Novel therapies for advanced squamous-cell carcinoma

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Organisers

IASLC International Association for the Study of Lung Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

European Society of Thoracic Surgeons 1993

etop Information | Research

Disclosure Statement

- Education-Advisory : Genesis Hellas, Janssen Hellas, Amgen Hellas
- Honoraria: Roche Hellas, AstraZeneca Hellas

Squamous-cell carcinoma (SqCC)

- Although declining proportion of NSCLC, still accounts for 30% of new cases
- Distinct epidemiological, clinicopathological and molecular characteristics (i.e stronger association with smoking, rarity of EGFR and KRAS mutations or ALK rearrangements)
- Limited treatment options: Platinum-based therapy in 1st-line, Docetaxel-based treatment or erlotinib in 2nd line and beyond[1].
- Advanced SqCC has enjoyed little of the benefit from new therapeutic options seen in ADC of the lung.

Vincent DM Front. Oncol Dec 2014

Anything new in chemotherapy?

- Cisplatin-gemcitabine still offers the best PFS (4.3 months) and OS (9.4 months), (ECOG1594)
- Pemetrexed has been shown inferior and contra-indicated
- Bevacizumab contra-indicated due to safety concerns
- Nab-paclitaxel with carboplatin appears to be superior to paclitaxel-carboplatin in SqCC with 41% ORR and less grade 3/4 neuropathy and arthralgia
- Japan: Carboplatin/S-1 superior to carboplatin-paclitaxel in SqCC (OS: 14.0 vs 10.6 months), (LETS study).

Hirsch et al. Expert Rev Anticancer Therapy 2014

Published in final edited form as:
Nature. 2012 September 27; 489(7417): 519–525. doi:10.1038/nature11404.

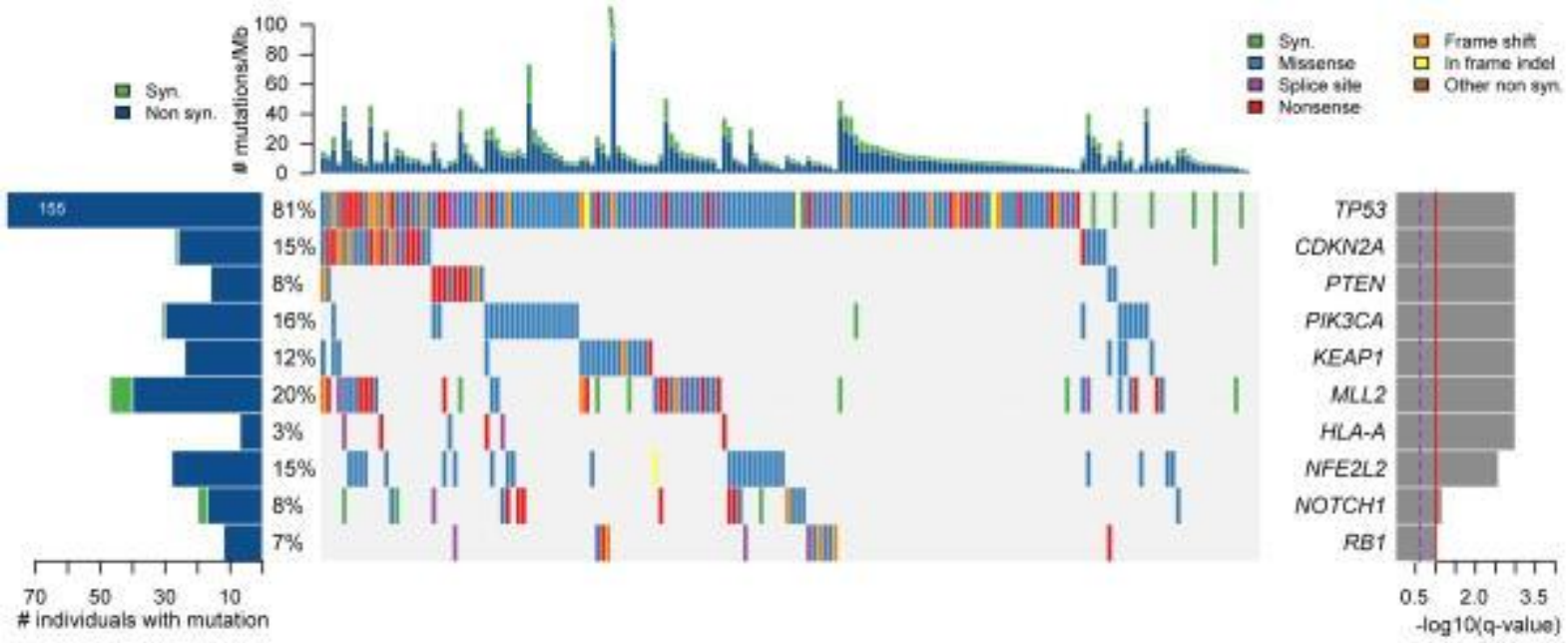
Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network

- 178 SqCC samples profiled as part of the TCGA project
- Complex genomic alterations
- A mean of 360 exonic mutations, 165 genomic rearrangements and 323 Copy number alterations per tumor
- Statistically recurrent mutations in 18 genes

Hammerman et al , Nature 2012

Mutational Landscape in Advanced SqCC



- Nearly universal presence of *TP53* mutations (81%)
- Cell cycle regulation genes altered in 72%
- Squamous differentiation genes in 44 %
- *RTKs - PI3K/AKT* and MAPK-mediated pathways in 69%, of tumors

Hammerman et al , Nature 2012

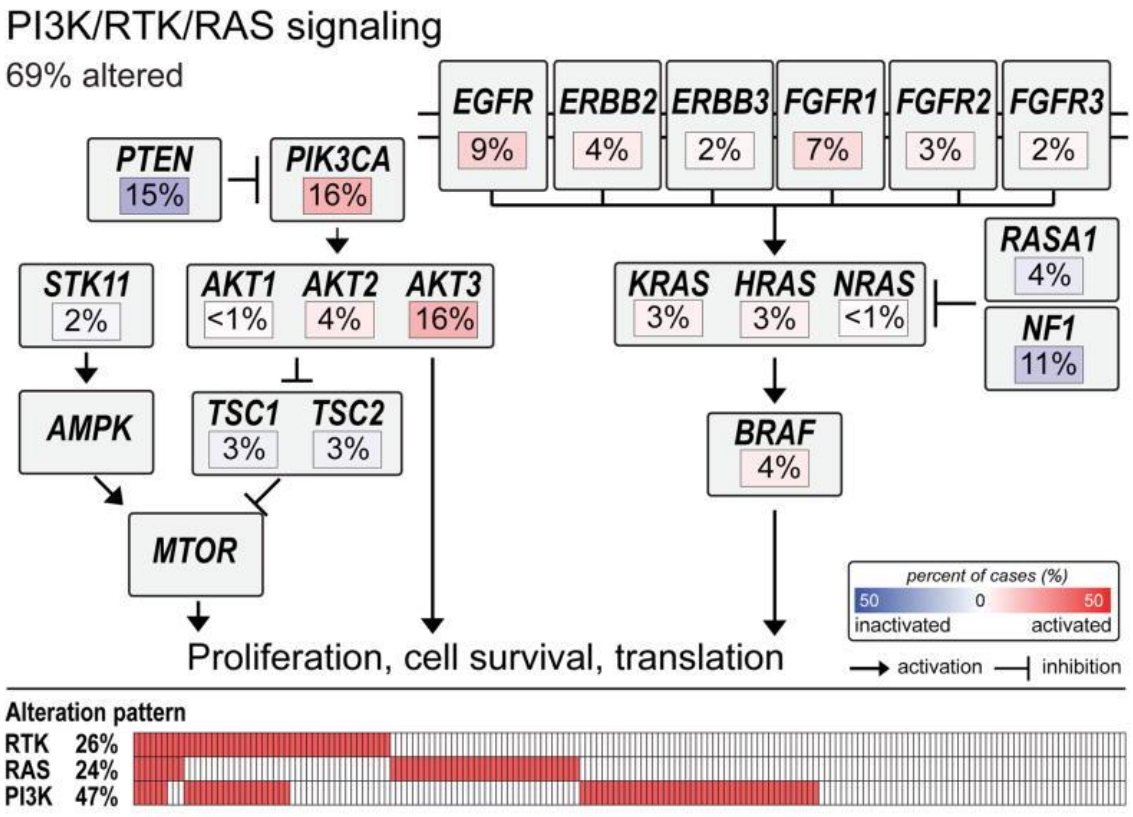
Table 1 | Selected genomic alterations in SqCC.

	Gene	Mutation rate	Normal function	Consequence of alteration	Comment
(a)	KEAP1	12%	Oxidative stress response	Loss-of-function	
(a)	NFE2L2	19%	Oxidative stress response	Activation	
(a)	CUL3	7%	Oxidative stress response	Loss–of-function	
(b)	SOX2	Zero	Squamous differentiation	Activation	Amplified in 21%
(b)	NOTCH1	8%	Squamous differentiation	Mostly loss-of-function	Mutually exclusive with TP63 or SOX2 alterations
(b)	TP63 (p40 isoform)	16%	Squamous differentiation	Activation, oncogene	
(c)	TP53	≥81%	Genomic integrity, apoptosis	Loss-of-function	Disabled in ~90% SqCC
(d)	CDKN2A	15%	Cell cycle control	Loss-of-function	Inactivated in 72% by several mechanisms
(d)	RB1	7%	Cell cycle control	Loss-of-function	Mutually exclusive with CDKN2A alterations
(e)	NF1	11%	RAS inhibitor	Loss-of-function	
(e)	BRAF	4%	Signal transduction	Activation	
(e)	RASA1	4%	RAS inhibitor	Loss-of-function	
(e)	KRAS	<1%	Signal transduction	Activation	Very uncommon in SqCC
(f)	HLA-A	3%	Antigen display	Loss-of-function	May permit avoidance of immune destruction
(g)	PTEN	8%	PI3K/Akt pathway inhibitor	Loss-of-function	
(g)	PIK3CA	16%	PI3K/Akt pathway growth and survival	Activation	AKT3 also activated in 16%
(h)	FGFR1	Few	RTK growth/survival	Activation	Amplified in 21%
(h)	EGFR	±1% L861Q mutation rate	RTK in growth/survival growth function	Activation	Amplified in 9%, rarely mutated
(i)	MLL2	20%	Chromatin regulation	?	

[1]*Vincent DM Front. Oncol Dec 2014*

Many of these mutations are inactivations of tumor suppressor genes!

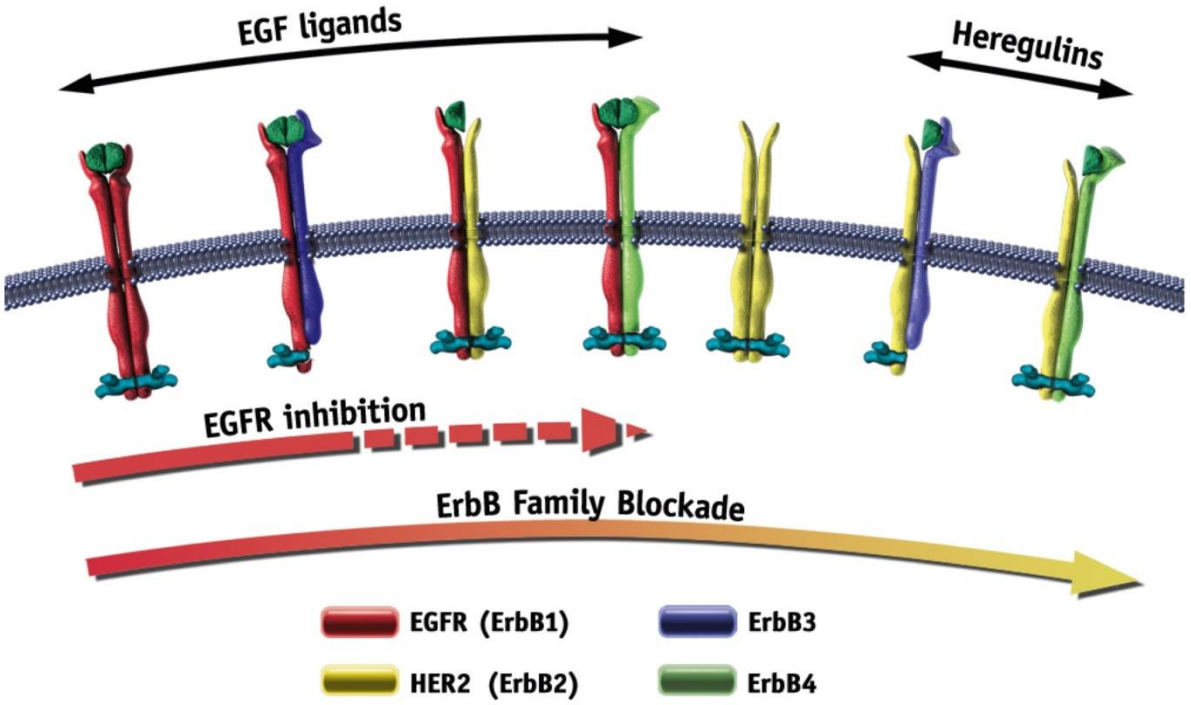
Targetable genetic alterations



Hammerman et al , Nature 2012

A. RTKs: ErbB family and Squamous-cell Lung Cancer

Afatinib: an irreversible ErbB Family Blocker



- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

Li D, et al. *Oncogene* 2008;**27**:4702–11.

LUX-Lung 8: Study Design

Primary endpoint – Progression-free survival by central independent radiology review (RECIST 1.1)

Advanced NSCLC (Stage IIIB/IV)a
Squamous histologyb
≥4 cycles of a first-line platinum doubletc
ECOG PS 0–1
Adequate organ function

→ Randomisation 1:1

- Afatinib 40 mg QD[d]
- Erlotinib 150 mg QD

→ **Treatment until disease progression or unacceptable AEs**

Excluded:

Patients without PD

Prior EGFR TKI or antibody

Active brain metastases, Interstitial lung disease

Stratification: East Asian versus Non-East Asian

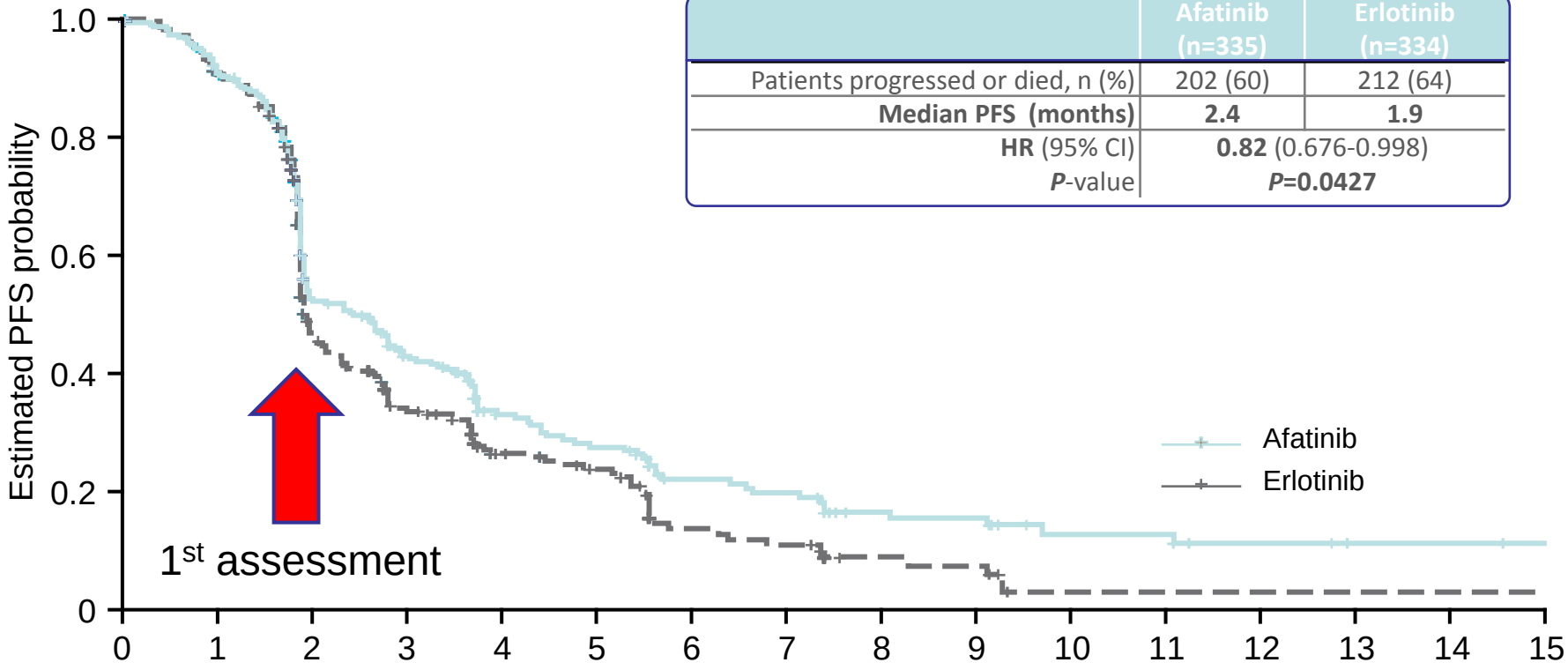
Tumour tissue collected for correlative science

Radiographic tumour assessment at baseline, Weeks 8, 12, 16; every 8 weeks thereafter

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: PFS (Independent Review)

	Afatinib (n=335)	Erlotinib (n=334)
Patients progressed or died, n (%)	202 (60)	212 (64)
Median PFS (months)	**2.4**	**1.9**
HR (95% CI)	**0.82** (0.676-0.998)	
P-value	***P*=0.0427**	

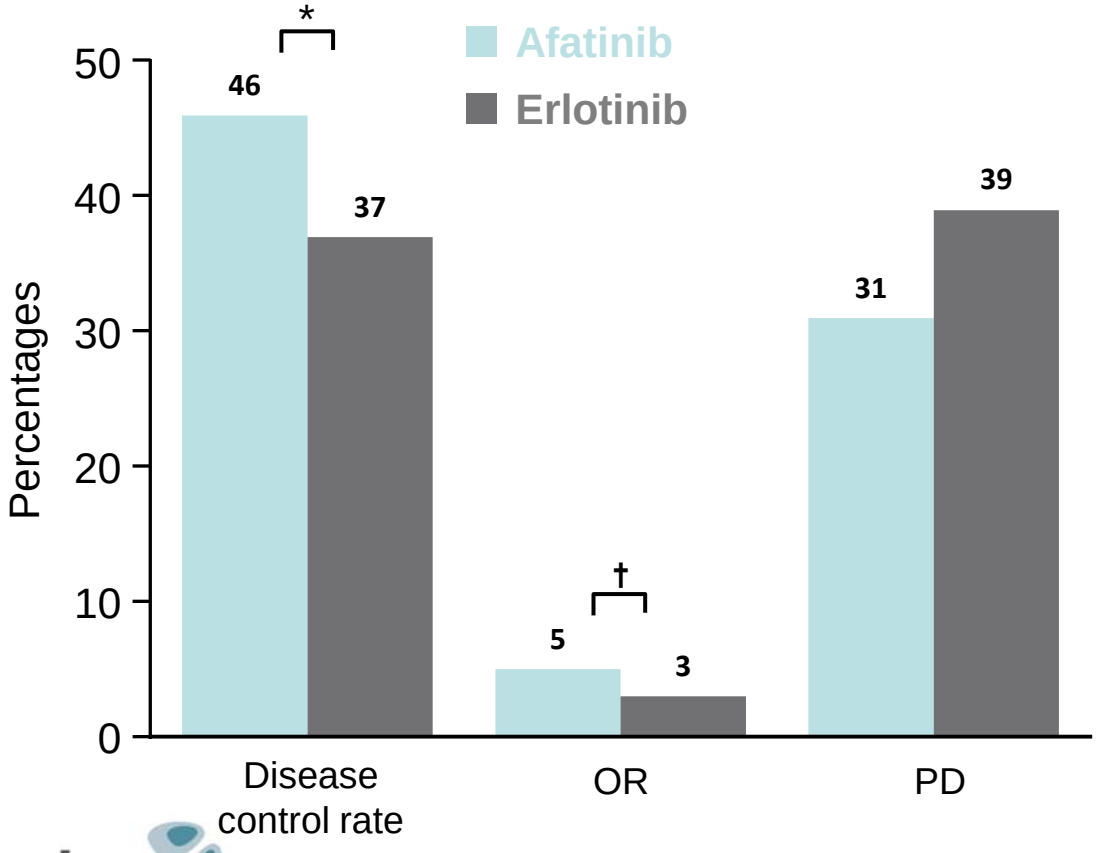


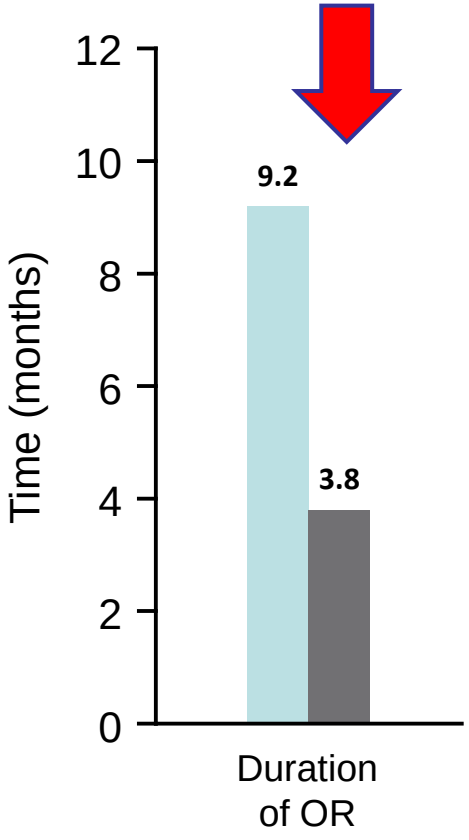
No. of patients

Afatinib	335	266	127	96	54	45	28	25	16	15	8	8	4	2	2	1
Erlotinib	334	256	112	72	43	34	15	12	6	5	0	0	0	0	0	0

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Objective Response (Independent Review)





Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Drug-Related AEs (>5%)

Grouped categories by CTCAE grades

	Afatinib (N=329) n, (%)			Erlotinib (N=332) n, (%)		
AE category	All	Grade 3	Grade 4§	All	Grade 3	Grade 4¶
Total with related AEs	298 (91)	75 (23)	4 (1)	266 (80)	48 (15)	1 (<1)
Diarrhoea	218 (66)	30 (9)	2 (<1)	103 (31)	7 (2)	1 (<1)
Rash/acne*	208 (63)	18 (6)		221 (67)	30 (9)	
Stomatitis*	90 (27)	11 (3)		28 (8)		
Fatigue*	44 (13)	3 (1)		43 (13)	6 (2)	
Decreased appetite	38 (12)	3 (1)		34 (10)	2 (<1)	
Nausea	38 (12)	3 (1)		24 (7)	3 (1)	
Paronychia*	35 (11)	1 (<1)		14 (4)	1 (<1)	
Pruritus	29 (9)	1 (<1)		36 (11)		
Dry skin	27 (8)†	2 (<1)		34 (10)		
Vomiting	25 (8) ‡	2 (<1)		10 (3)	2 (<1)	

Goss et al. ESMO 2014. Abstract 12220.

Overview of Second-Line Trials testing EGFR-TKIs and MoAbs in patient cohorts including SqCC

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
BR.21	**Erlotinib vs placebo (n=727)** Squamous *(n=222)*	**2.2 vs 1.8**	**0.61**	**6.7 vs 4.7** 5.6 vs. 3.6	**0.70** 0.67*	9 vs 1 4 vs ?	
ZEST	**Vandetanib vs erlotinib (n=1240)** Squamous *(n=272)*	**2.6 vs 2.0**	**0.98** 1.09	**6.9 vs 7.8**	**1.01** 1.25	12vs12	50% grade ≥ 3 AEs
BETA	**Erlotinib +bev vs erlotinib (n=636)** Squamous *(n=28)*	**3.4 vs 1.7**	**0.62**	**9.3 vs 9.2**	**0.97** 0.91	13 vs 6	60% grade ≥ 3 AEs
TITAN	**Doce/pem vs erlotinib, (n=304)** Squamous *(n=154)*	**2.2 vs 1.6**	**1.19**	**5.5 vs 5.3**	**0.96** 0.86	8 vs 6	31% grade ≥ 3 AEs
SUN1087	**Sunitinib + erlotinib vs erlotinib (n=960)** Squamous *(n=270)*	**3.6 vs 2.0**	**0.81** 0.8	**9.0 vs 8.5**	**0.92** 0.94	11 vs 7	
TAILOR	**Doce vs erlotinib, EGFR wt (n=222)** Squamous *(n=54)*	**2.9 vs 2.4**	**0.72** 0.57	**8.2 vs 5.4**	**0.78** 0.90	15 vs 3	5% FN
Thatcher et al. JCO 2014 (Suppl)	**Cisplatin-Gemcitabine ± Necitumumab (Mab Against EGFR)** **N=545, ALL SQUAMOUS!**			**11.5 vs 9.9**	**0,84 (P=0.012)**		11% ° 3 diarrhoea

Second-line trials with FGFR, RET and VEGFR TKIs

Trial	Target	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
ZODIAC	RET VEGFR EGFR	**Vandetanib + docetaxel vs docetaxel(n=727)**	**4.0 vs 3.2**	**0.79**	**10.6 vs 10.0**	**0.91**	**17 vs 10**	9% FN
		Squamous *(n=344)*		0.79		0.98		
ZEAL	RET VEGFR EGFR	**Vandetanib + pem vs pem (n=1391)**	**4.1 vs 2.8**	**0.86**	**10.5 vs 9.2**	**0.86**	**19 vs 8**	52% grade ≥ 3 AEs
		Squamous *(n=114)*		1.04		1.08		
LUME-Lung 1	**FGFR VEGFR PDGFR**	**Nintedanib + doce vs doce (n=1314)**	**3.4 vs 2.7**	**0.79**	**10.1 vs 9.1**	**0.94**	**4.4 vs. 3.3**	>70% grade ≥ 3 AEs; 7% FN
		Squamous (n=487)	2.9 vs 2.6	0.77	8.6 vs 8.7	1.01	4.7 vs. 2.2	
REVEL	**VEGFR**	**Ramucimurab + doce vs doce (n=1253)**	**4.5 vs 3.0**	**0.76**	**10.5 vs 9.1**	**0.86**	**23.0 vs 13.6**	>70% grade ≥ 3 AEs; 16% FN;
		Squamous (n=328)	4.2 vs 2.7	0.76	9.5 vs 8.2	0.88	26.7 vs 10.5	

Hanna N et al. *J Clin Oncol. (2004)* 1;22(9):1589-97.
Scagliotti G et al. *The Oncologist (2009);* 14(3):253-263.
Herbst RS et al. The Lancet Oncology (2010); 11(7):619-626
De Boer RH et al. J Clin Oncol. (2011);29(8):1067-74
Reck M et al. *Lancet Oncology (2014):* 143-155
Garon E et al Lancet Oncology (2014):epub

FN: febrile neutropenia

The FGFR-mediated pathway in SqCC

- Amplified in 12% of SqCC cases (TCGA data)
- Preclinical efficacy evidence for cediranib, nintedanib, pazopanib and ponatinib
- LUME-LUNG-1 study (phase III in 2nd line: 42,1% with SqCC):

  Docetaxel+nintedanib vs Docetaxel plus placebo
- Disease control rate superior to SqCC compared to ADC:

  49.3% vs 35.5 % ($p<0.001$)
- HR for PFS identical in both groups (HR=0.77)
- Surprisingly, OS favored the ADC group…
- Ponatinib (NCT01761747) and Pazopanib (NCT01208064) in phase II ongoing

Hirsch et al. Expert Rev Anticancer Therapy 2014

Other molecular targeted agents under investigation in advanced SqCC

Target	Frequency	Drug	Phase	RESULTS	COMMENTS
IGF1R	Mutated 4-6%	Figitumumab	II-III	Phase III NEGATIVE	
MET	Amplified 6%	Onartuzumab + Erlotinib	II-III	Phase III NEGATIVE	Randomized phase II Pacltaxel-Carbo ± Onartuzumab Ongoing (NCT01519804)
PDGFRA	Amplified 8-10%	Sunitinib	I-II	Pending	
CDK4/6	*Mutated 15%*	Palbociclib	II	Pending	
PARP		Veliparib	II Randomized	HR=0.72 for OS Ramalingam et al, ESMO 2014	Phase III Pacltaxel-Carbo ± Veliparib Ongoing (NCT01560104)

Modified from Beck JT et al Cancer Treatment Reviews 2014

B. MAPK-MEK-mediated pathway and SCC

- Most patients with SqCC are current or ex-smokers

- *KRAS* mutations associated with tobacco use

- Inhibition of signaling by downstream MEK inhibition can reverse resistance in KRAS mutant cells

BUT: KRAS mutations are rare in SqCC! (6% in the west, 1.8 % in Asia)

Califano et al. Cancer Treatment Reviews 2015 (in press)

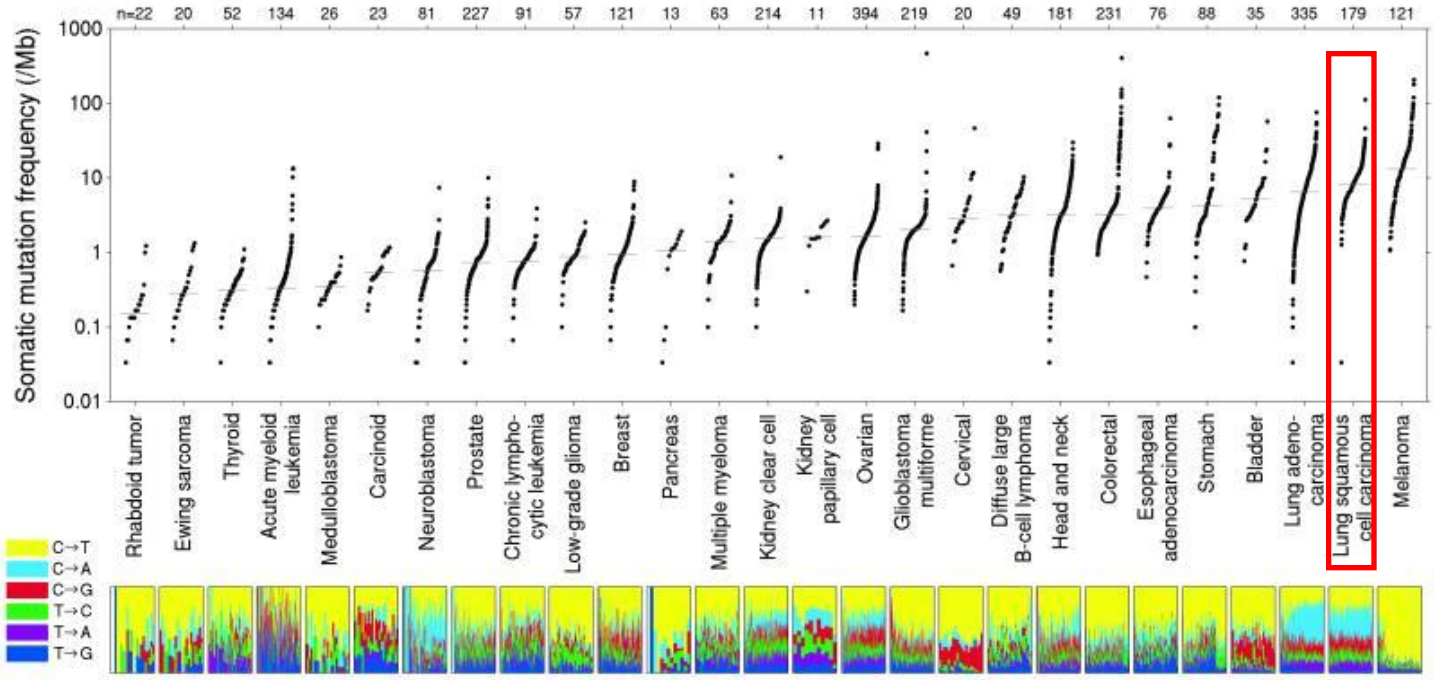
C: PI3K-Akt-mTOR pathway and SCC

Molecule Mutated/	Frequency	Drug	Phase	RESULTS	COMMENTS
PI3KCA	Mut 6.5% Copy No gain >20%	Buparsilib GDC-0032	II II	Pending	
AKT	Mut 5%	Several small molecules in early clinical development	I-II	Pending	
DDR2	Mut 4%	Dasatinib	I	Pending	
PTEN	*Mut 15%*	PI3KCA inhibitors	II	Pending	

Modified from Beck JT et al Cancer Treatment Reviews 2014

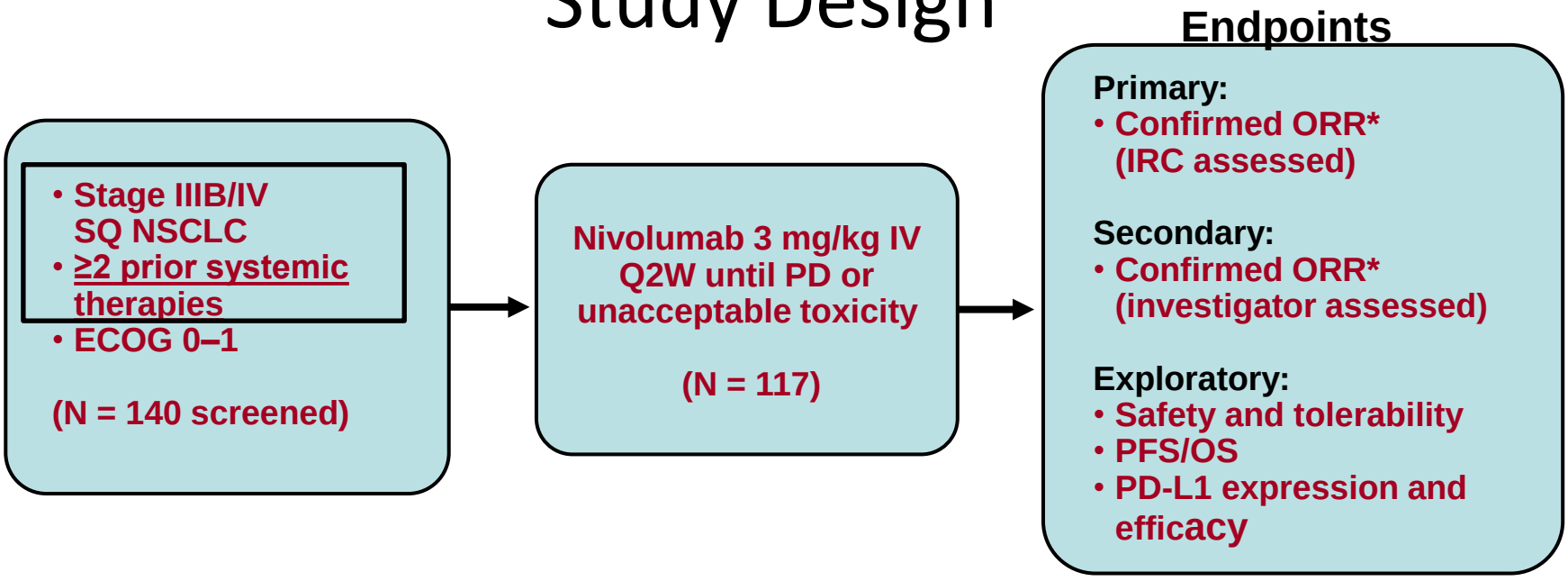
D. SCC of the lung is a highly mutated tumour: Potentially immunogenic

Mean rate of somatic exonic mutations: 8.1 per Megabase



Scotline et al. Nature, 2014

Nivolumab: CA209-063 (CheckMate 063) Study Design

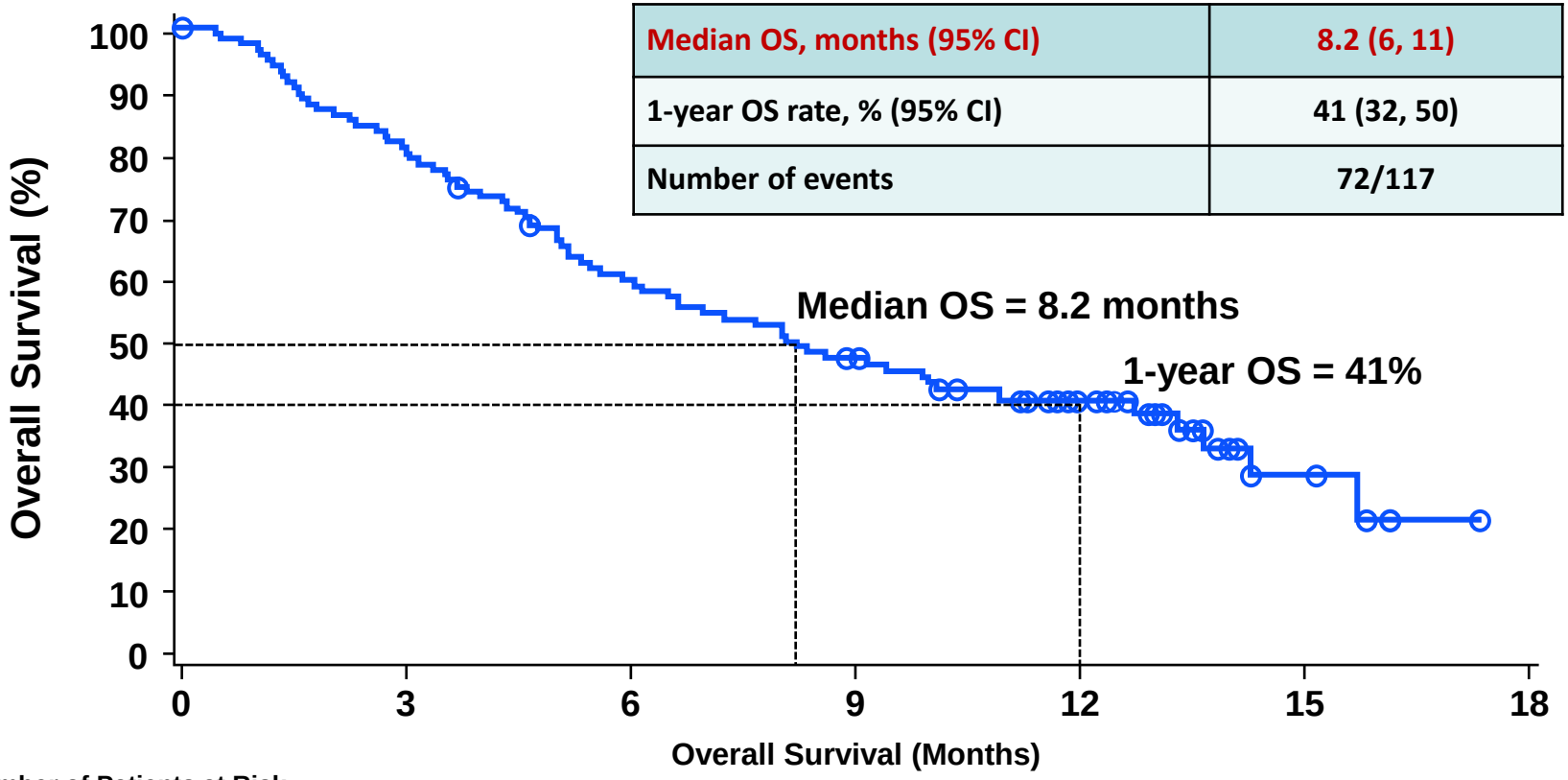


- Planned to treat approximately 100 patients
  - Expected ORR of 10–50%, with 20% maximum width of exact 2-sided 95% confidence interval
- Assessments (RECIST v1.1) performed at week 8 and Q6W

S. Ramalingam et al. ASCO 2014

063 - Overall Survival (OS) : All Treated Patients

Median OS, months (95% CI)	8.2 (6, 11)
1-year OS rate, % (95% CI)	41 (32, 50)
Number of events	72/117

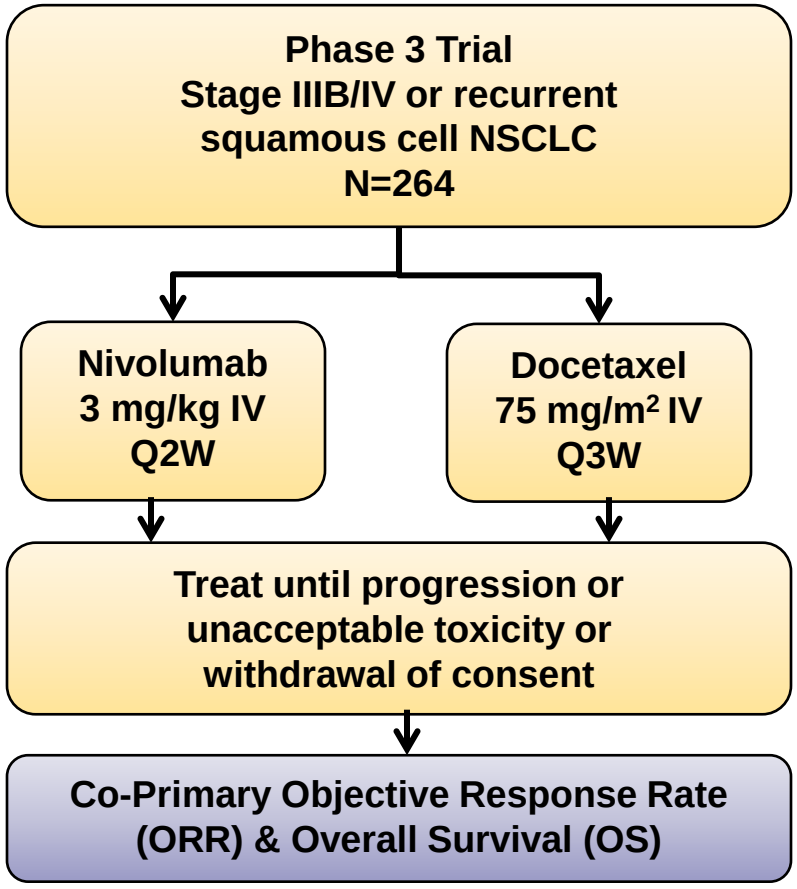


Number of Patients at Risk

Nivolumab 3mg/kg	117	93	68	51	28	5	0

Median follow-up for survival: 8 months (range, 0–17 months)

Phase 3, Open-Label Randomized Trial of Nivolumab vs. Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC) (CA209-017)



Primary Endpoints

- ORR
- OS

Secondary Endpoints

- PFS
- ORR and OS in PD-L1^{+} vs. PD-L1^{-} subgroups
- DOR (IRC assessed)
- QoL

Key Eligibility Criteria

- ≥ 18 years of age
- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Platinum-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

Study Positive:
mOS 9.2m vs 6m, HR: 0.59
March 2015: FDA Approval for 2nd line Squamous NSCLC

elcc

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Immunotherapy in SqCC: Main ongoing trials

DRUG	DESIGN	Phase	TRIAL NAME	Clinicaltrials.gov
Ipilimumab (BMS)	*Paclitaxel-Carboplatin* ± Ipilimumab	III		NCT01285609
Pembrolizumab (MSD) Anti-PD1	Chemo backbone ± Pembrolizumab	II-III	KEYNOTE 010 KEYNOTE 024	NCT01905657 NCT0214738
MEDI4736 (AZ) Anti-PDL1	Chemo backbone ± MEDI4736	II-III	ATLANTIC PACIFIC	NCT02087423 NCT 02344129
MPDL3280a (GENETECH)	*Docetaxel vs MPDL3280A In 2nd line*	III		NCT02008227

Towards the future: The "umbrella" study concept

- LUNGSCAPE and SPECTALUNG initiatives in Europe (ETOP, ESMO and EORTC)

- LUNGMAP initiative in USA (MDACC): The Master-Lung-1 Protocol for 2nd-line treatment of SCC (SWOG S1400)
  - PIK3CA mut ➔ Chemotherapy + PIK3 inhibitor
  - CCND1 mut ➔ CDK4/6 inhibitor
  - FGFR ampl ➔ FGFR inhibitor
  - c-MET ampl ➔ HGF inhibitor + erlotinib
  - PDL1 (+) IHC ➔ MEDI4736 (anti-PDL1 mAb)

Herbst RS et al Clin Cancer Res 2015

Conclusions-Future challenges

- Exome sequencing reveals genetic heterogeneity, still discloses recurrent genetic alterations, some of which are targetable
- Focus on Receptor Tyrosine kinases, cell cycle regulation, the PI3K-Akt pathway and immune checkpoint regulation.
- OS benefit seen with ramucirumab, necitumumab, cetuximab, erlotinib and nivolumab.
- Special emphasis on immune checkpoint inhibition (recent FDA approval of Nivolumab in 2nd-line setting of SCC).
- SCC of the lung may not be looked at as the “neglected sibling” of lung ADC anymore!