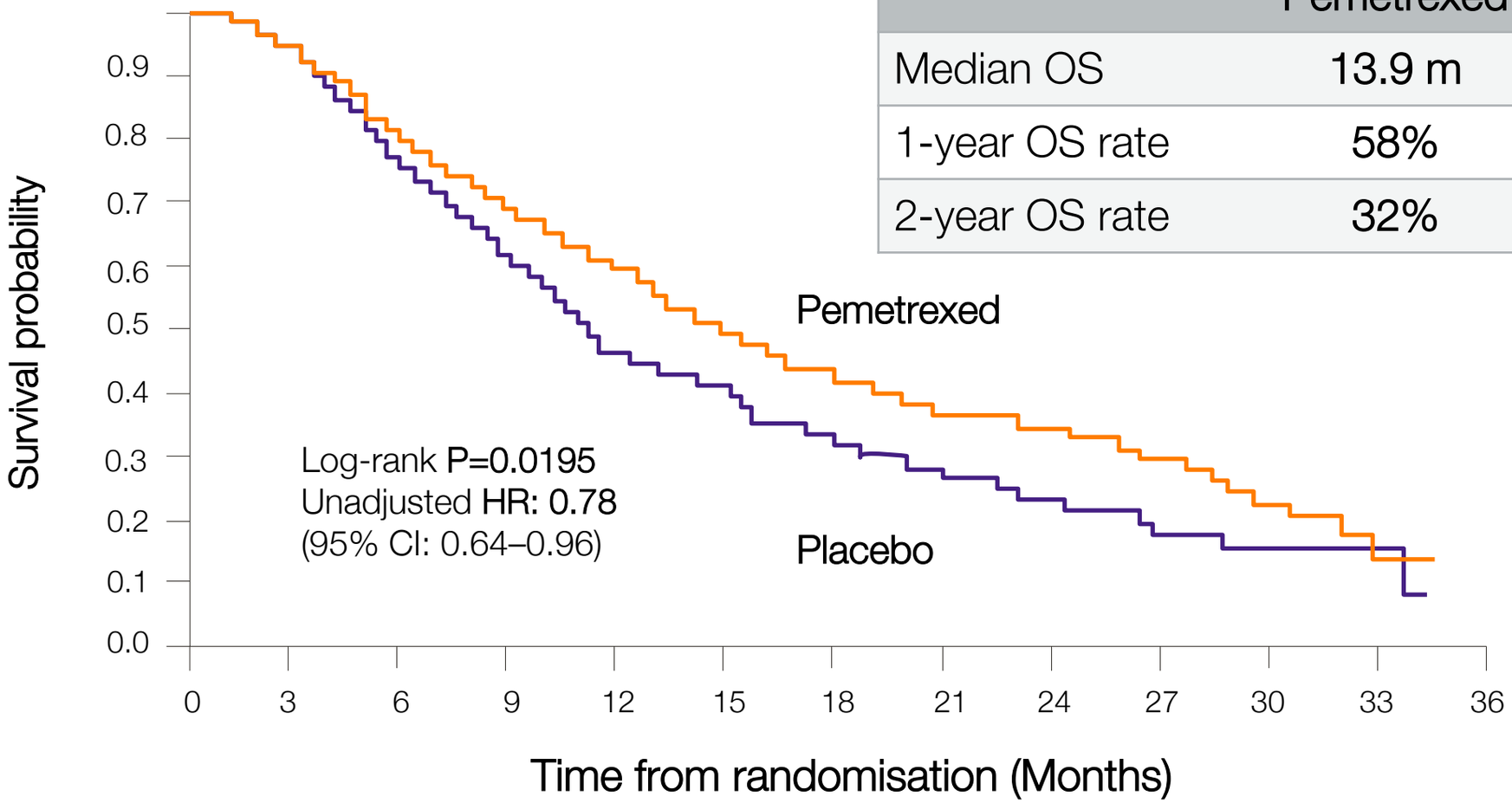


Significant improvement in 1[ary] endpoint PFS (HR 0.62) already previously published (Paz-Ares ea. *Lancet Oncology* 2012)

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

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

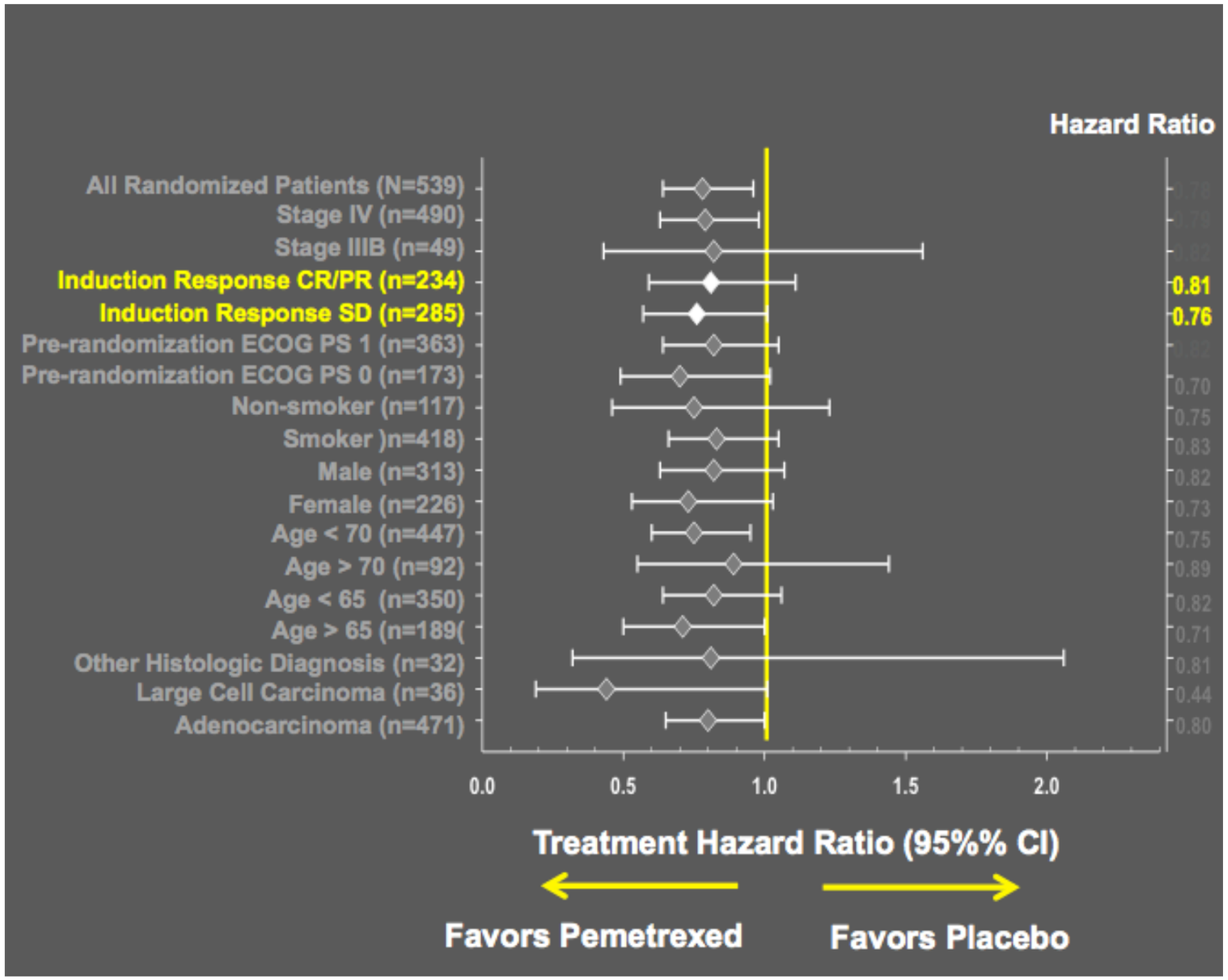
PARAMOUNT: possible drug-related CTCAEs

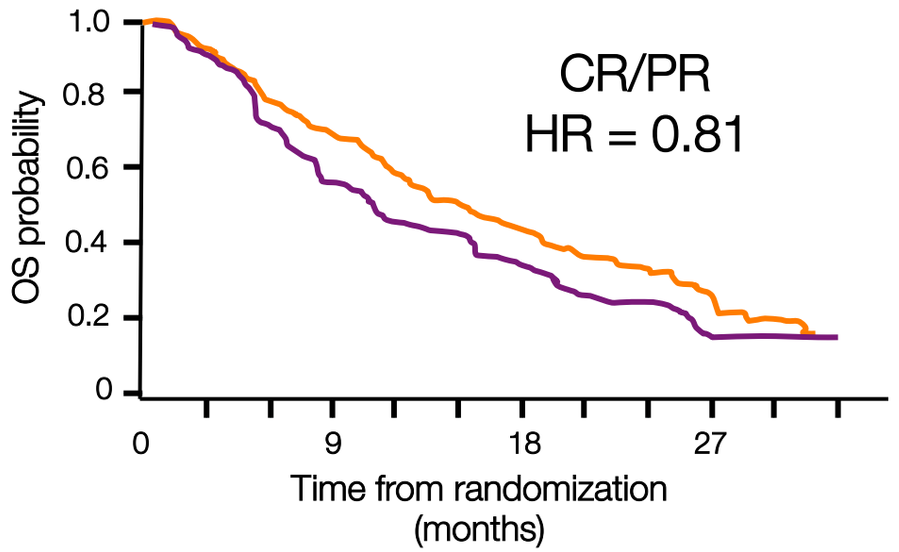
	Pemetrexed (N=359)		Placebo (N=180)	
	Grade 1/2 %	Grade 3/4 %	Grade 1/2 %	Grade 3/4 %
Fatigue *	**17.5**	**4.7**	**10.6**	**1.1**
Nausea	13.4	0.6	2.2	0
Anemia *	**11.7**	**6.4**	**4.4**	**0.6**
Vomiting	7.5	0.3	1.1	0
Mucositis/stomatitis	5.8	0.6	2.2	0
Neuropathy/sensory	5.3	0.3	6.1	0.6
Neutropenia *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

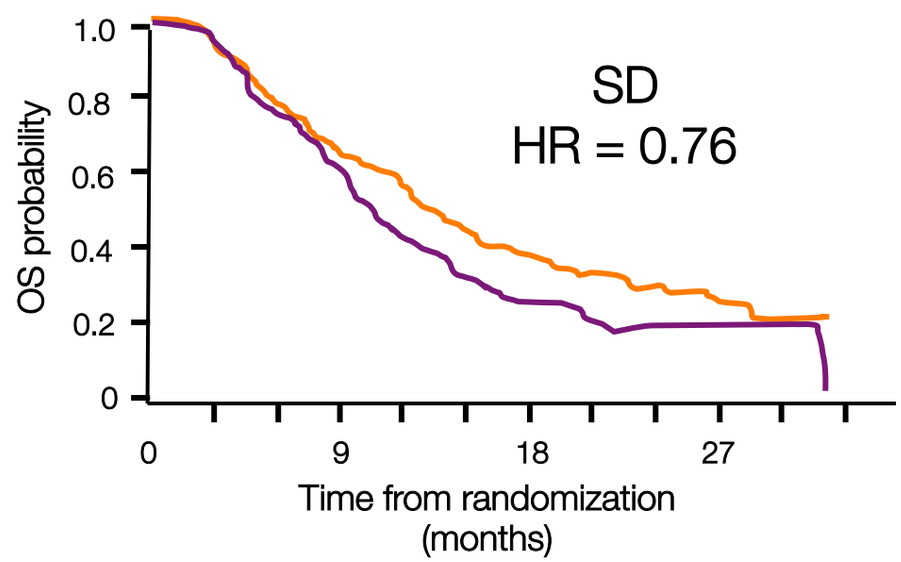
Maintenance safety similar to known profile of single-agent pemetrexed

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.

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)

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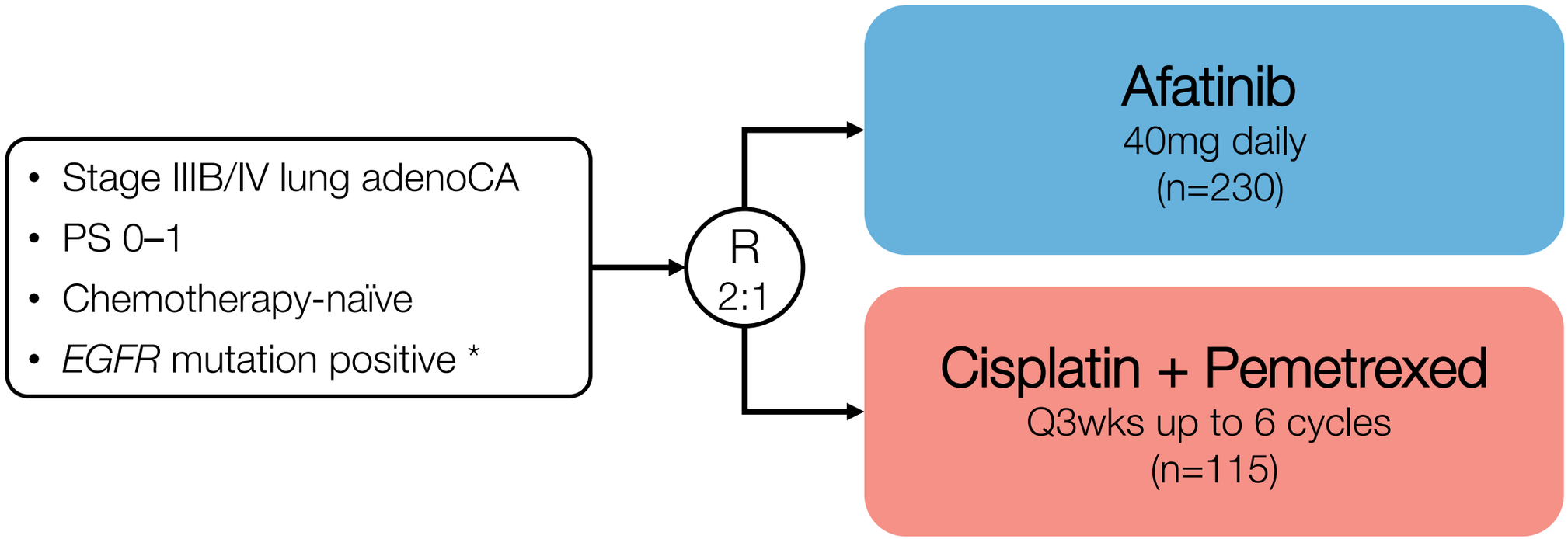
EGFR-TKIs for Treatment of molecularly selected NSCLC

- 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.

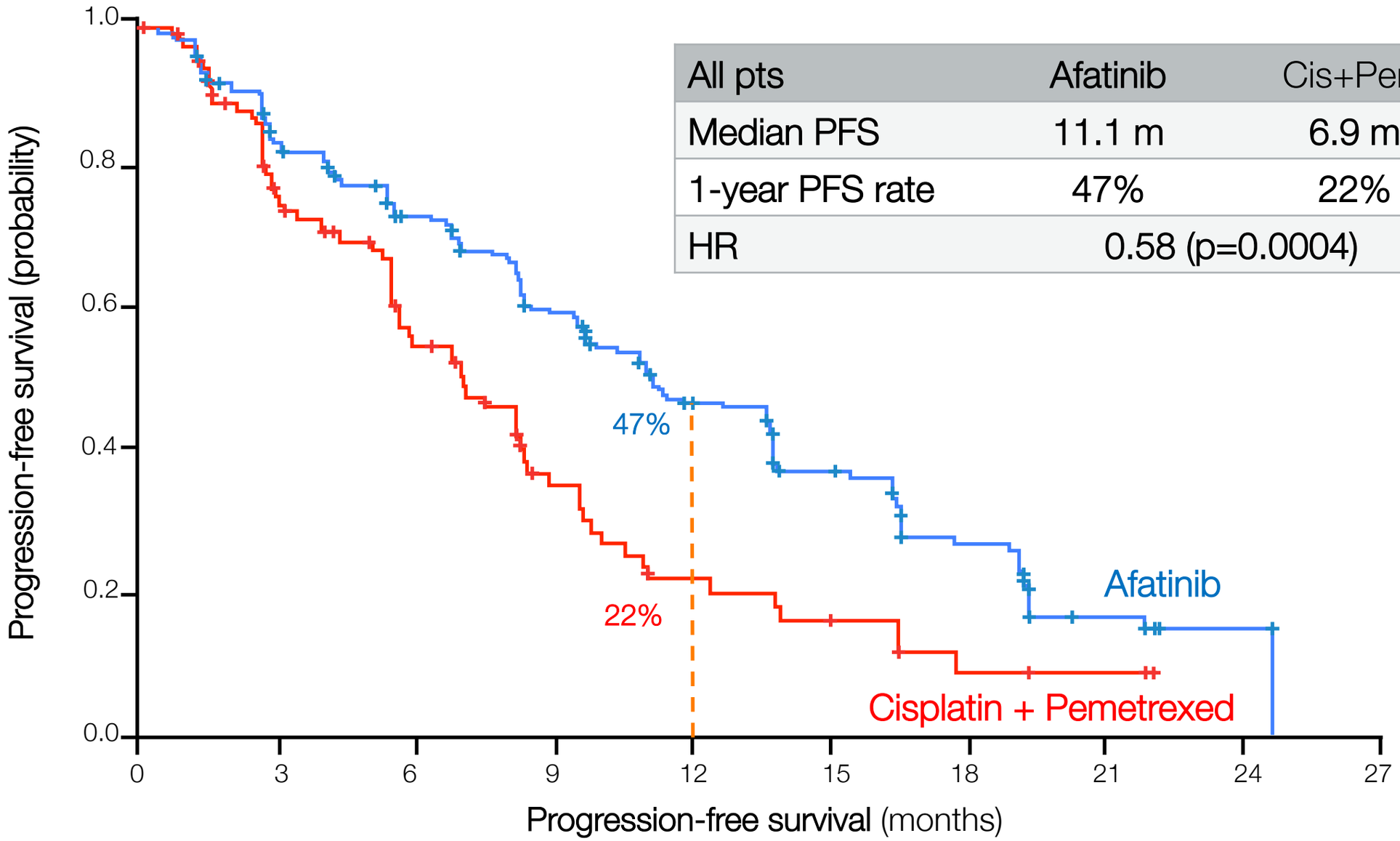
Yang et al. LBA7500

LUX-Lung 3: demographics

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

Yang et al. LBA7500

Lux-Lung 3: progression-free survival

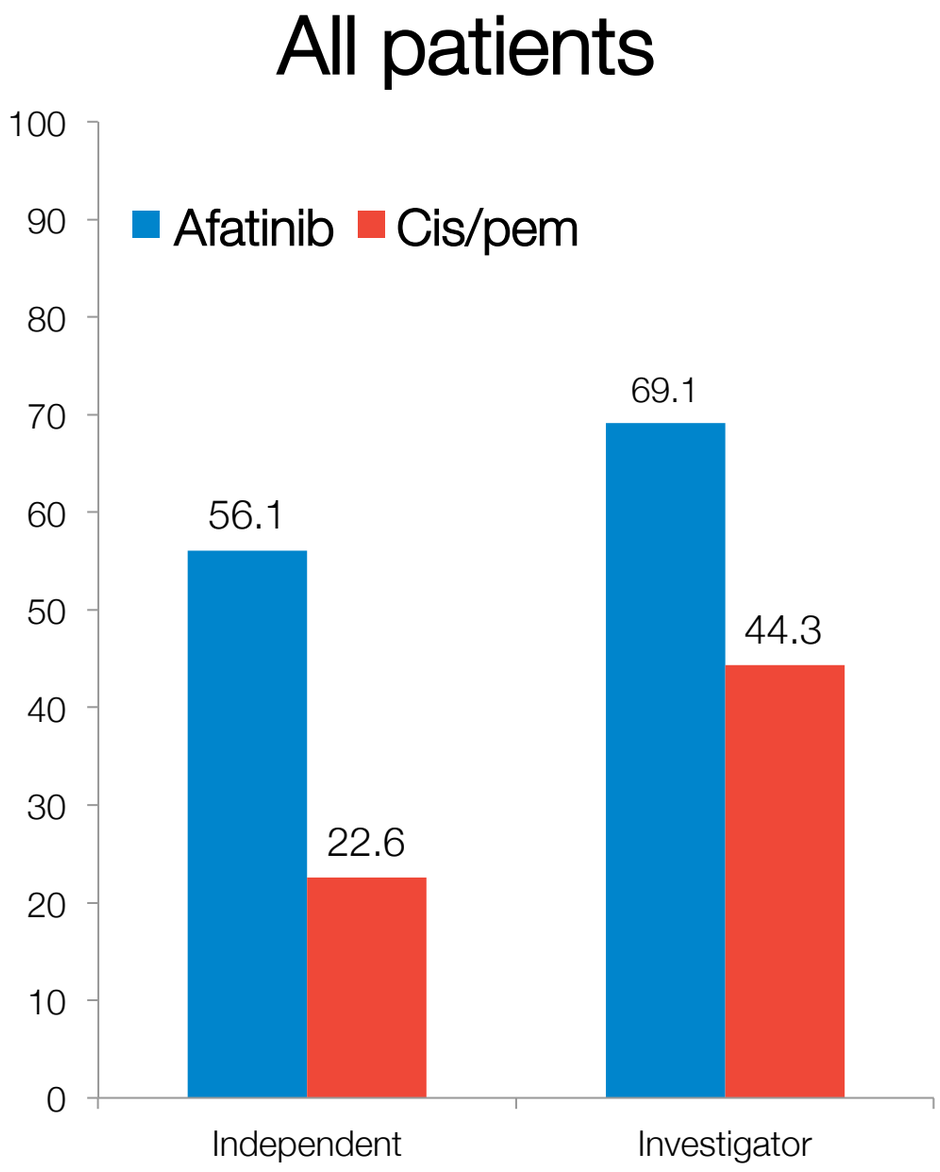


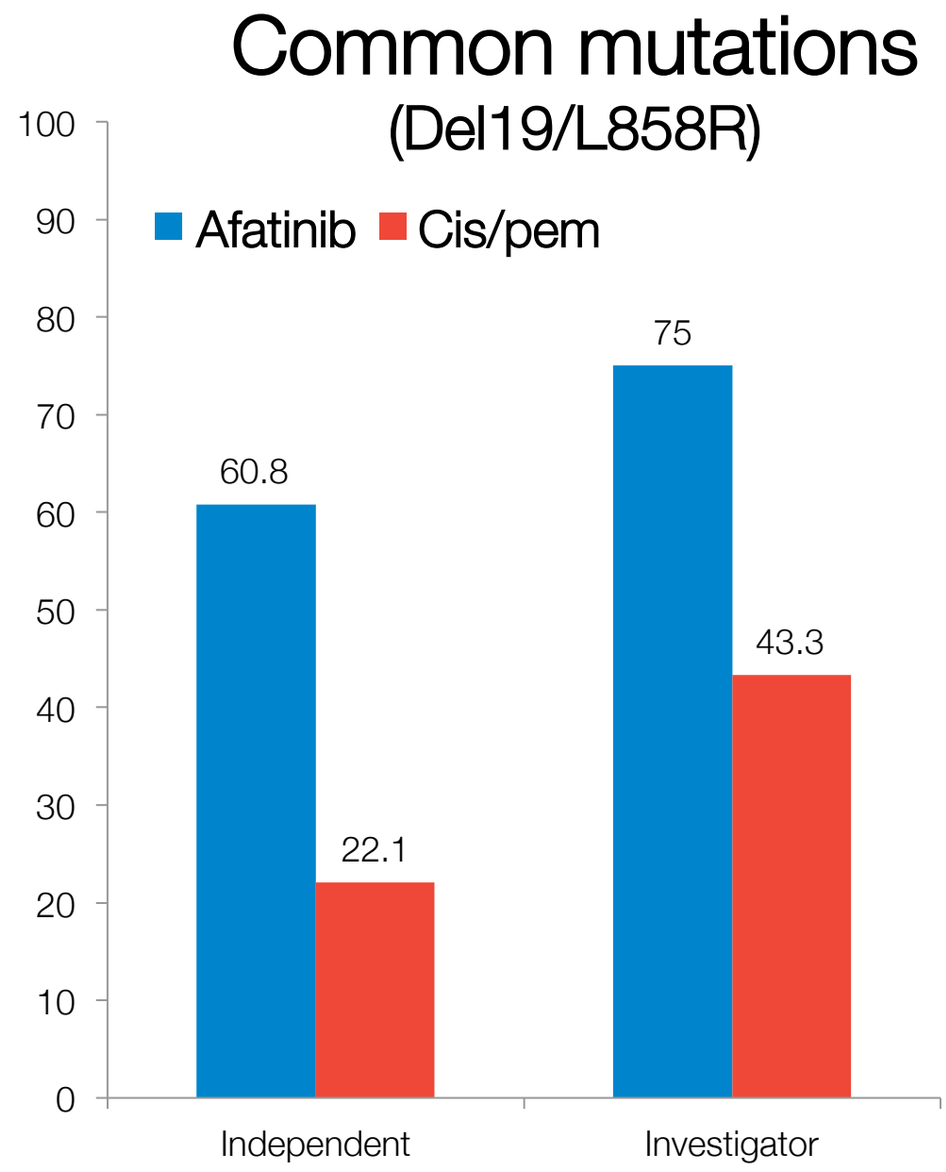
All pts	Afatinib	Cis+Pem
Median PFS	11.1 m	6.9 m
1-year PFS rate	47%	22%
HR	0.58 (p=0.0004)	

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)

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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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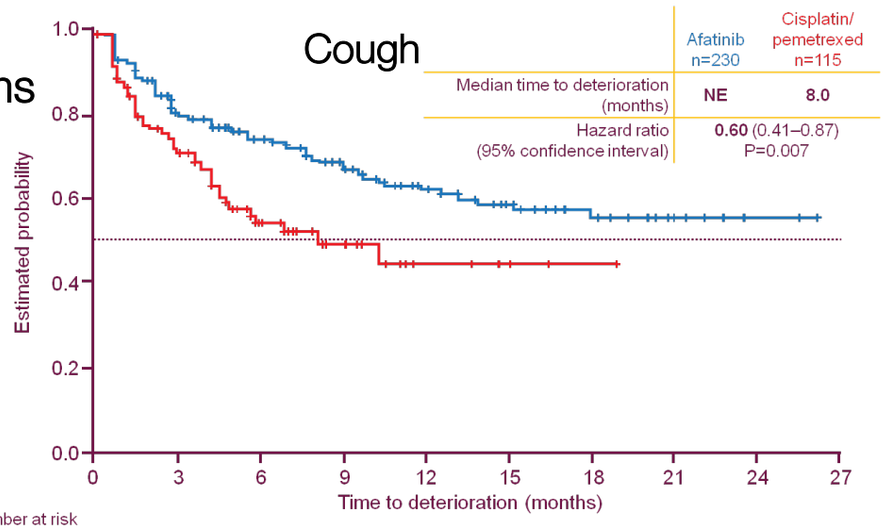
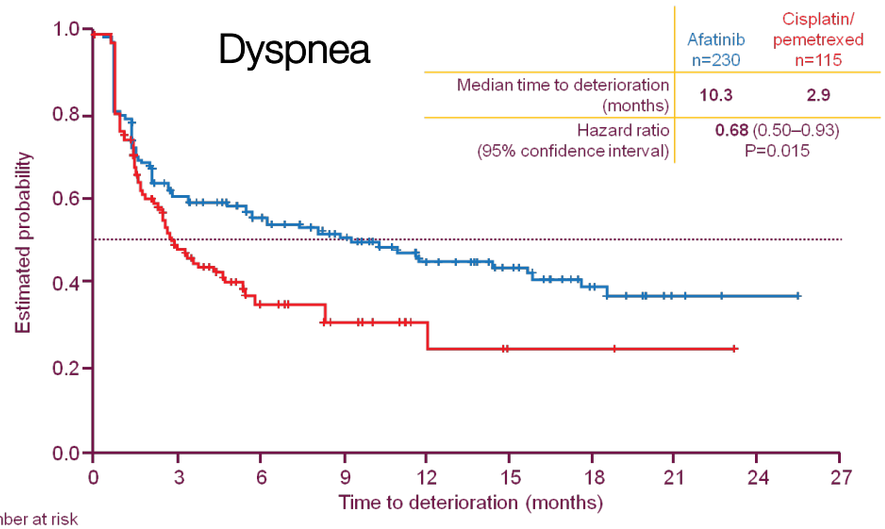
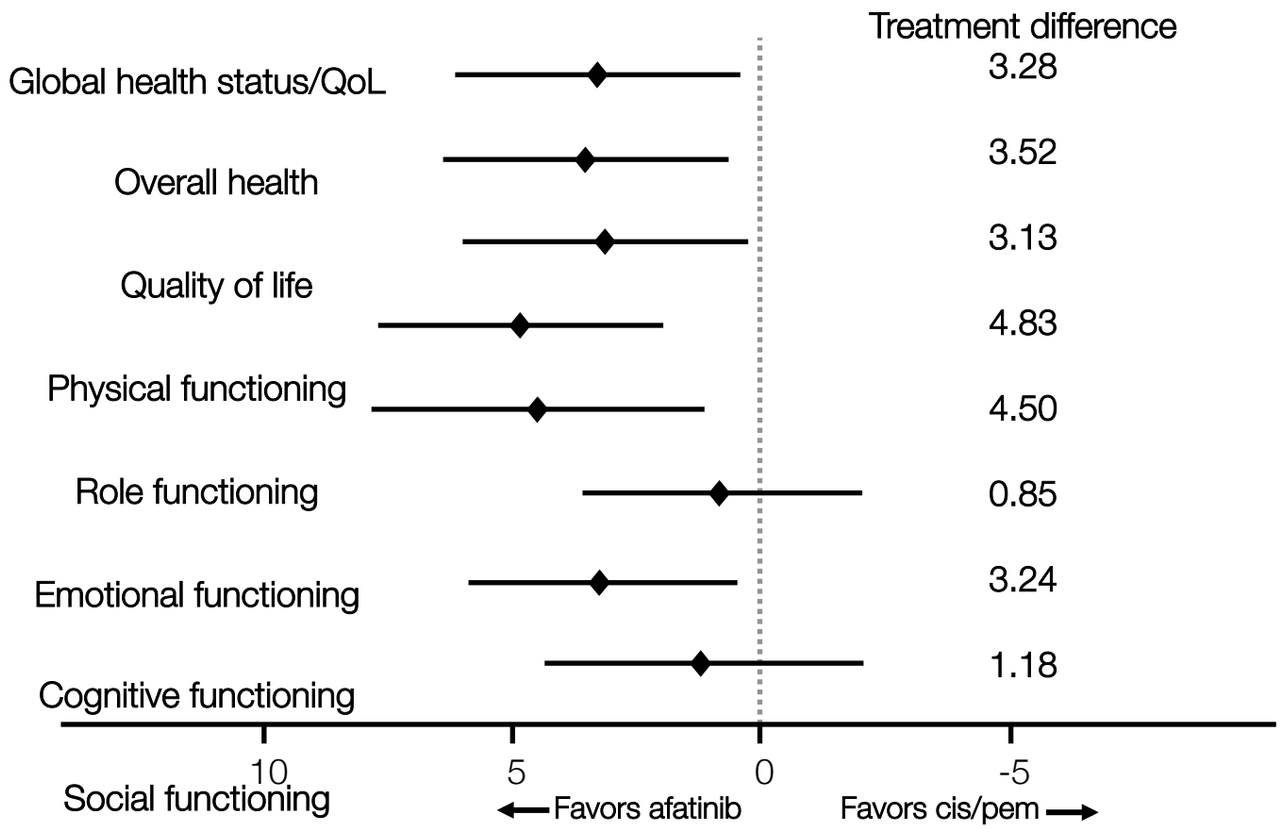
LUX-Lung 3: patient reported outcomes

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

Yang et al. LBA7500

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)

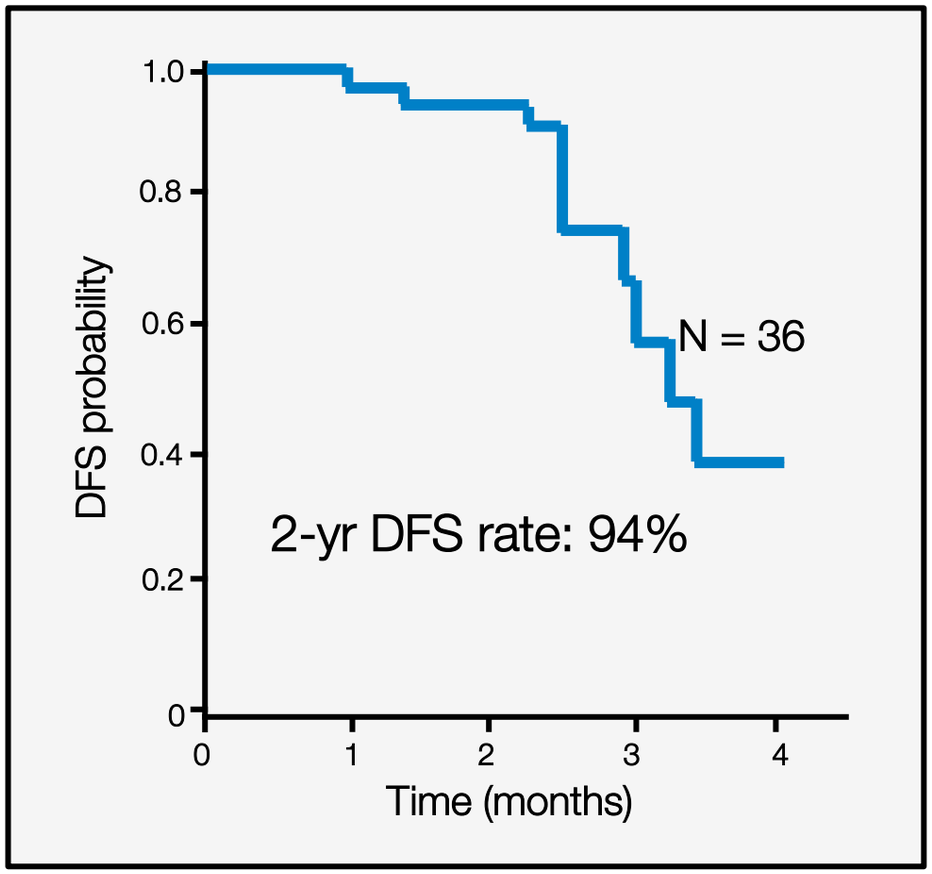
Trial	*EGFR* mutations	RR (%) †	PFS (m) †	HR PFS †
IPASS (subgroup)	19Del/L858R + other (8%)	71 vs 47	9.6 vs 6.3	0.48
WJTOG3405	19Del/L858R	62 vs 3	9.2 vs 6.3	0.49
NEJ002	19Del/L858R + other (6%)	74 vs 31	10.8 vs 5.4	0.30
OPTIMAL	19Del/L858R	83 vs 36	14.7 vs 4.6	0.16
EURTAC	19Del/L858R	58 vs 15	9.7 vs 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

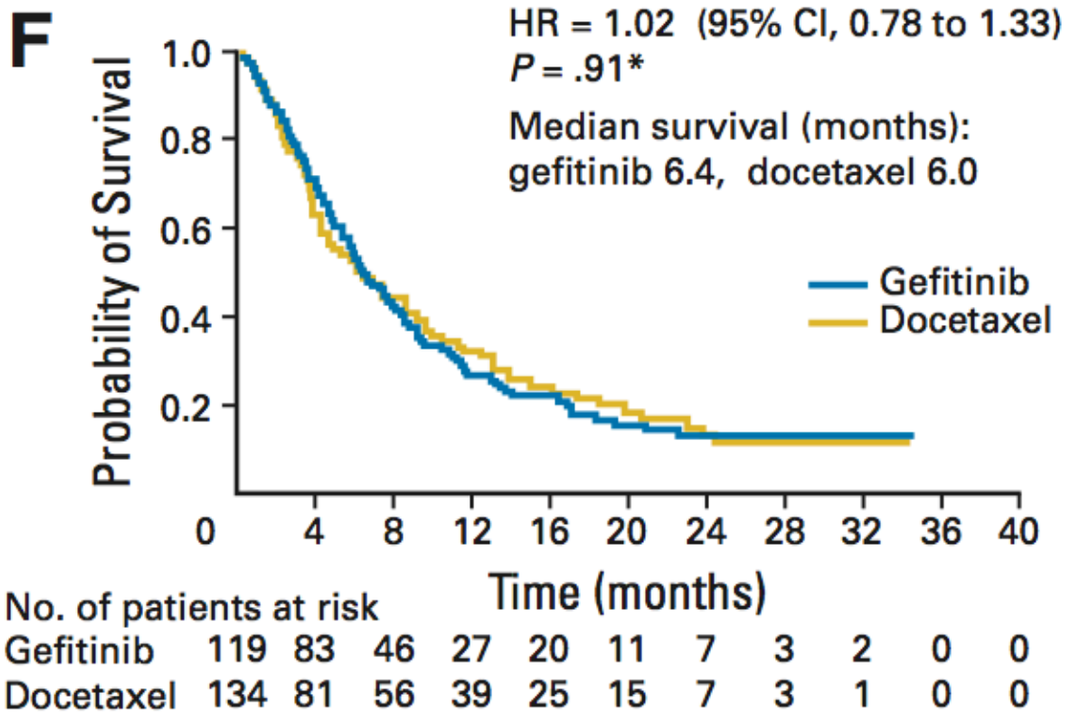
Chemotherapy *vs* EGFR-TKI in previously treated unselected patients

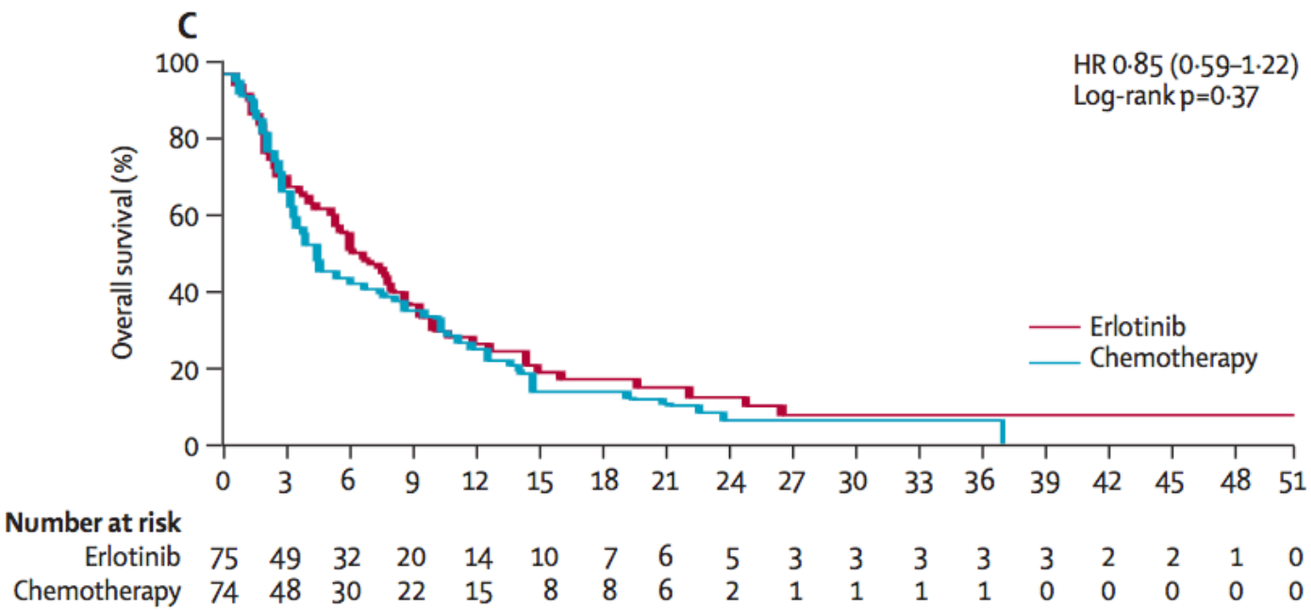
Study	Comparison	N	PFS	OS	Conclusion
INTEREST	Docetaxel vs. Gefitinib	1466	HR 1.04	HR 1.02	Non-inferiority demonstrated
V-15-32	Docetaxel vs. Gefitinib	489	HR 0.9	HR 1.12	Not significantly different
ISTANA	Docetaxel vs. Gefitinib	161	HR 0.73	HR 0.87	Gefitinib better
TITAN	Docetaxel vs. Erlotinib	421	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

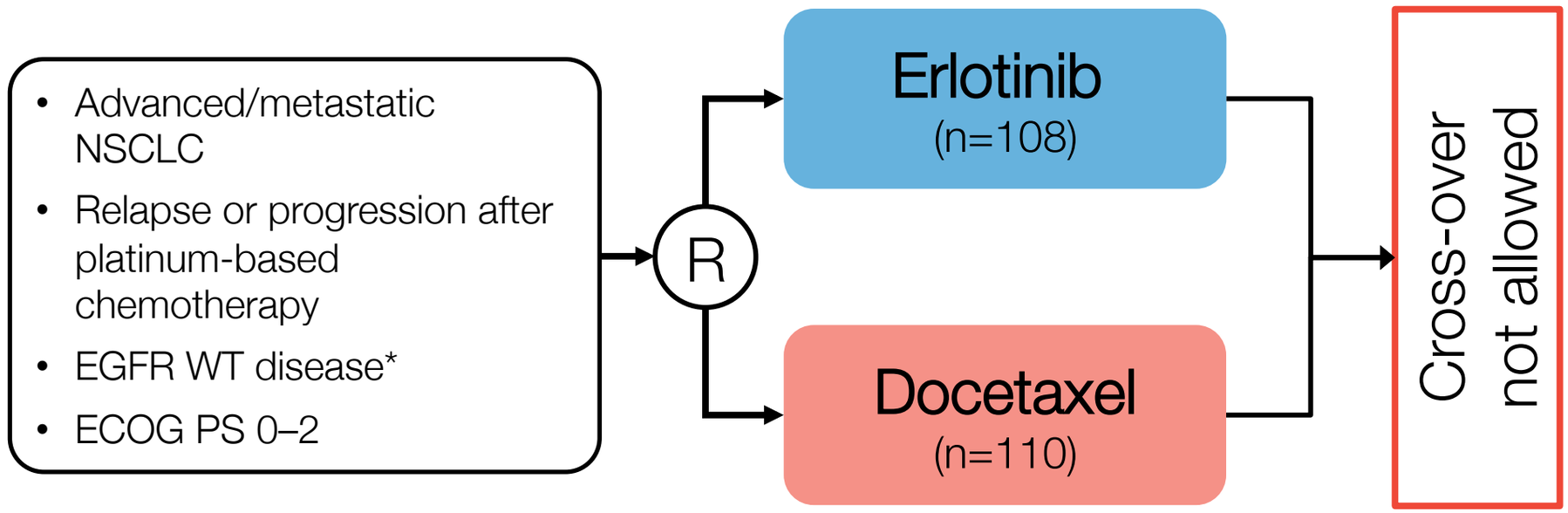
TITAN trial





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

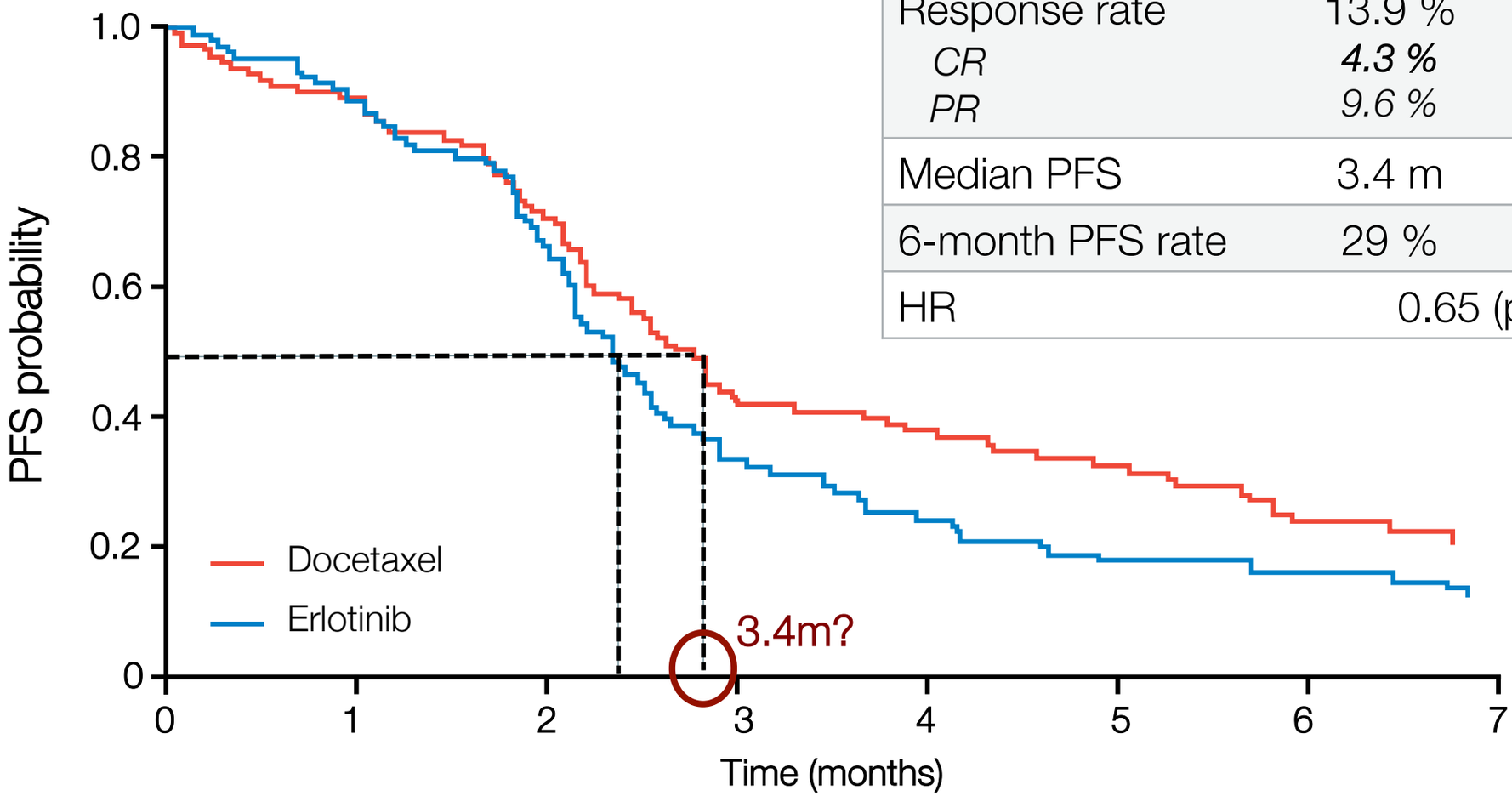
TAILOR: 2nd-line erlotinib *vs* docetaxel in *EGFR* wild-type advanced NSCLC



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

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

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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)

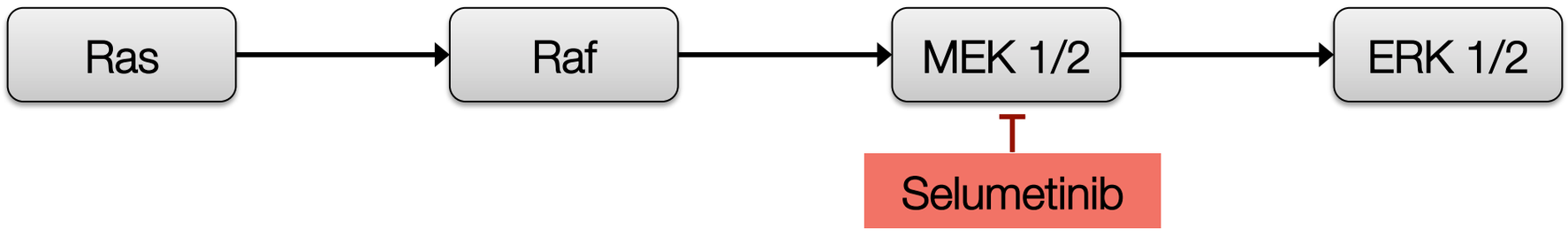
Shepherd et al. 7007

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

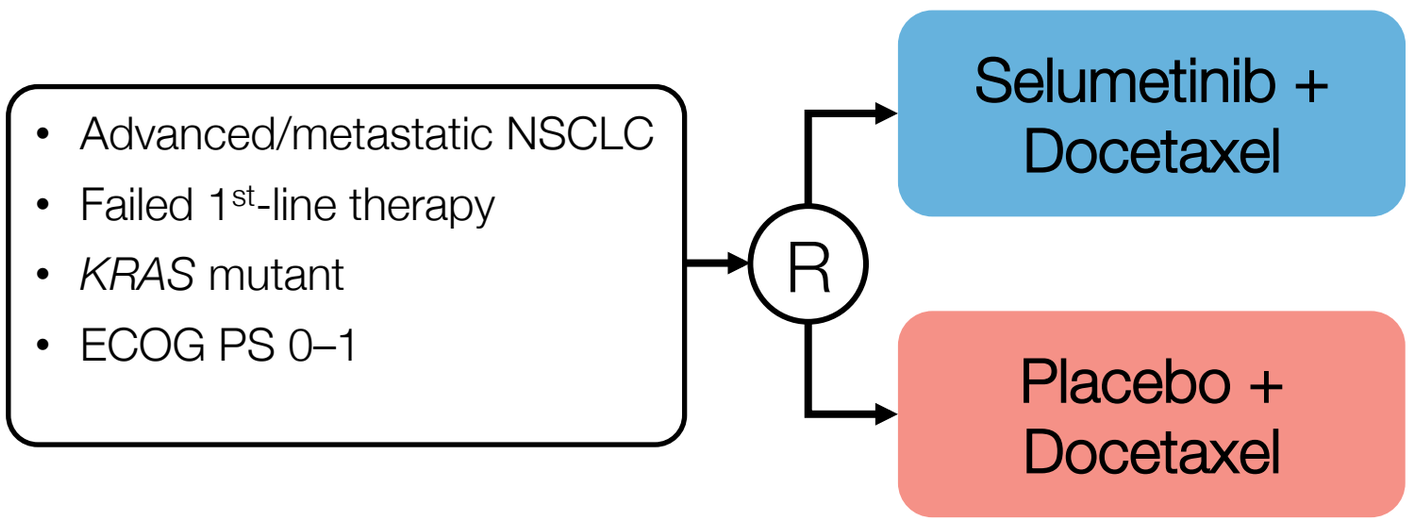
- Results:
  - In the observation arm there was an almost 3-fold increase in the rate of second primary cancers in KRAS-mutant NSCLC compared to KRAS wild-type.
  - In the adjuvant chemotherapy arm there was a 34% reduction of this rate in the KRAS-mutant cases compared to the wild-type.
- Conclusion:
  - **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

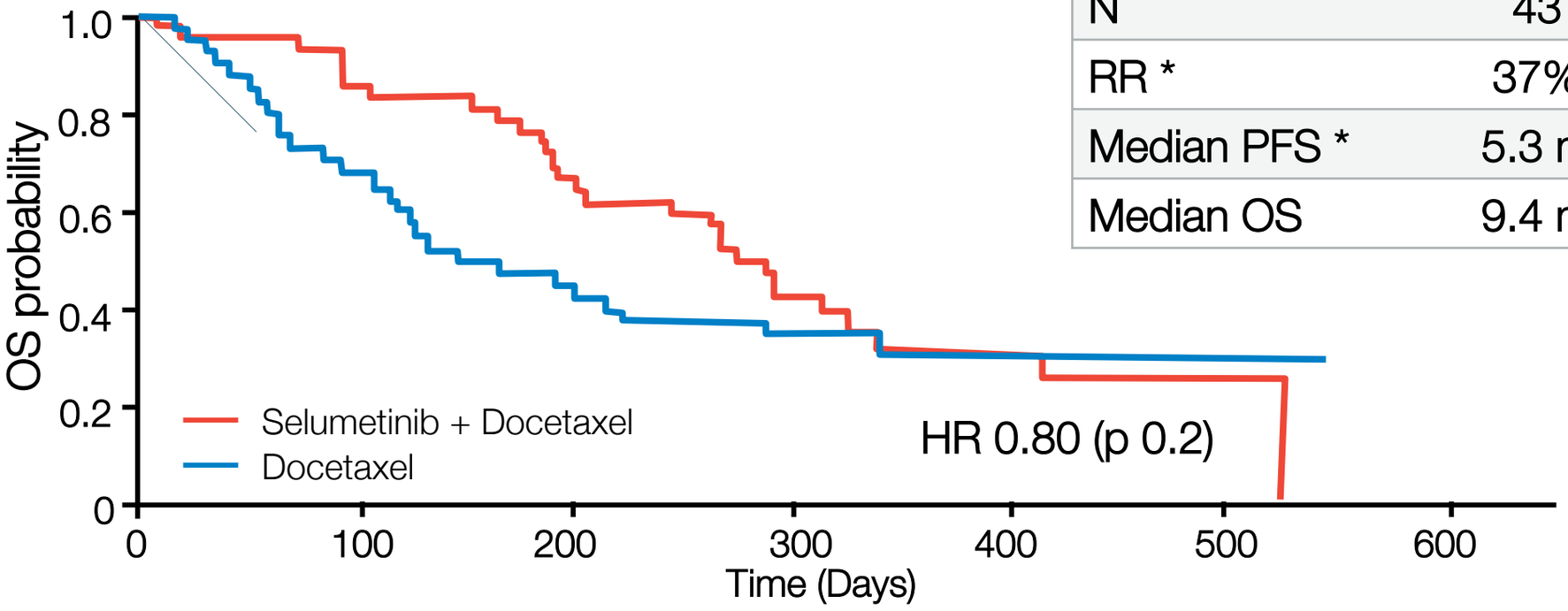


- Selumetinib is a potent and selective inhibitor of MEK ½.
- Selumetinib monotherapy has clinincal activity in pretreated NSCLC (but not superior to pemetrexed)
- The combination of selumitinib with docetaxel produced tumor regression in a preclinical *KRAS* mutant cancer model.



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:

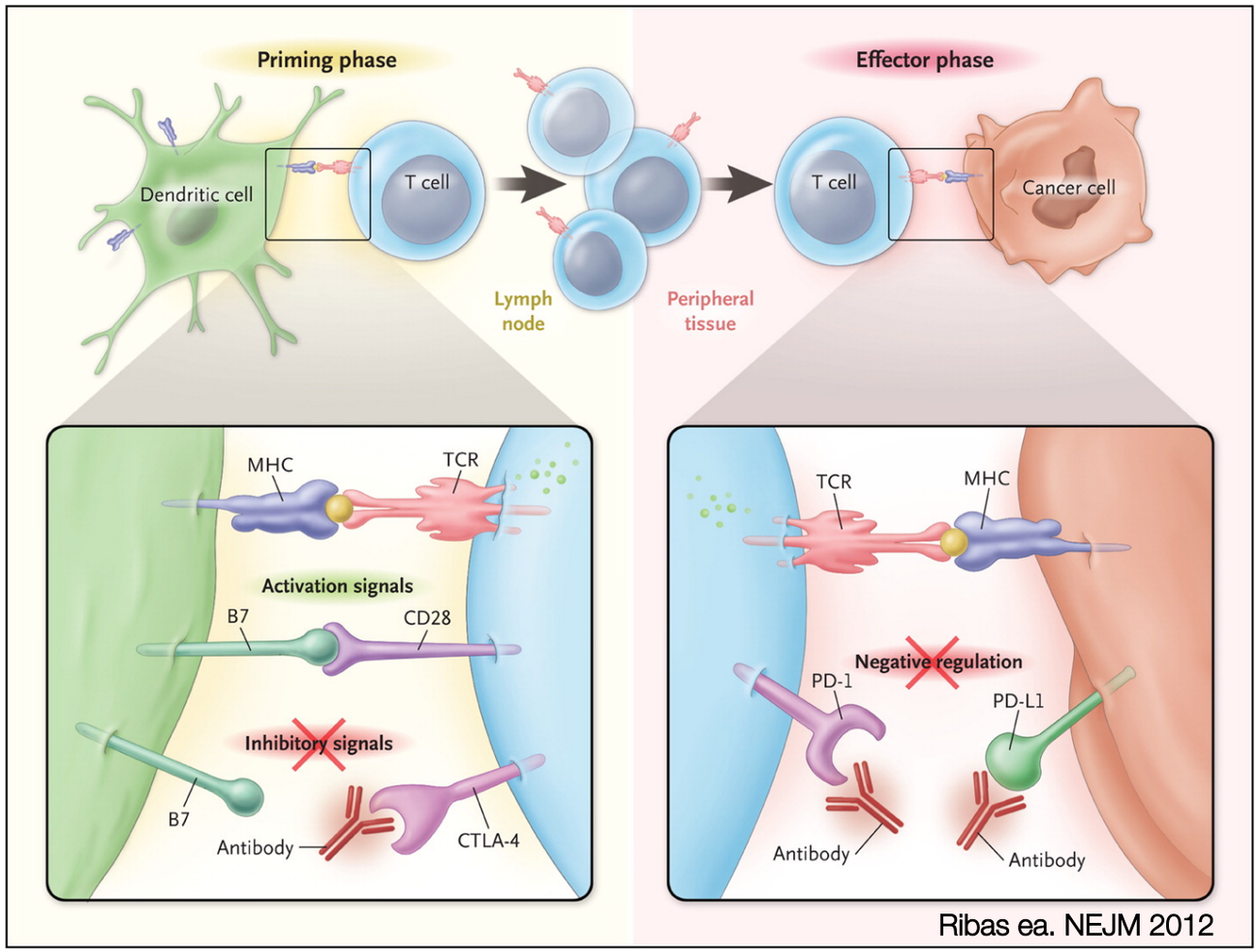
- This is the first prospective study to demonstrate a clinical benefit of a targeted therapy (selumetinib + docetaxel) for patients with *KRAS* mutant cancer of any type
- Further investigation of selumetinib + docetaxel in *KRAS* mutant NSCLC required

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



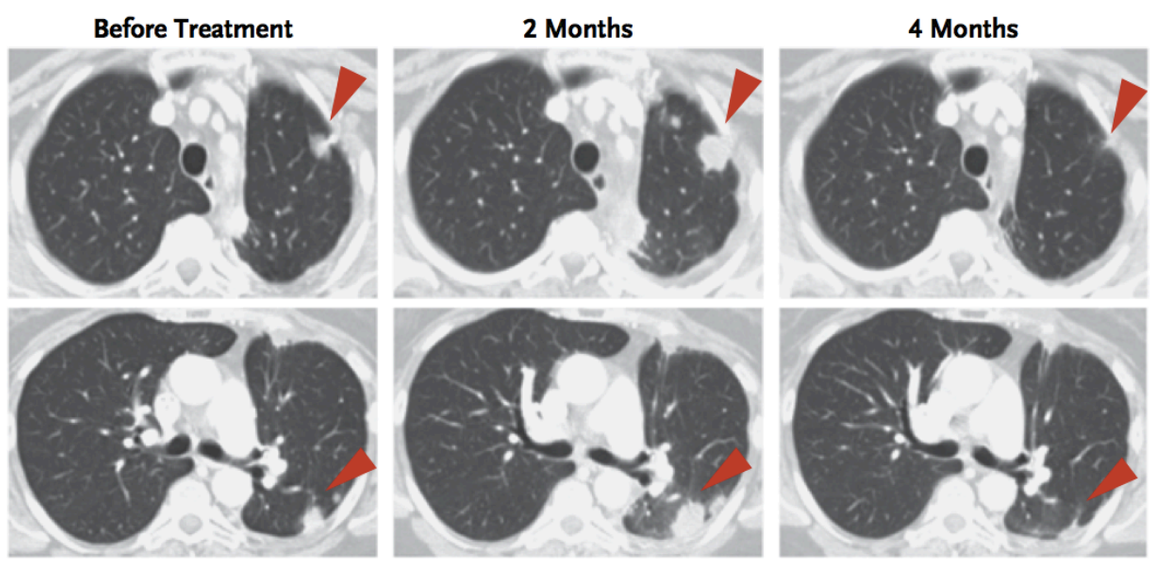
- Programmed death 1 (PD-1) is a key immune-checkpoint receptor expressed by activated T cells that mediates immunosuppression
- Expression of the PD-1 ligand (PD-L1) has been noted in NSCLC
- Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical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



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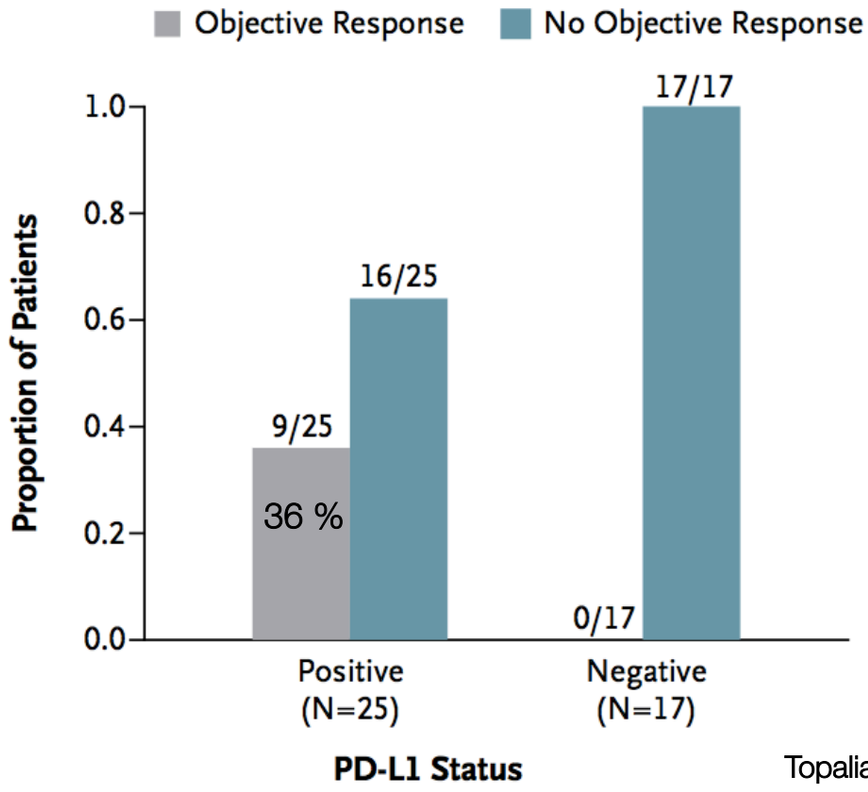
Clinical activity of **anti-PD-1** in advanced NSCLC



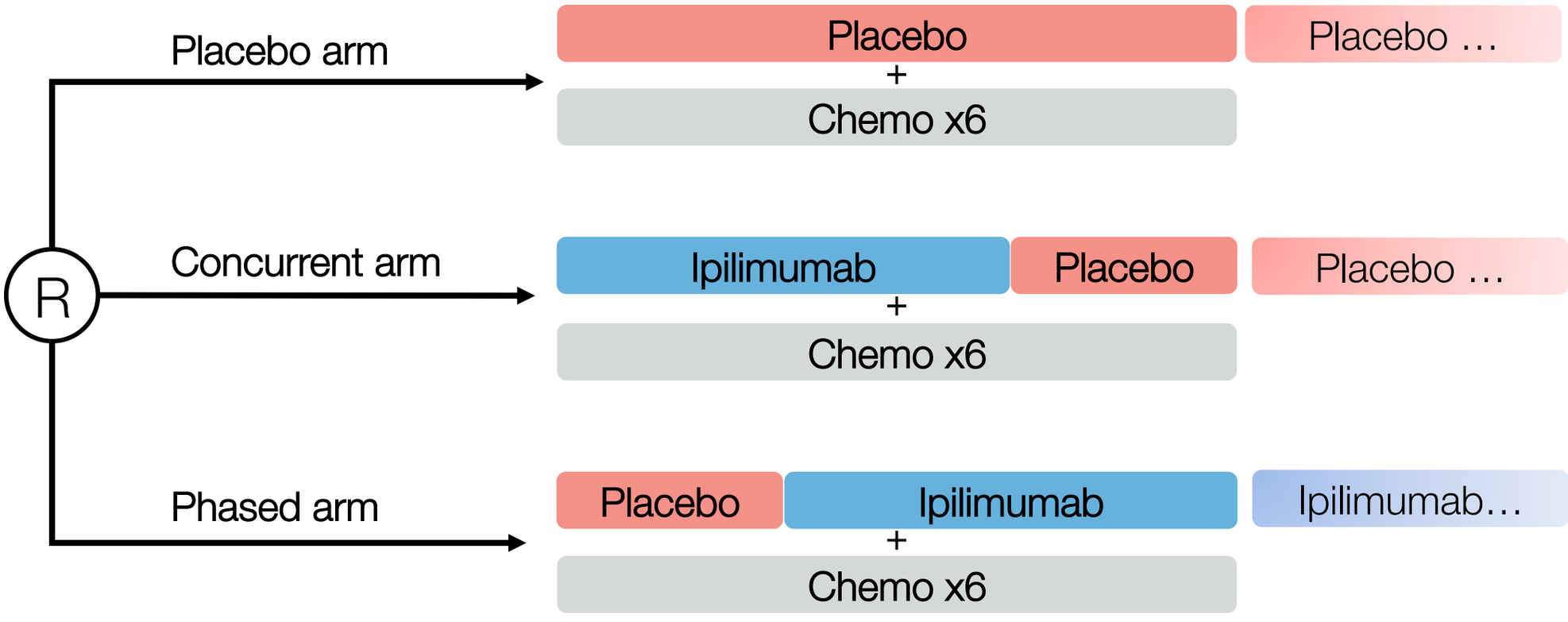
Topalian ea. NEJM 2012.

- 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

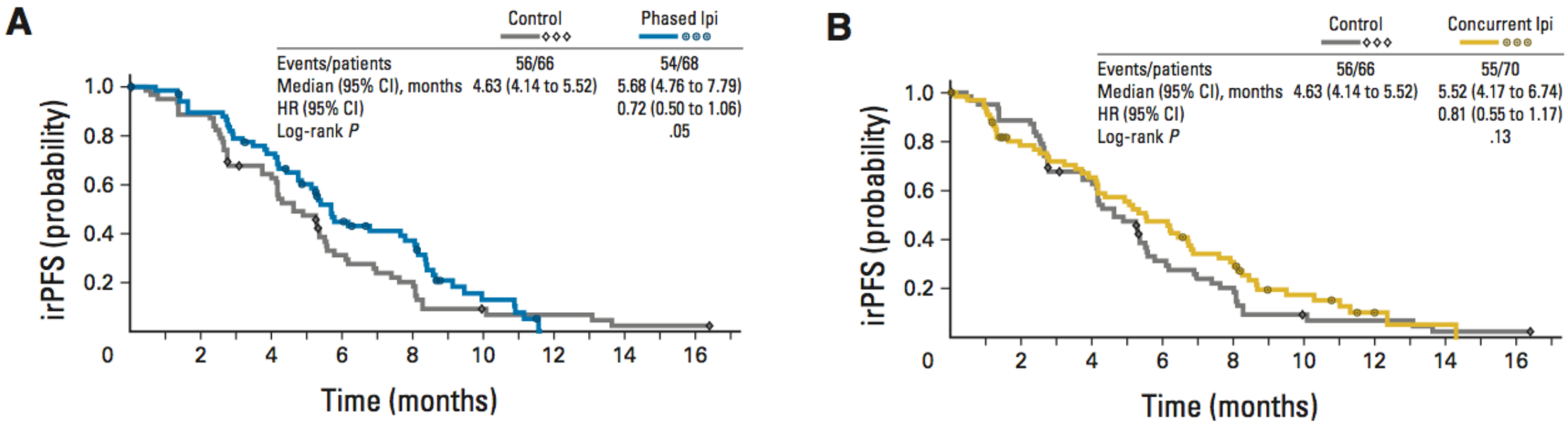
- Ipilimumab: fully human monoclonal Ab blocking the binding of CTLA-4 to its ligands



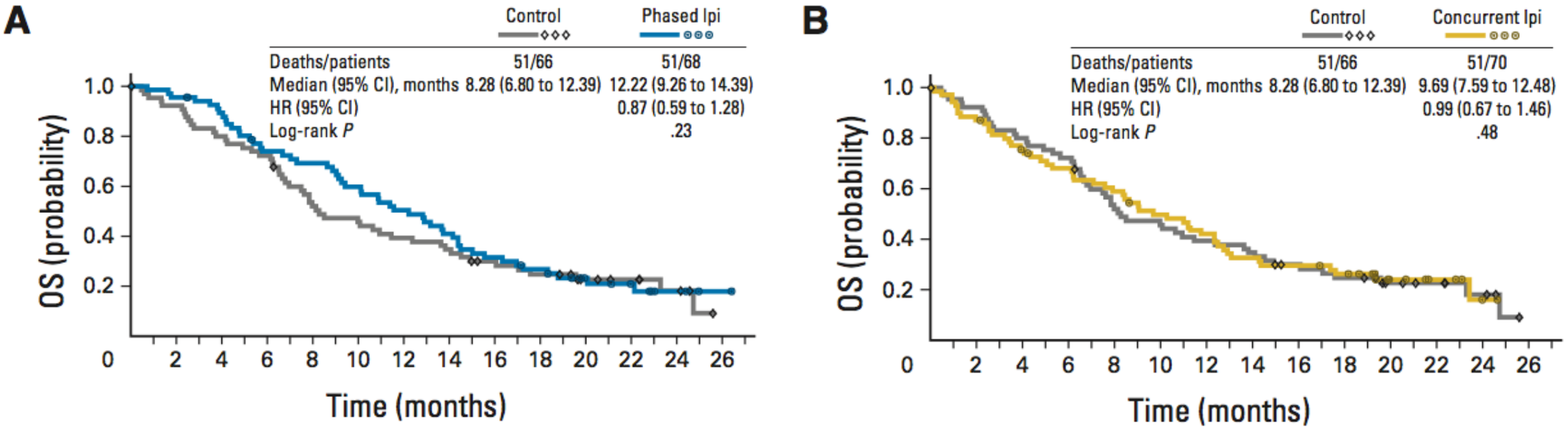
Lynch et al. *J Clin Oncol* 2012; 30:2046-2054

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

Progression-free survival



Overall survival



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

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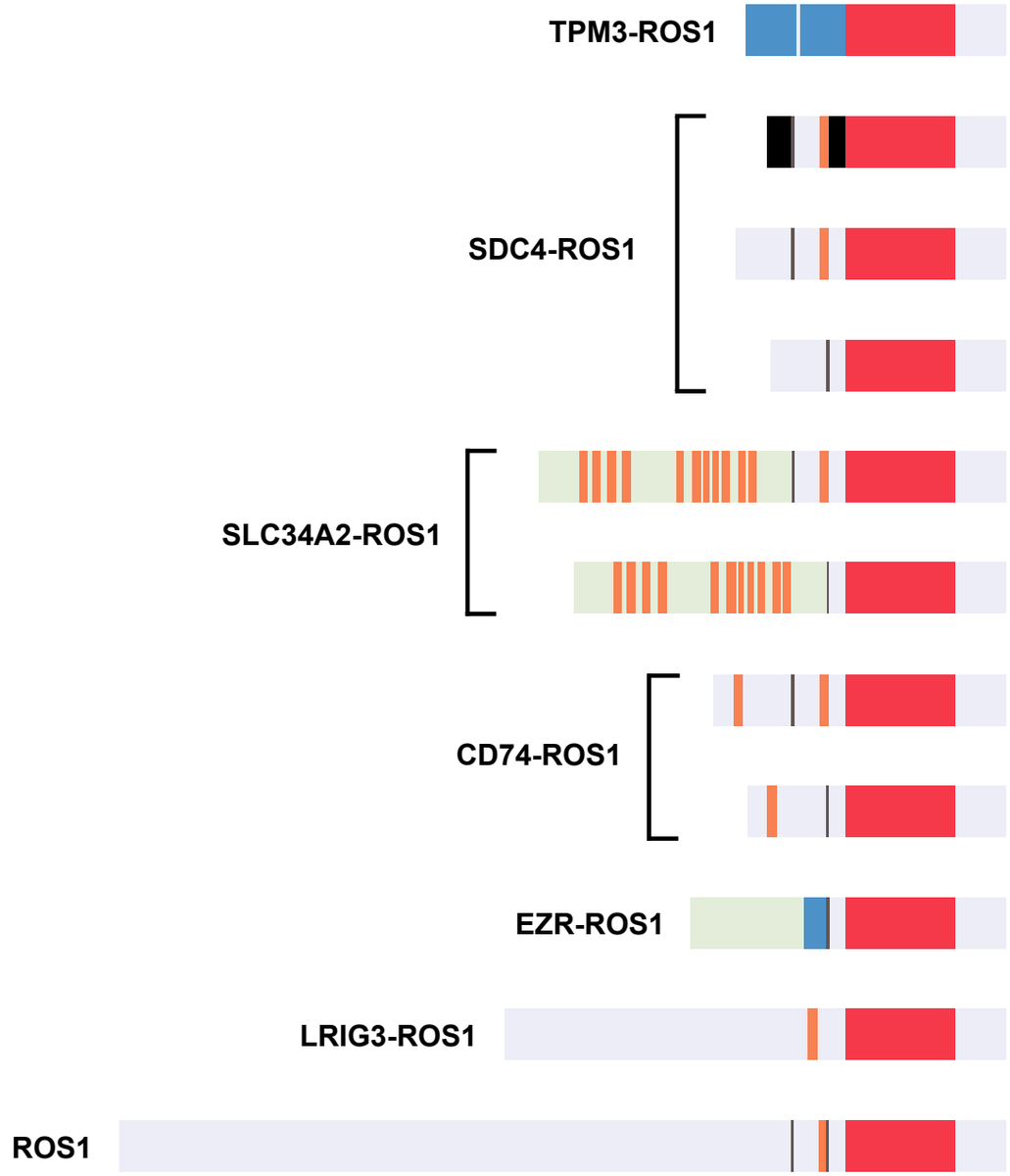
New molecular targets for NSCLC

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

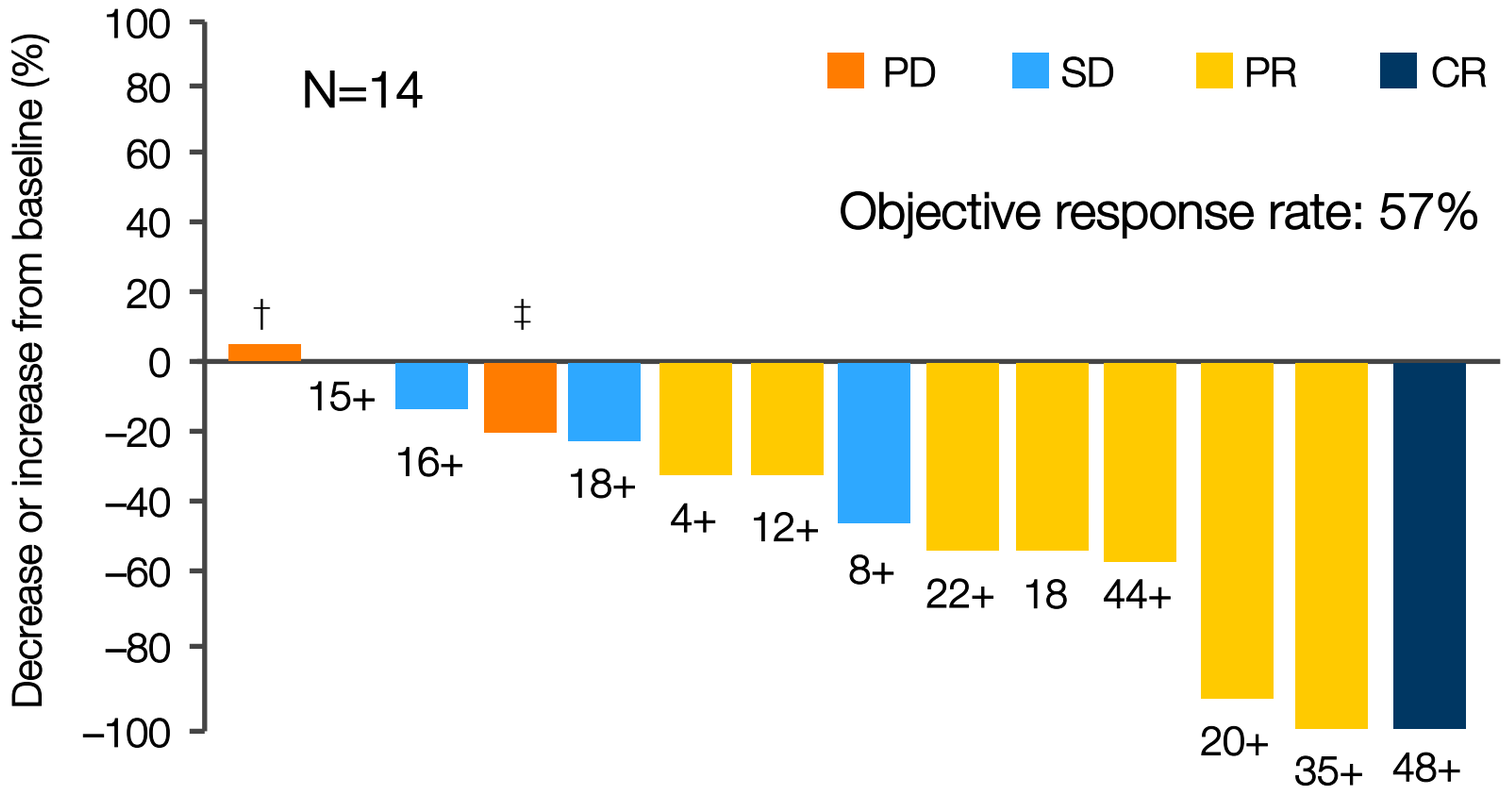
ROS1 rearrangements in NSCLC



- 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

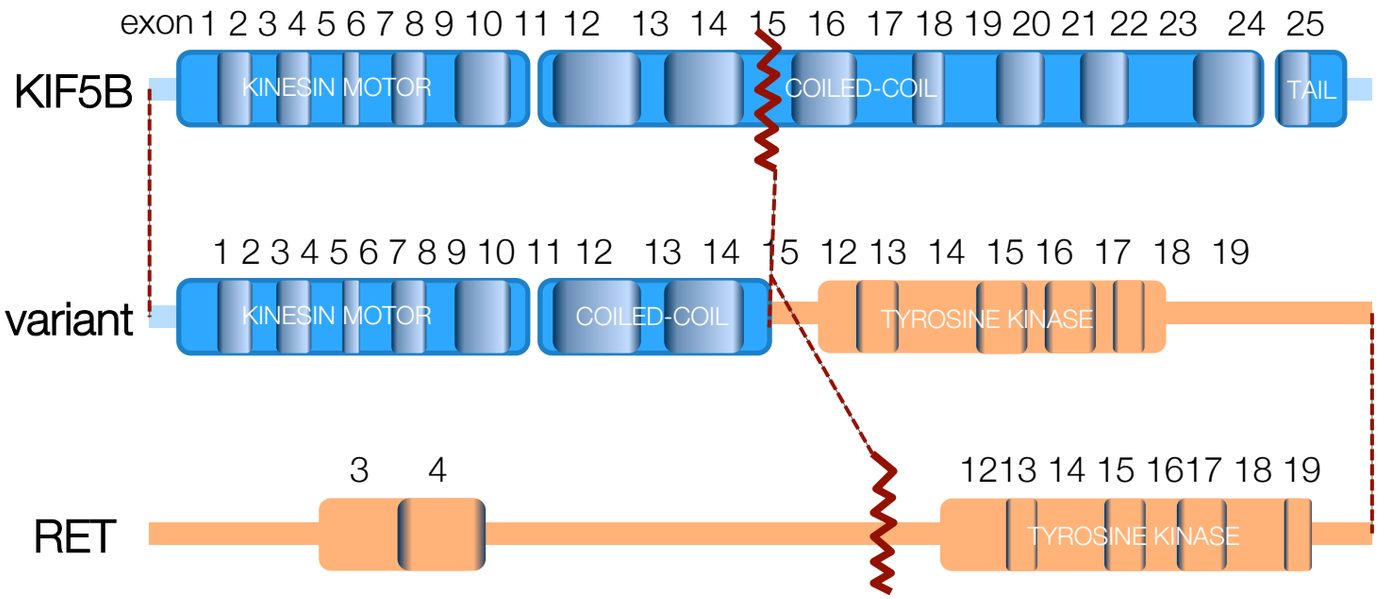


- Crizotinib demonstrates marked antitumour activity in patients with advanced NSCLC with *ROS1* gene rearrangement
- This study represents the first clinical validation of ROS as a therapeutic target in cancer

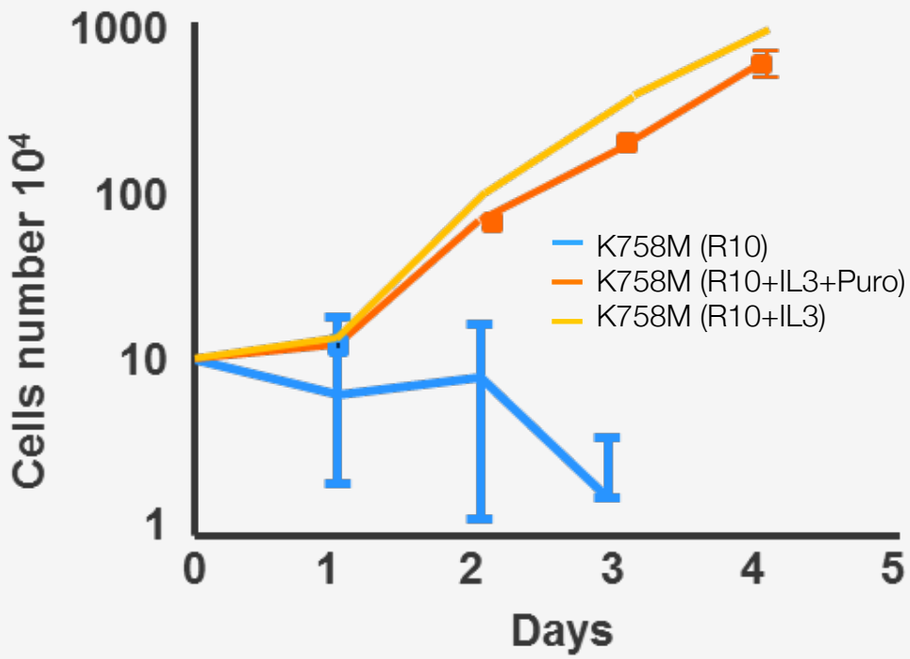
Shaw et al. 7509

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



K15:R12 was introduced into Ba/F3 cells



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

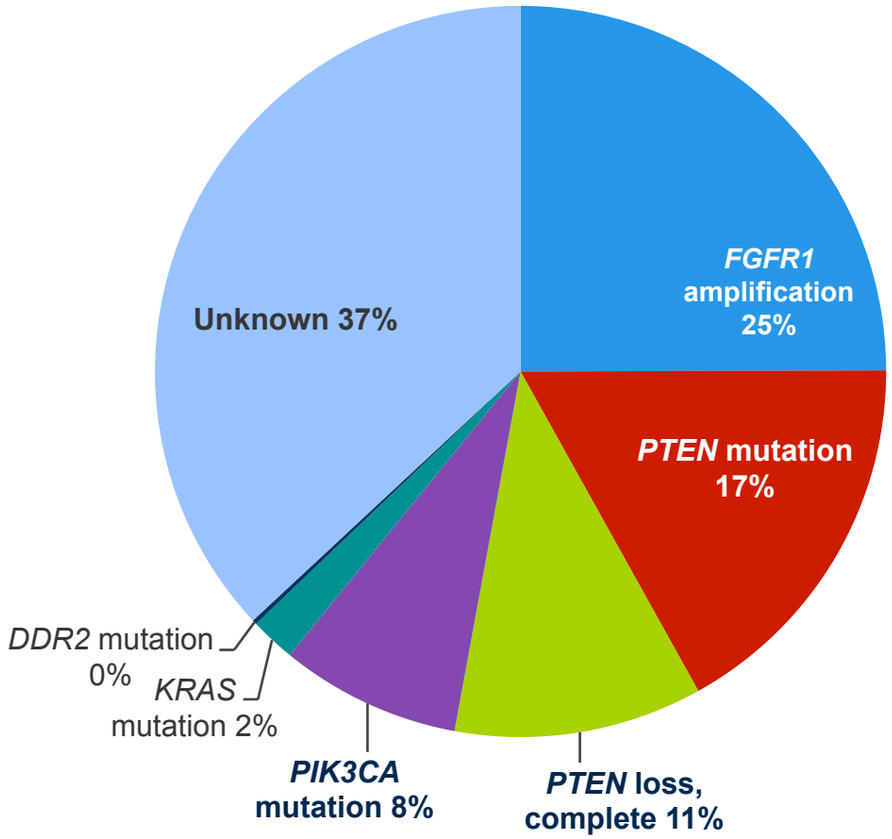
The Cancer Genome Atlas:
genetics of squamous cell lung carcinomas

- 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