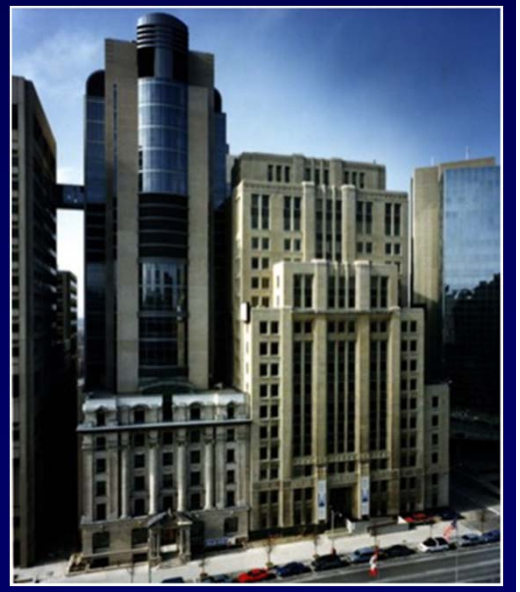
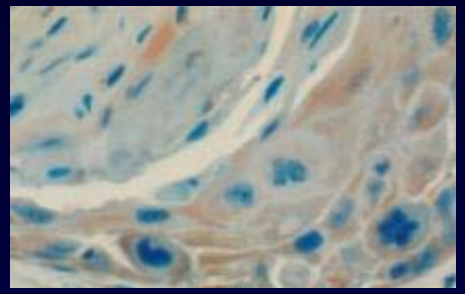
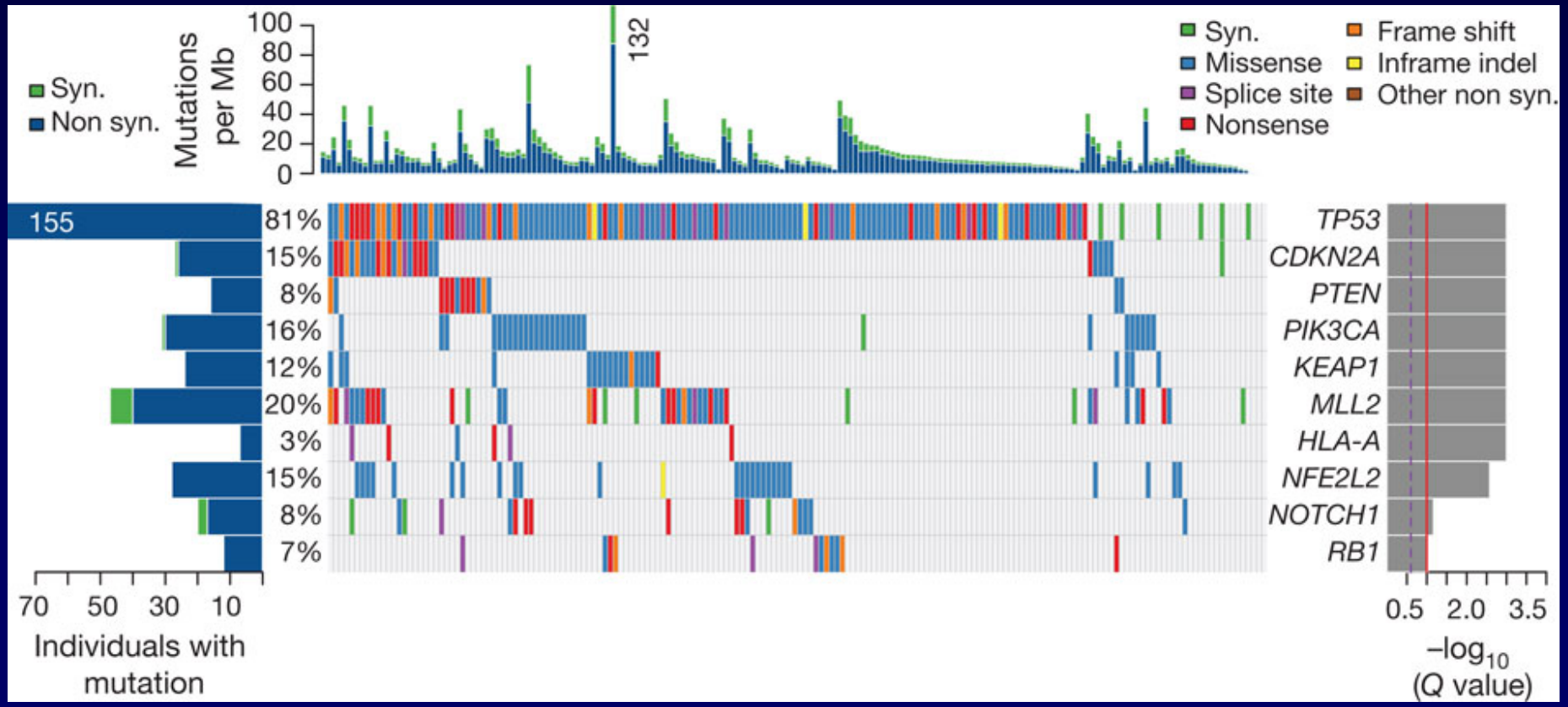
Case #5–Squamous Cell Lung Cancer: The Changing Treatment Paradigm

Natasha Leighl, MD, MMSc, FRCPC
OSI Pharmaceuticals Foundation
Drug Development Chair
Princess Margaret Hospital
Toronto, Ontario, Canada



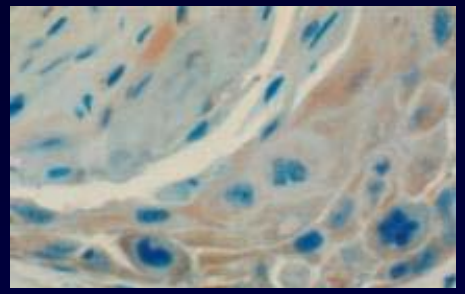
Squamous Lung Carcinoma (CK5/6+, P63/40+, CK7-)

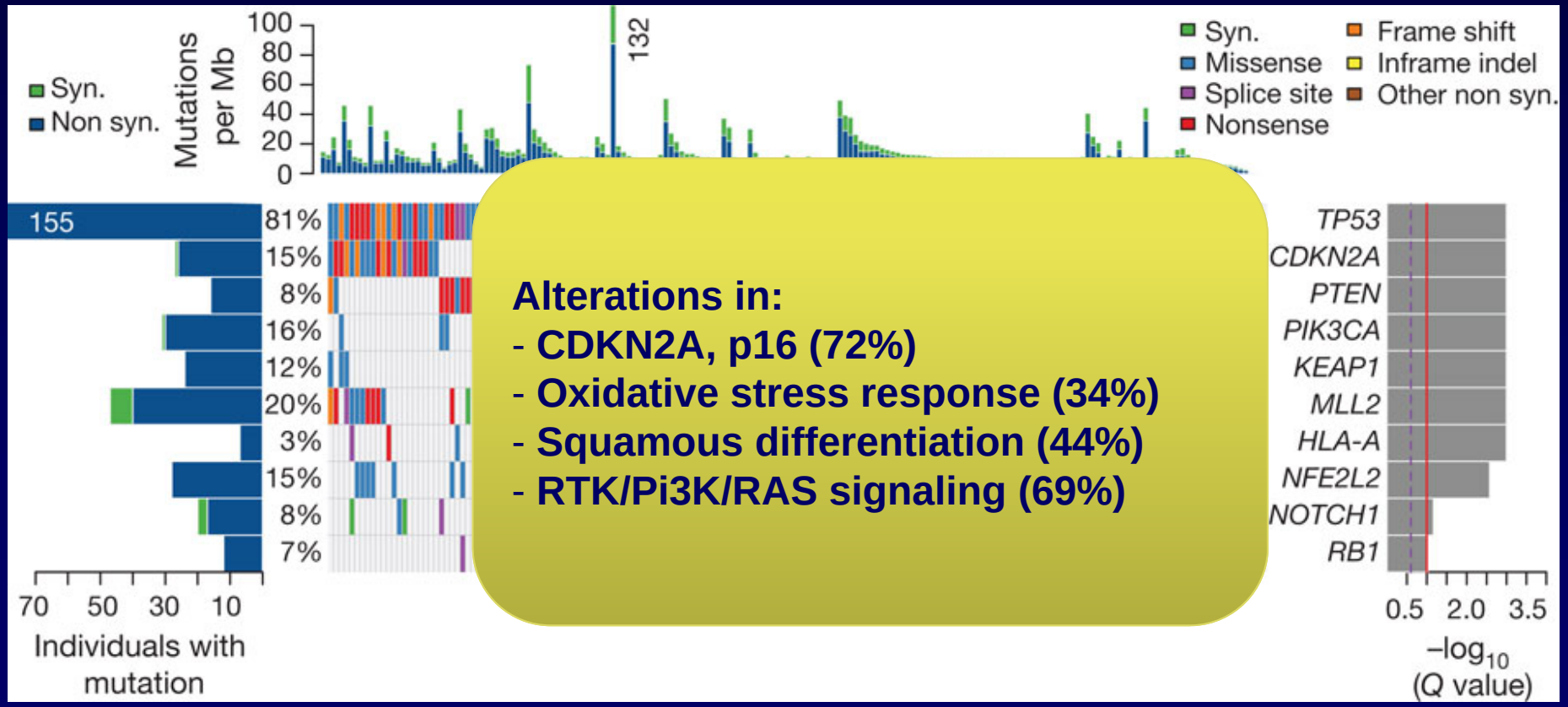




Cancer Genome Atlas Research Network. *Nature*. 2012; 489(7417): 519-525.

Squamous Lung Carcinoma (CK5/6+, P63/40+, CK7-)

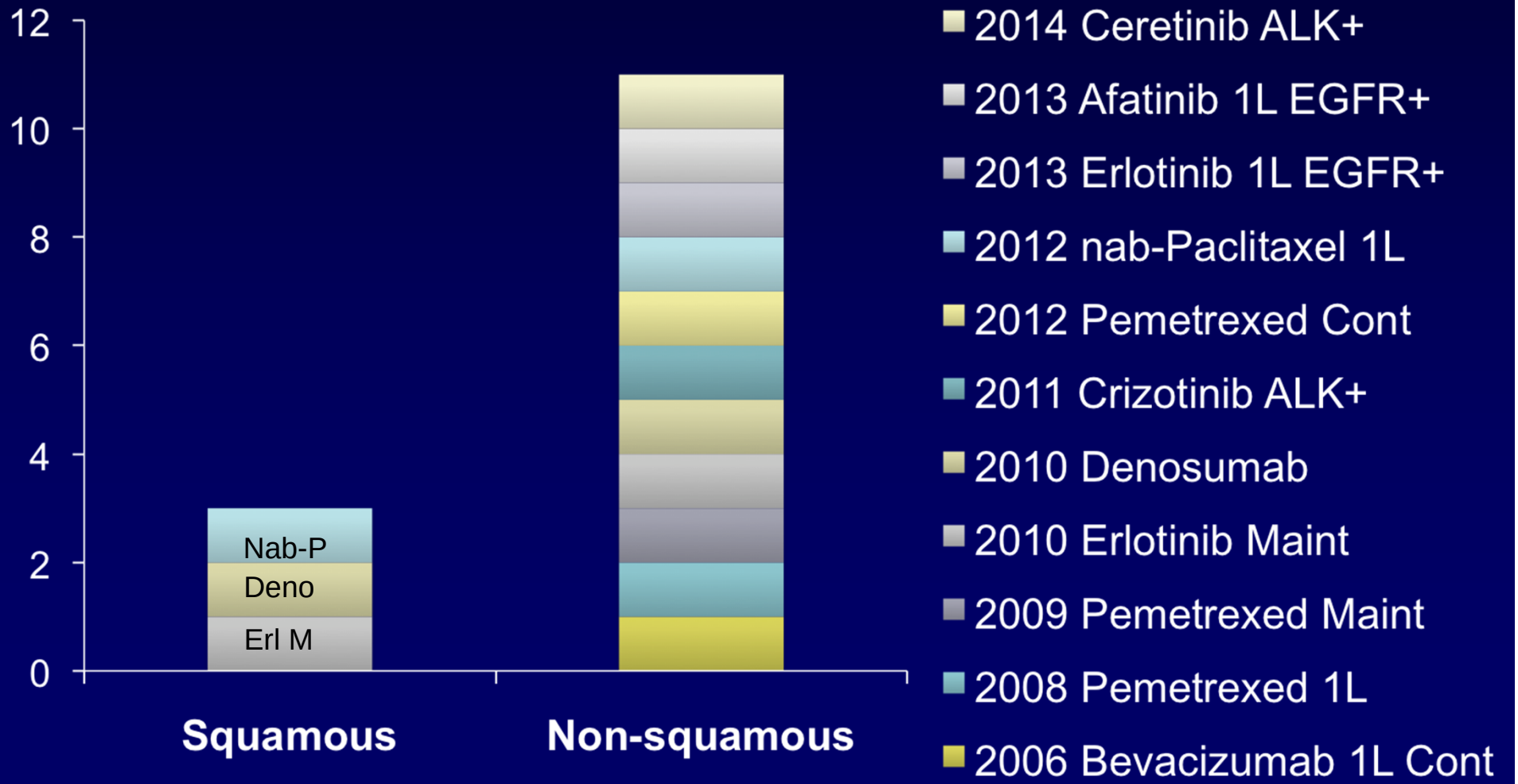




Alterations in:
- **CDKN2A, p16 (72%)**
- **Oxidative stress response (34%)**
- **Squamous differentiation (44%)**
- **RTK/Pi3K/RAS signaling (69%)**

Cancer Genome Atlas Research Network. *Nature*. 2012; 489(7417): 519-525.

FDA Drug Approval by Histology: an Uneven Playing Field



1L, first-line; Cont, continuation maintenance; Maint, maintenance

EGFR Mutation ~5%
ALK Rearrangement <0.5%

Histologic Subtype	% *EGFR* mutation (N)	Number of studies	% *ALK* rearranged (N)	Number of studies
Squamous	5% (14/278)	17	0.2% (1/523)	6
Adeno-squamous	36% (5/14)	4	0 (0/19)	3

CAP/IASLC/AMP guidelines:

- Testing not recommended if pure squamous
- For smaller samples where ADC component cannot be excluded (biopsies, cytology), testing *may* be performed (eg, never smokers)

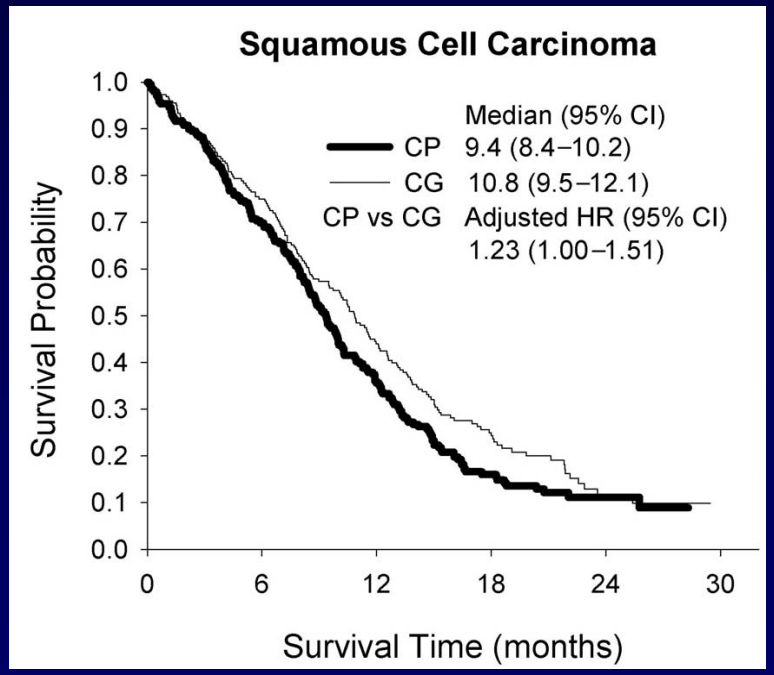
Lindeman NI, et al. *J Thorac Oncol*. 2013;8(7):823-859.

Current Standard Options for Advanced Squamous Lung Carcinoma

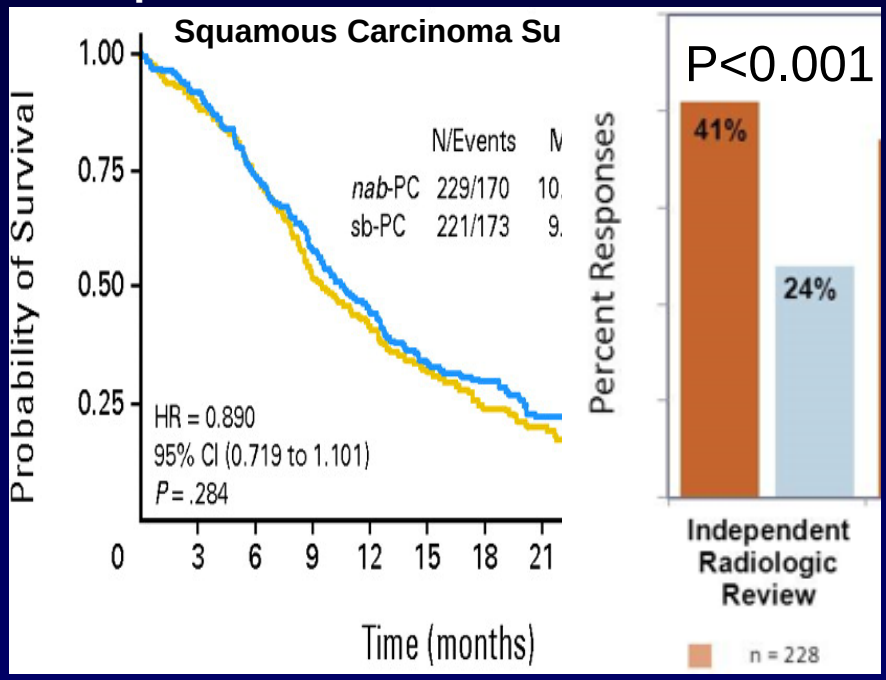
- First-line platinum doublet (without pemetrexed)
- Maintenance erlotinib
- Second-line docetaxel
- Erlotinib (after failure of chemotherapy)

First-Line Platinum Doublet: Any Non-Pemetrexed Combination

Cisplatin + Gemcitabine vs Cispaltin + Pemetrexed



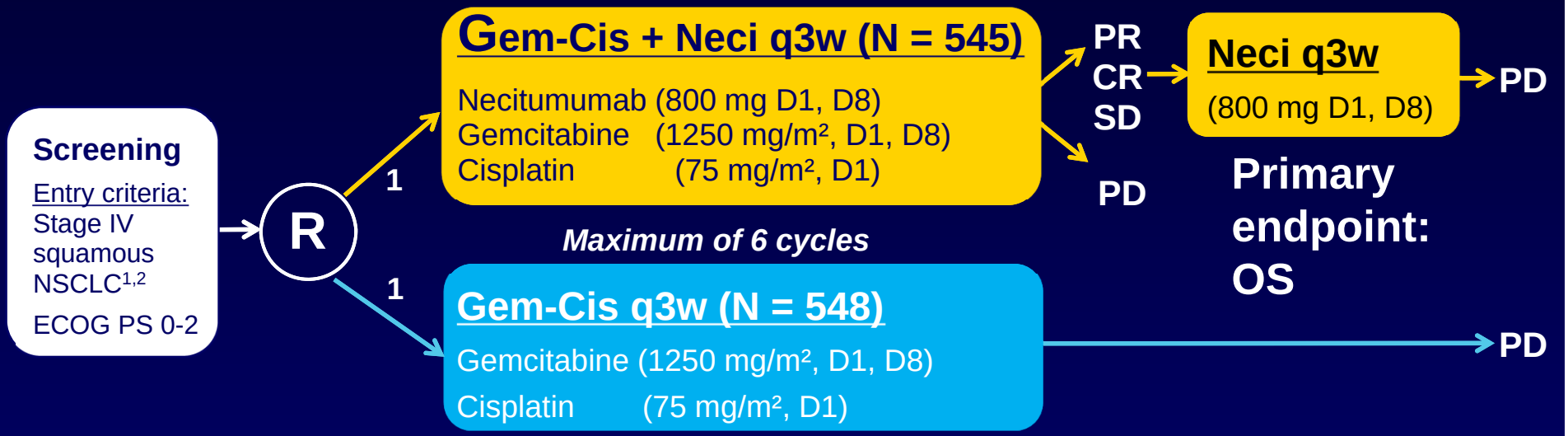
Carboplatin + *nab*-Paclitaxel vs Carboplatin + Paclitaxel



- **Similar outcomes with vinorelbine-, taxane-, gemcitabine-platinum doublets in large randomized trials**

Scagliotti GV, et al. *J Thorac Oncol.* 2009;4(12):1568-1571. Socinski MA, et al. *J Clin Oncol*. 2012;30(17):2055-2062. Kelly K, et al. *Clin Lung Cancer*. 2013;14(6):627-635. Hoang T, et al. *Lung Cancer*. 2013;81(1):47-52. Scagliotti GV, et al. *J Thorac Oncol*. 2013;8(12):1529-1537.

Necitumumab – Anti-EGFR IgG1 mAb SQUIRE Trial in 1st L Squamous NSCLC



Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe, and Australia; vs South America, South Africa, and India; vs Eastern Asia)

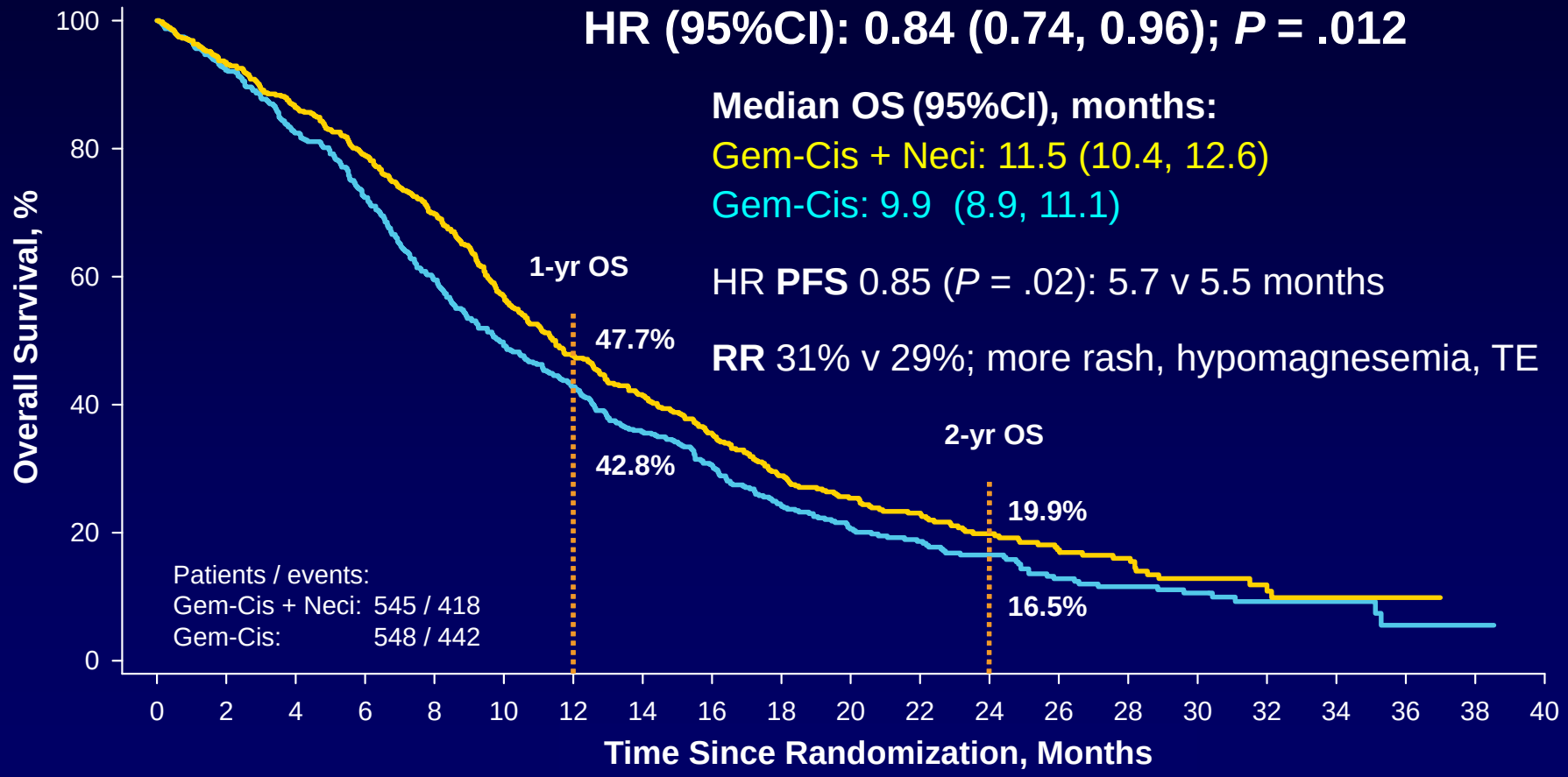
SQUIRE TRIAL

- **Patient selection not based on EGFR protein expression**
- **Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD**
- **Mandatory tissue collection**

[1] AJCC TNM Classification, 7th edition, 2009; [2] UICC TNM Classification of Malignant Tumors, 7th edition, 2009

Thatcher N, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8008.

SQUIRE: Overall Survival (ITT)



HR (95%CI): 0.84 (0.74, 0.96); *P* = .012

Median OS (95%CI), months:

Gem-Cis + Neci: 11.5 (10.4, 12.6)

Gem-Cis: 9.9 (8.9, 11.1)

HR **PFS** 0.85 (*P* = .02): 5.7 v 5.5 months

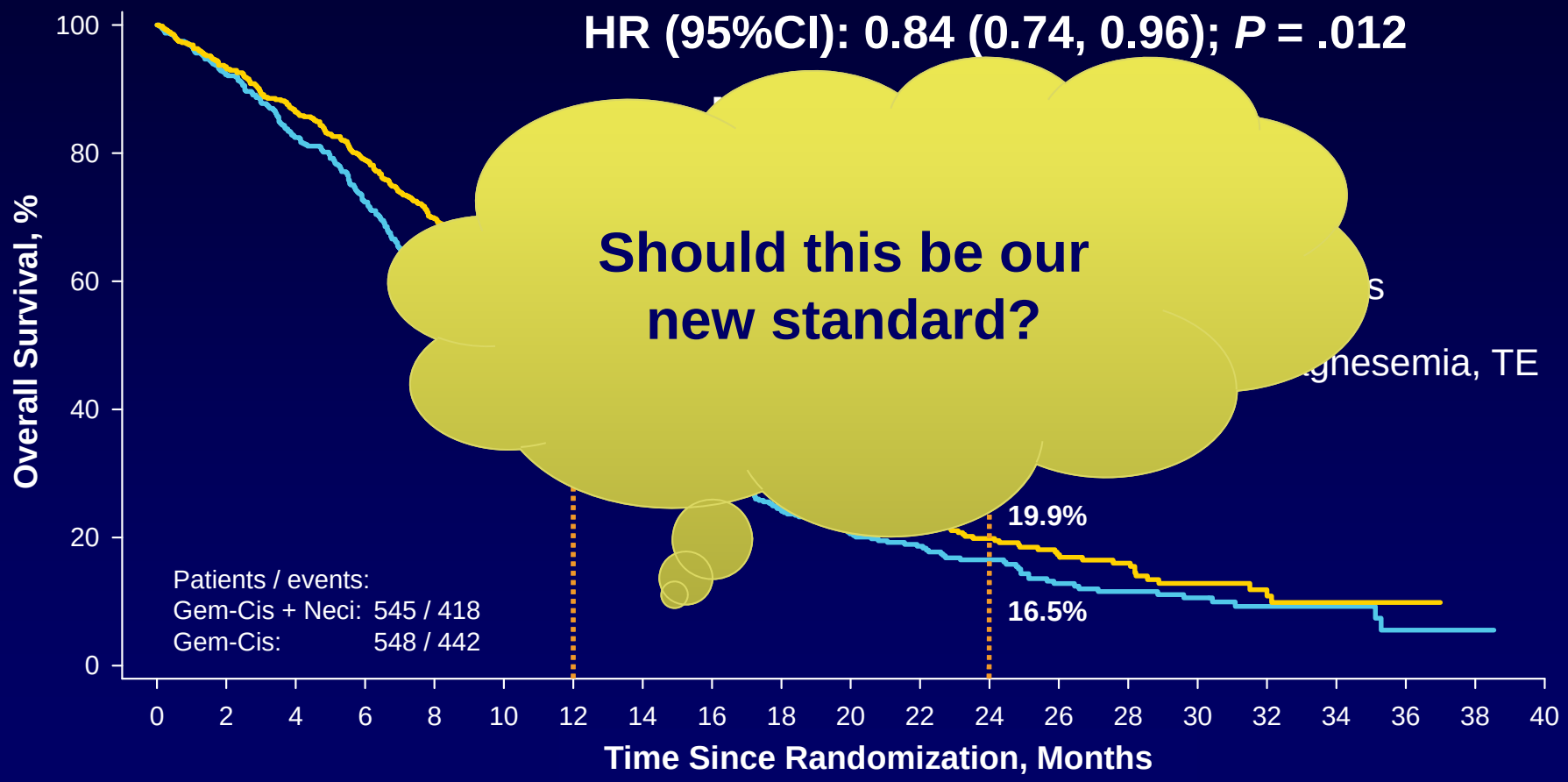
RR 31% v 29%; more rash, hypomagnesemia, TE

Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

No difference by EGFR IHC H-score

Thatcher N, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8008.

SQUIRE: Overall Survival (ITT)

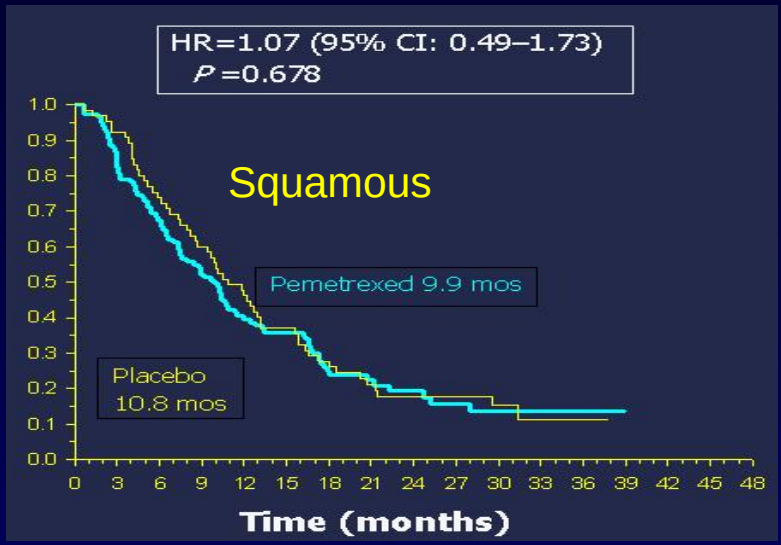


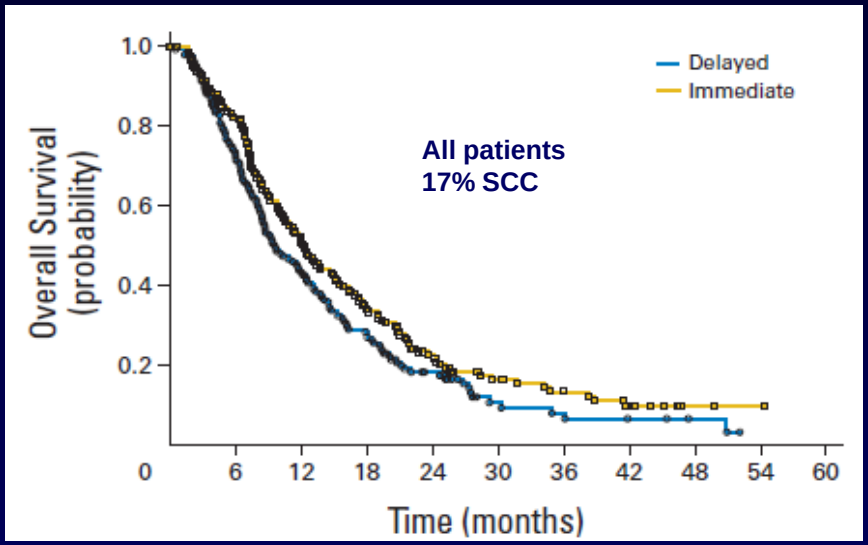
Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

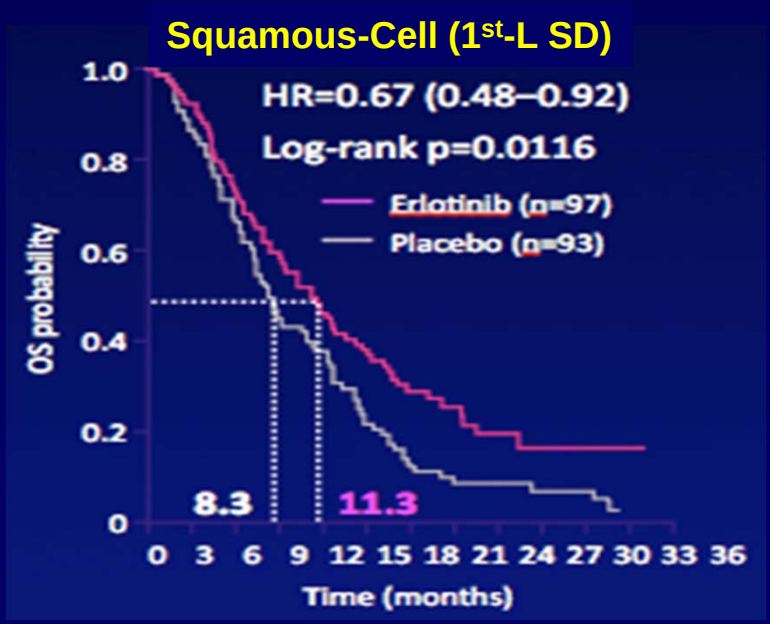
No difference by EGFR IHC H-score

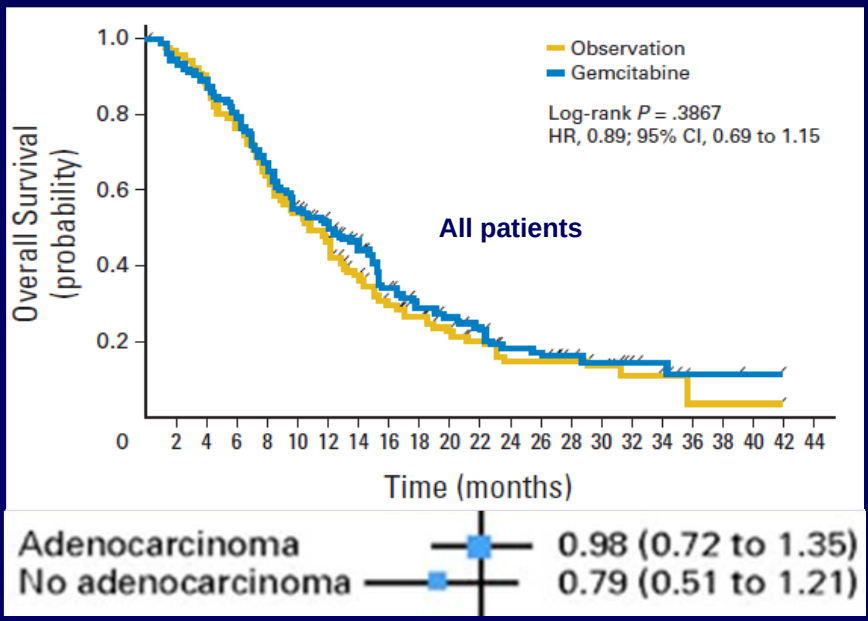
Thatcher N, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8008.

Maintenance Therapy in SCC



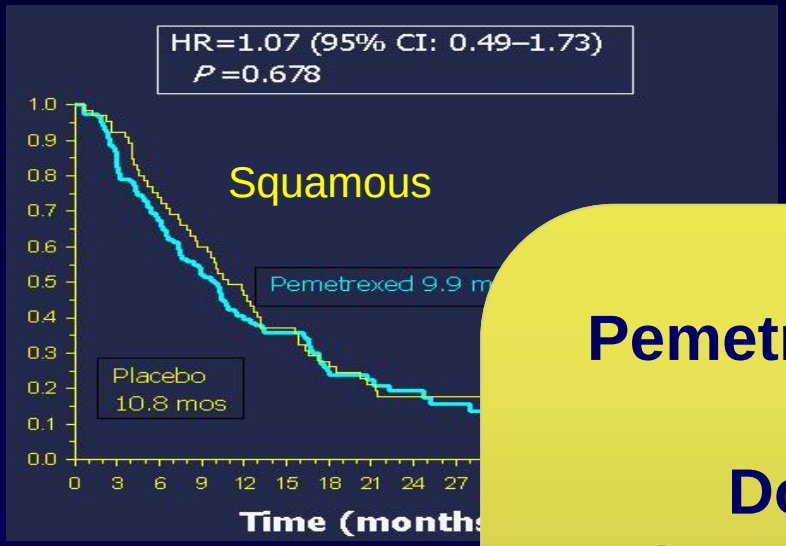


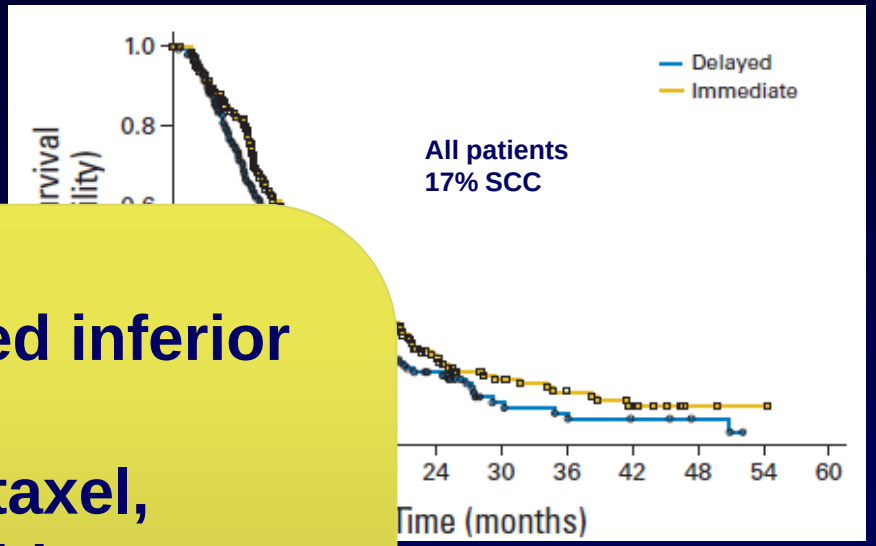




Ciuleanu T. et al. *Lancet* 2009;374(9699):1432-1440; Coudert B, et al. *Ann Oncol.* 2012; 23(2):388-394; Fidias PM, et al. *J Clin Oncol.* 2009;27(4):591-598; Pérol M, et al. *J Clin Oncol.* 2012;30(28):3516-3524.

Maintenance Therapy in SCC

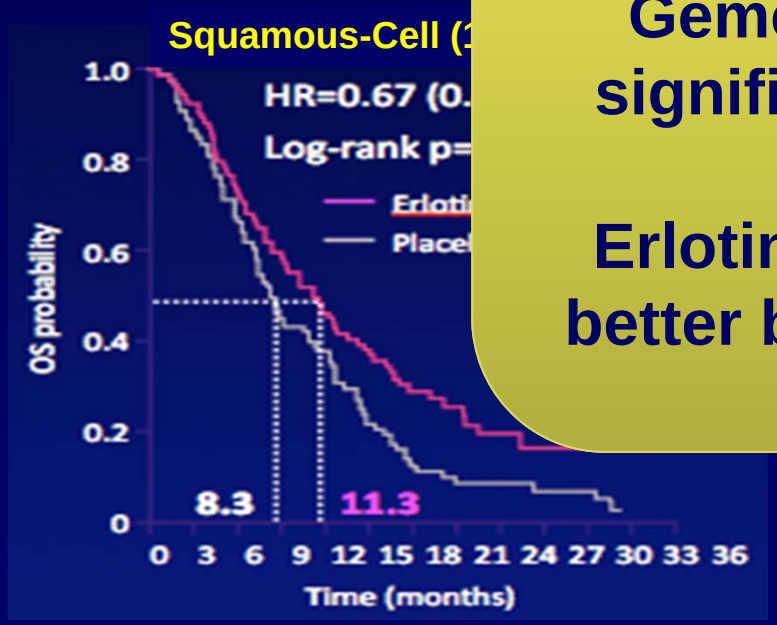


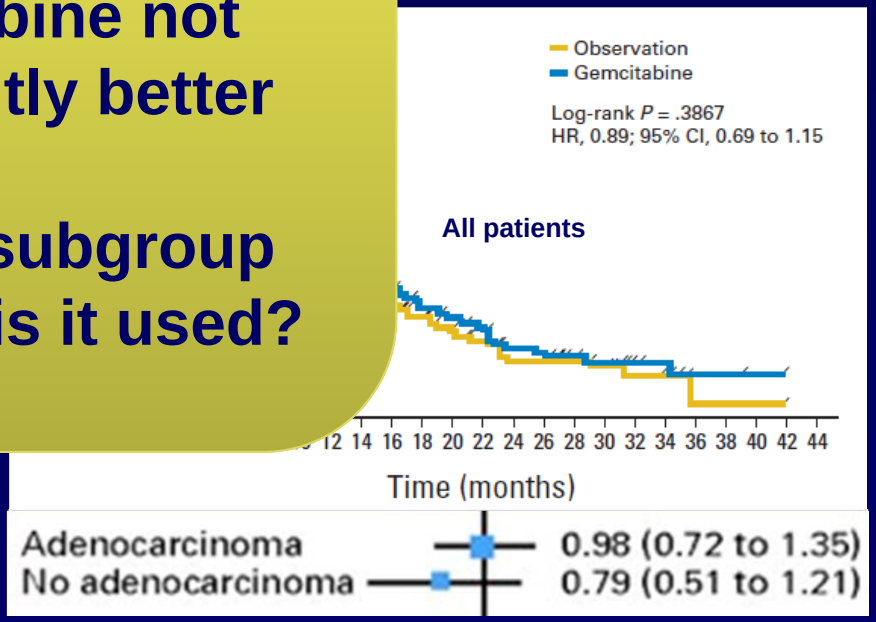


Pemetrexed inferior

Docetaxel, Gemcitabine not significantly better

Erlotinib subgroup better but is it used?

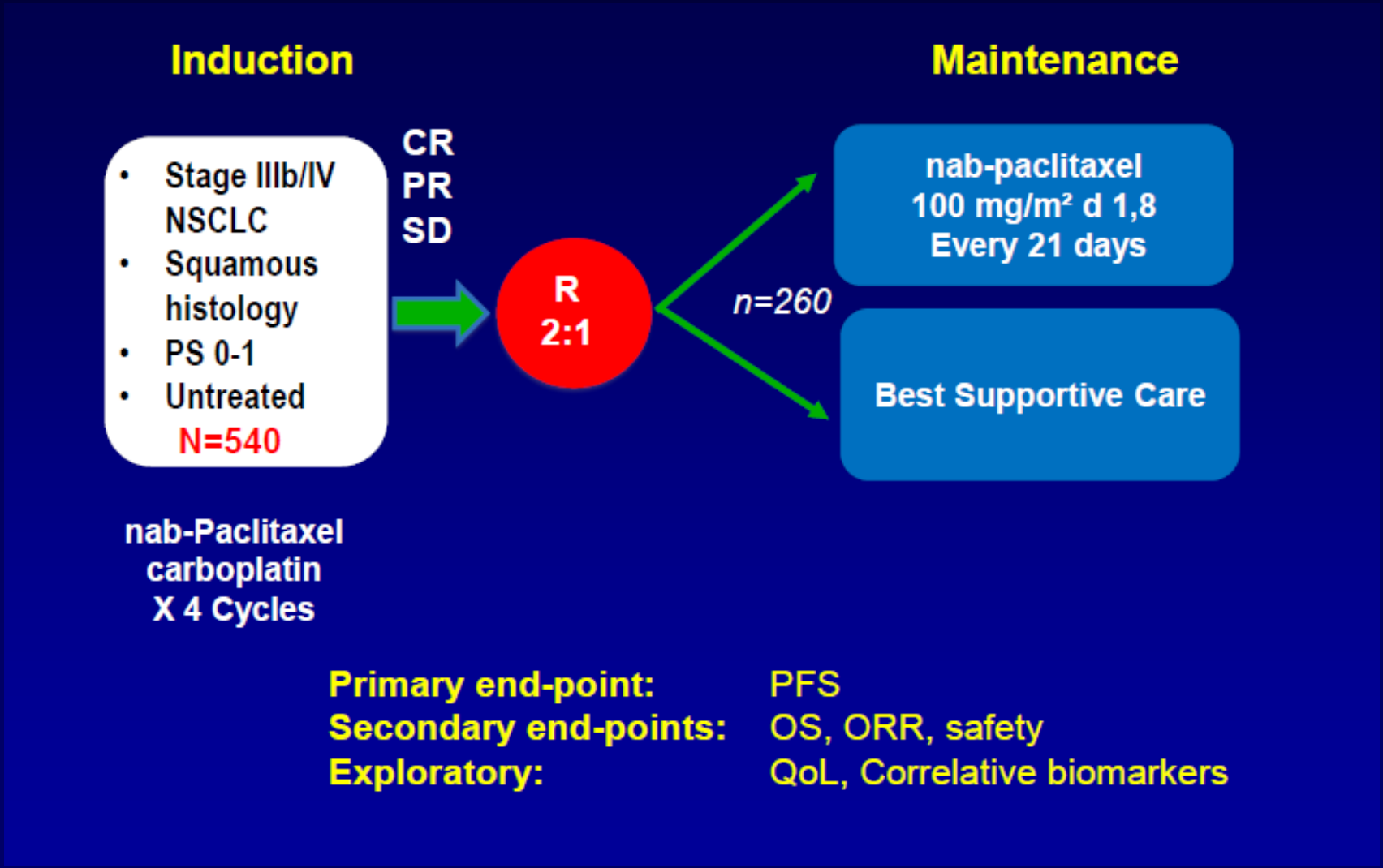




Ciuleanu T. et al. *Lancet* 2009;374(9699):1432-1440; Coudert B, et al. *Ann Oncol.* 2012; 23(2):388-394; Fidias PM, et al. *J Clin Oncol.* 2009;27(4):591-598; Pérol M, et al. *J Clin Oncol.* 2012;30(28):3516-3524.

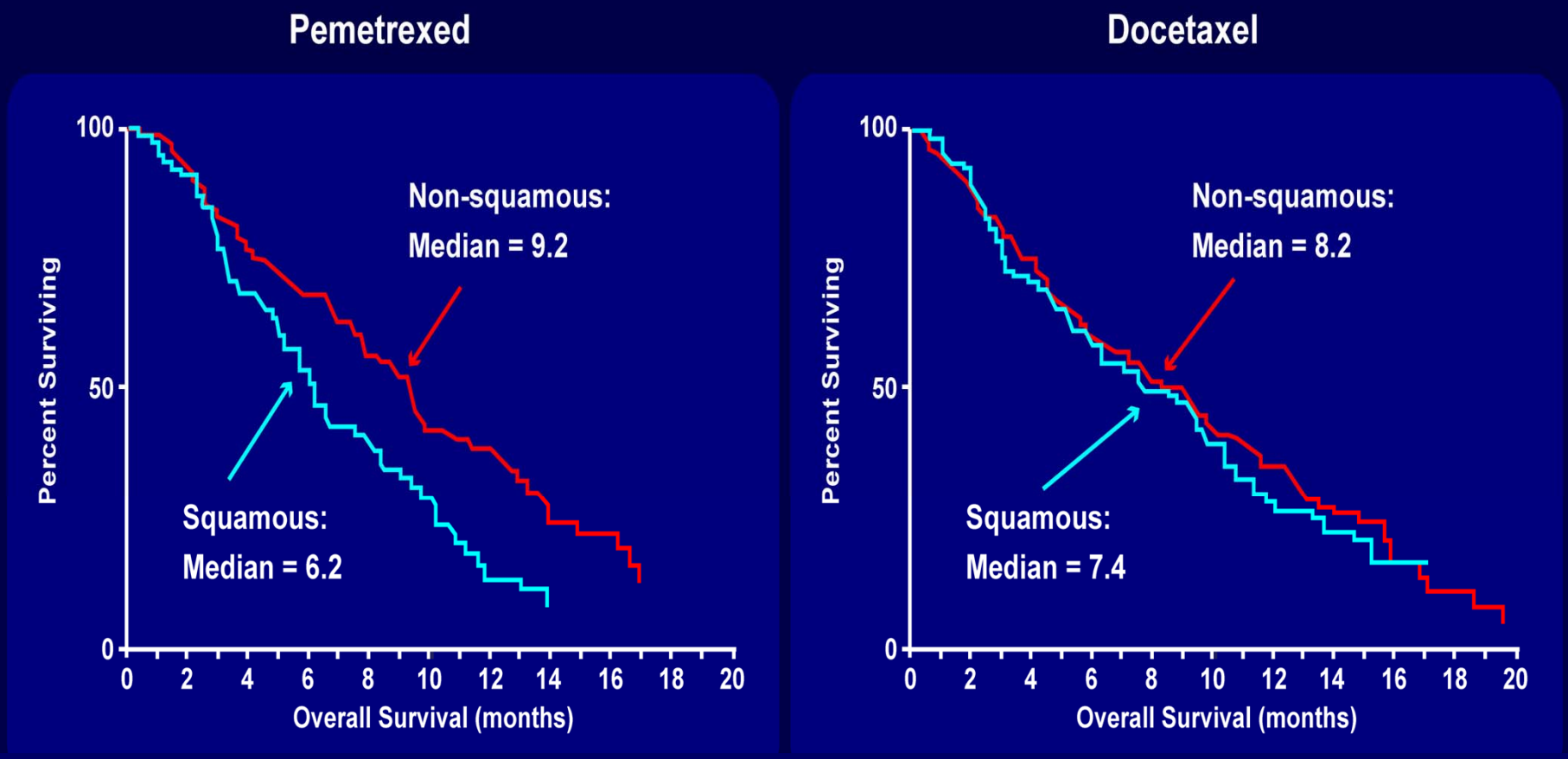
*na*b-Paclitaxel – ABOUND.sqm Trial

Phase III Squamous Maintenance



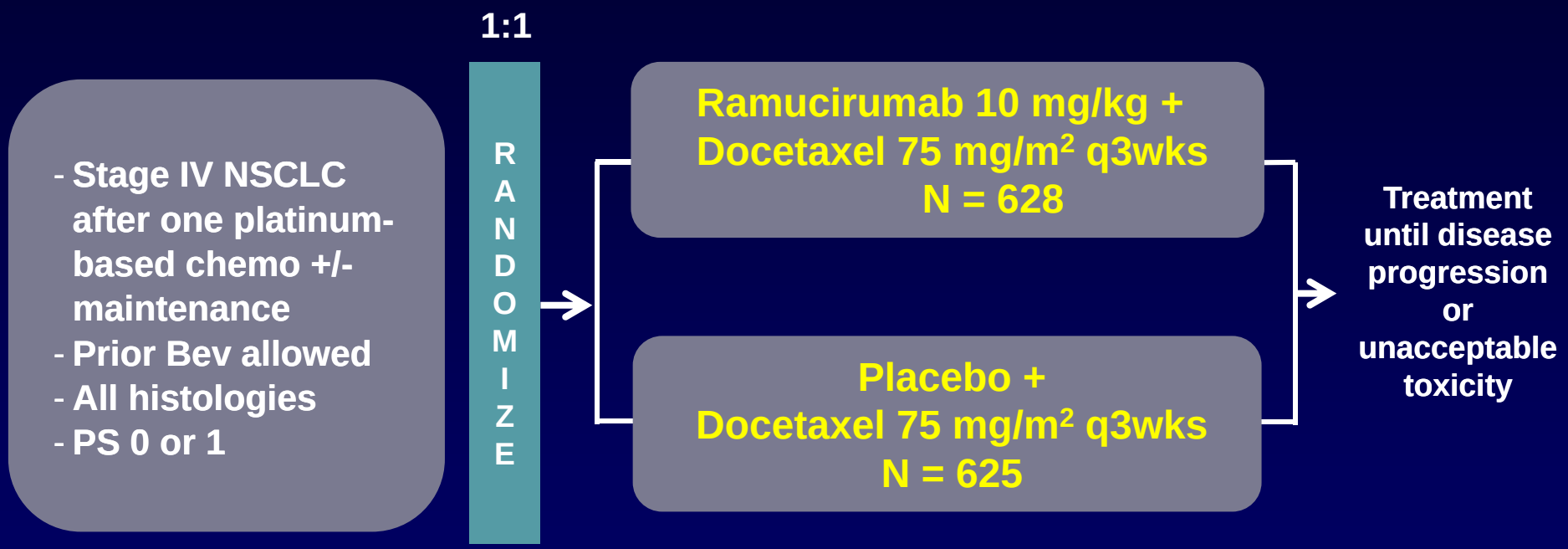
National Institutes of Health. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02027428. Accessed December 12, 2014.

Docetaxel Standard Second-Line for Squamous Carcinoma



Peterson P, et al. *Eur J Cancer Suppl.* 2007;5(4): Abstract 6521.

REVEL: Targeting VEGFR2 2nd Line



Stratification factors:

- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs ROW

Primary endpoint: Overall Survival

Secondary endpoints:

PFS, ORR, safety, patient-reported outcomes

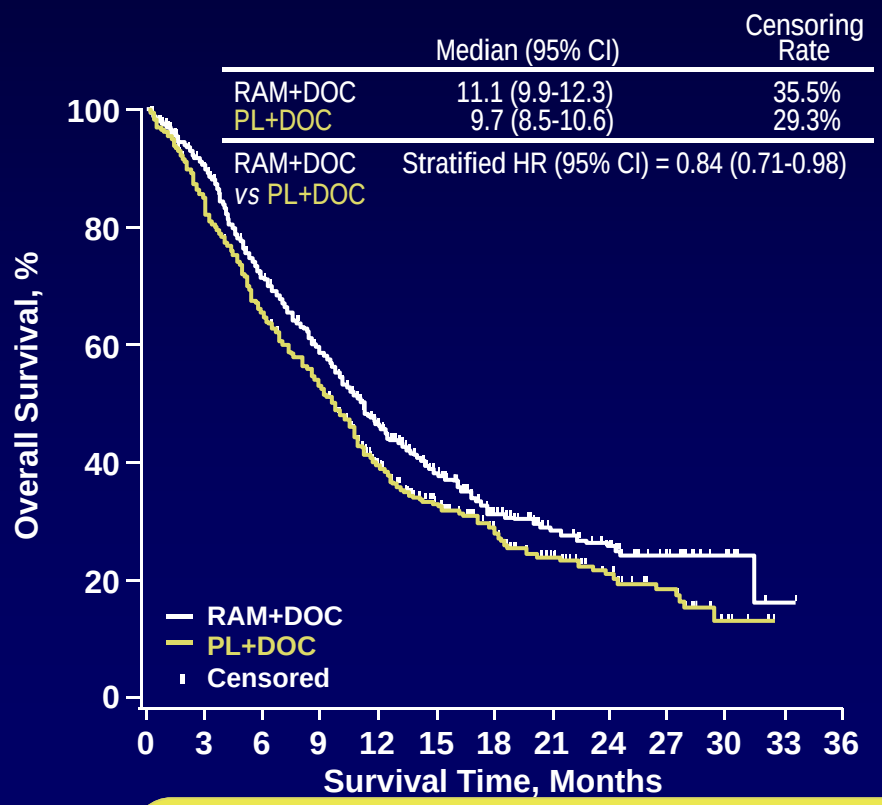
~26% squamous

Garon EB, et al. *Lancet*. 2014;384(9944):665-673.

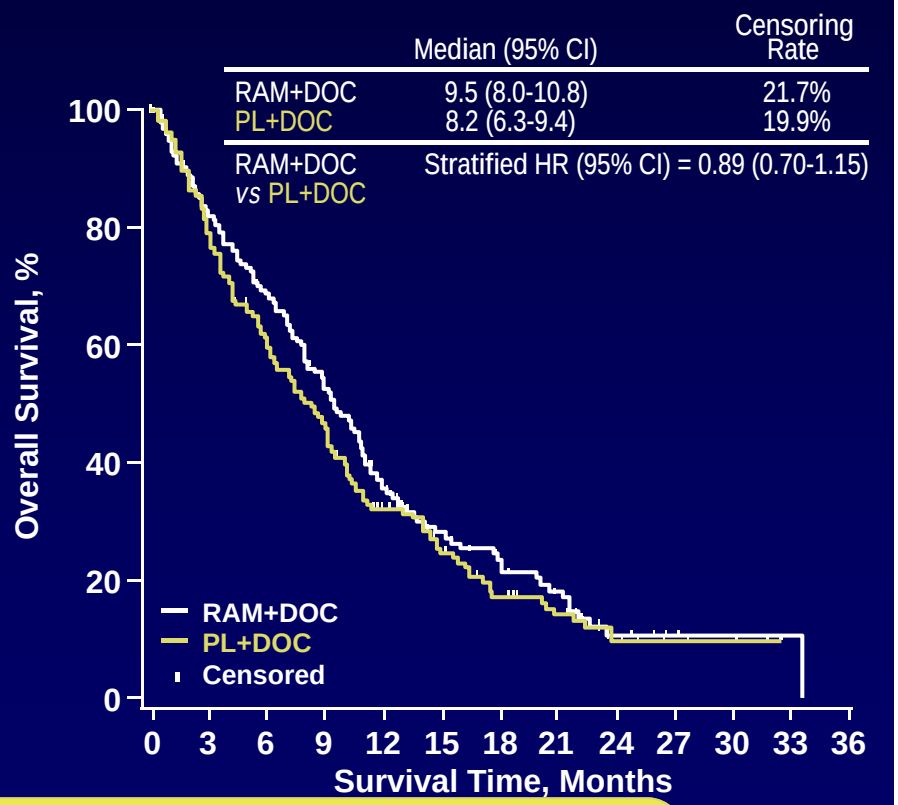
Ramucirumab Improves OS in All Histologies

RR 23 v 14%, mPFS 4.5 v. 3.0 m, mOS 10.5 v. 9.1 m (HR 0.857 *P* = .0235)

Nonsquamous OS



Squamous OS



Number at risk

RAM+DOC												1	0
PL+DOC												0	0

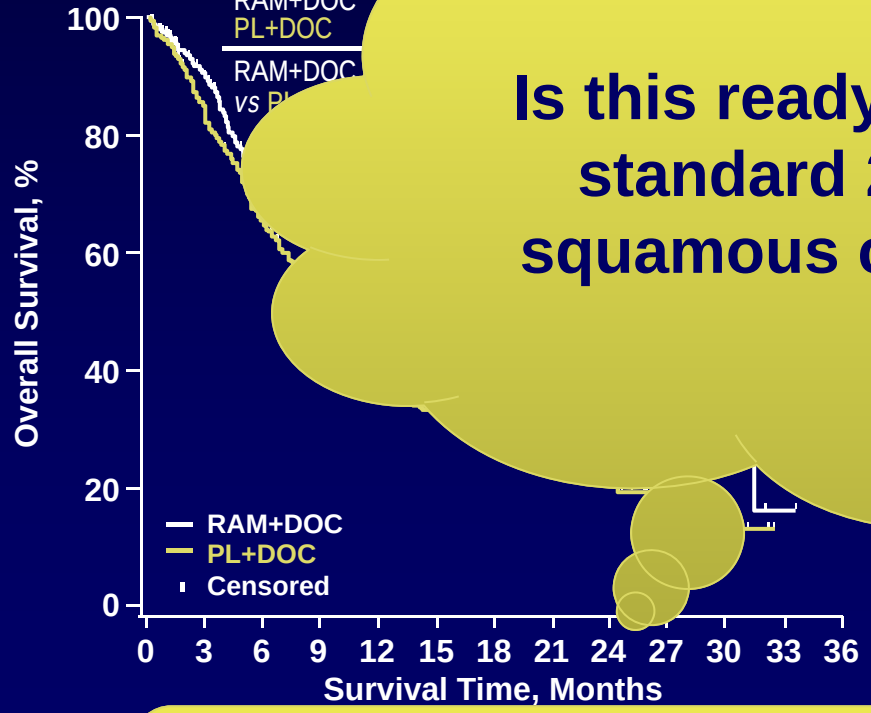
Increased febrile neutropenia, low-grade stomatitis, peripheral edema, epistaxis

Garon [illegible] 6.

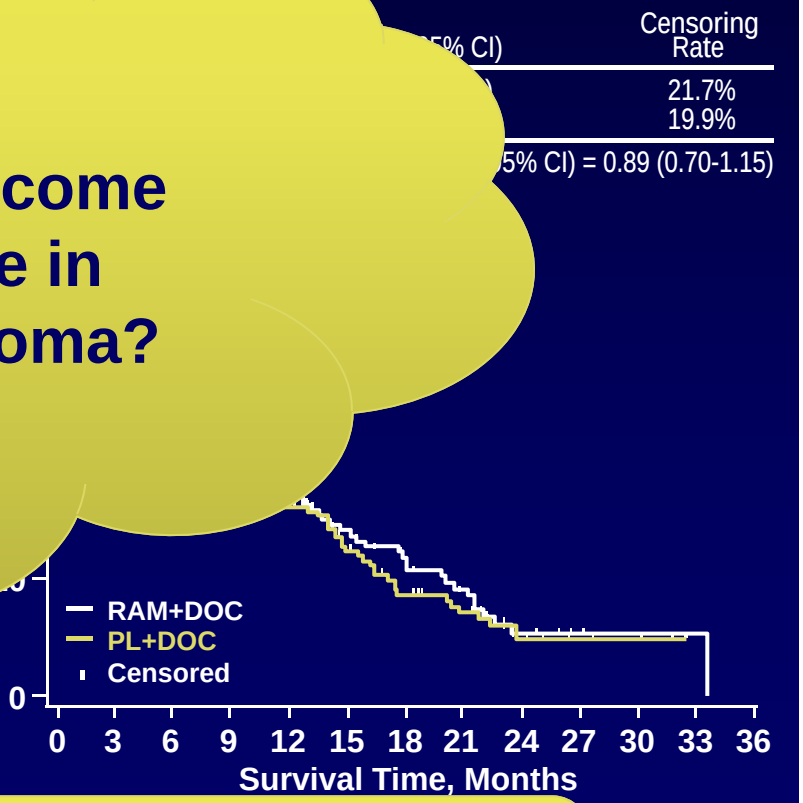
Ramucirumab Improves OS in All Histologies

RR 23 v 14%, mPFS 4.5 v. 3.0 m, mOS 10.5 v. 9.1 m (HR 0.857 *P* = .0235)

Nonsquamous OS



Squamous OS



Is this ready to become standard 2nd-line in squamous carcinoma?

Number at risk

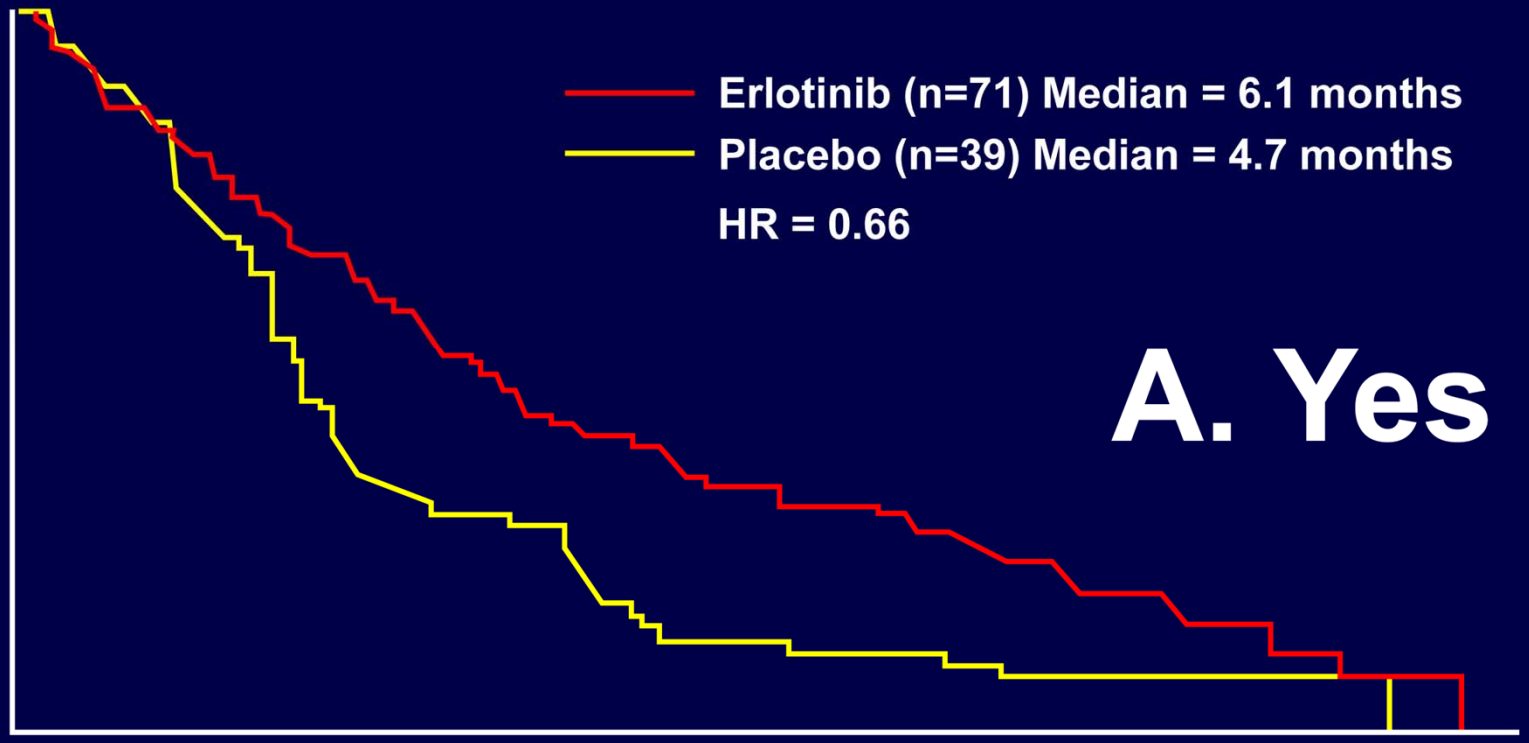
RAM+DOC												1	0
PL+DOC												4	0

Increased febrile neutropenia, low-grade stomatitis, peripheral edema, epistaxis

Garon [illegible] 6.

Would I Offer Erlotinib *After* (All) Chemotherapy Failure?

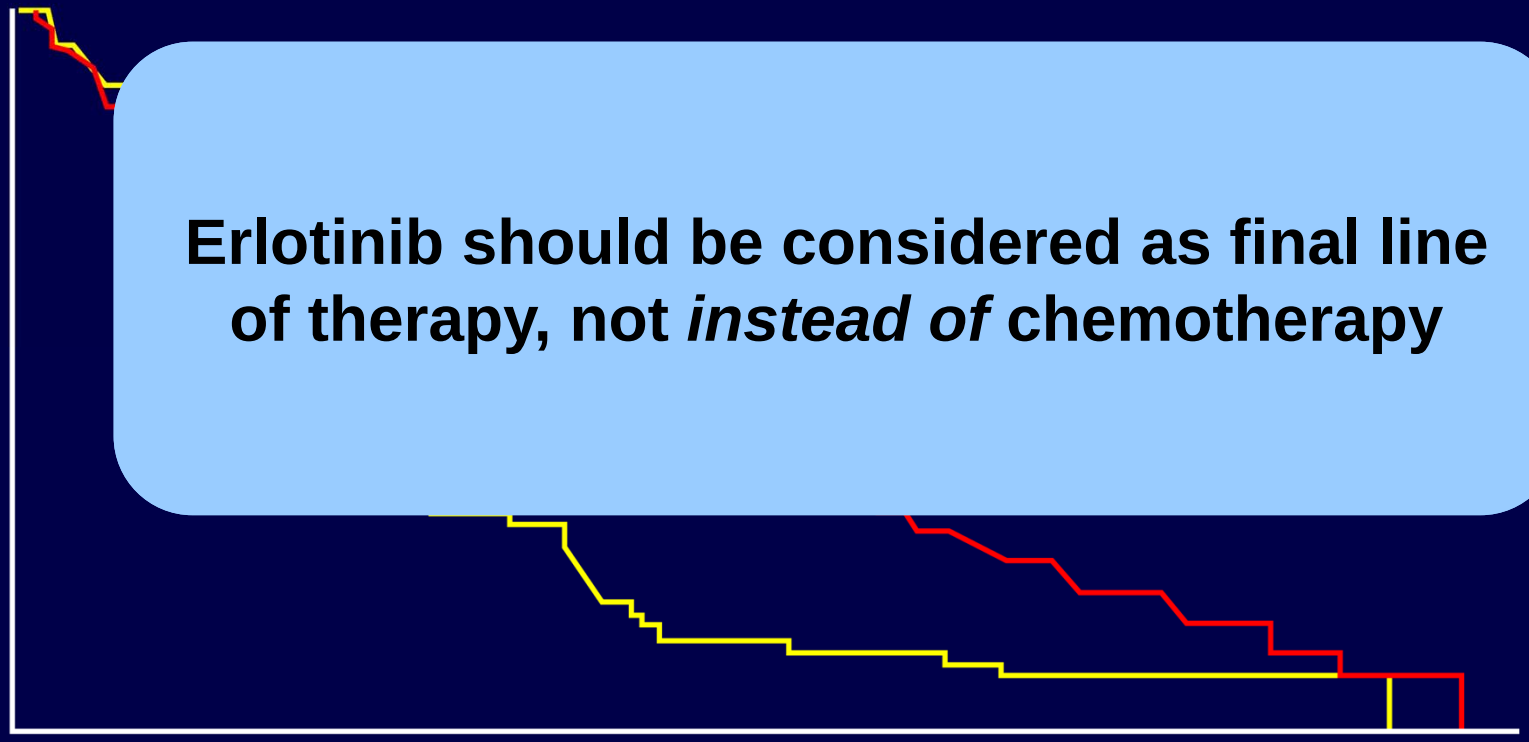
Can male smokers with squamous carcinoma benefit from erlotinib? Subgroup analysis of NCIC CTG BR.21



Clark GM, et al. *J Clin Oncol.* 2006; 24(18S): Abstract 7166.

Would I Offer Erlotinib *After* (All) Chemotherapy Failure?

Can male smokers with squamous carcinoma benefit from erlotinib? Subgroup analysis of NCIC CTG BR.21



Erlotinib should be considered as final line of therapy, not *instead of* chemotherapy

Clark GM, et al. *J Clin Oncol.* 2006; 24(18S): Abstract 7166.

What About Other EGFR TKIs? LUX-Lung 8: Afatinib vs Erlotinib in SCC

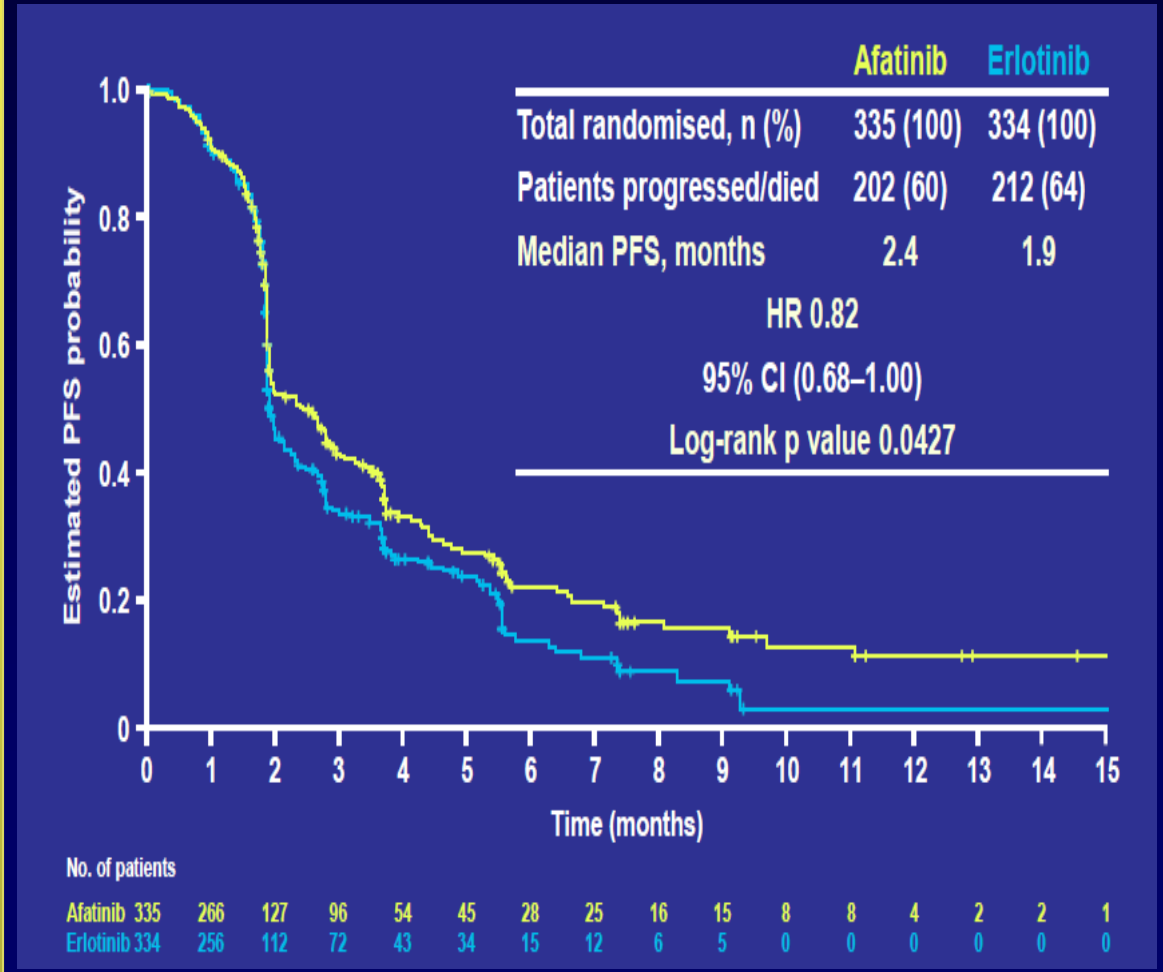
Advanced squamous lung carcinoma

2nd-line afatinib (40 mg) or erlotinib (150 mg)

PS 0-2
PD after 4 cycles of platinum doublet

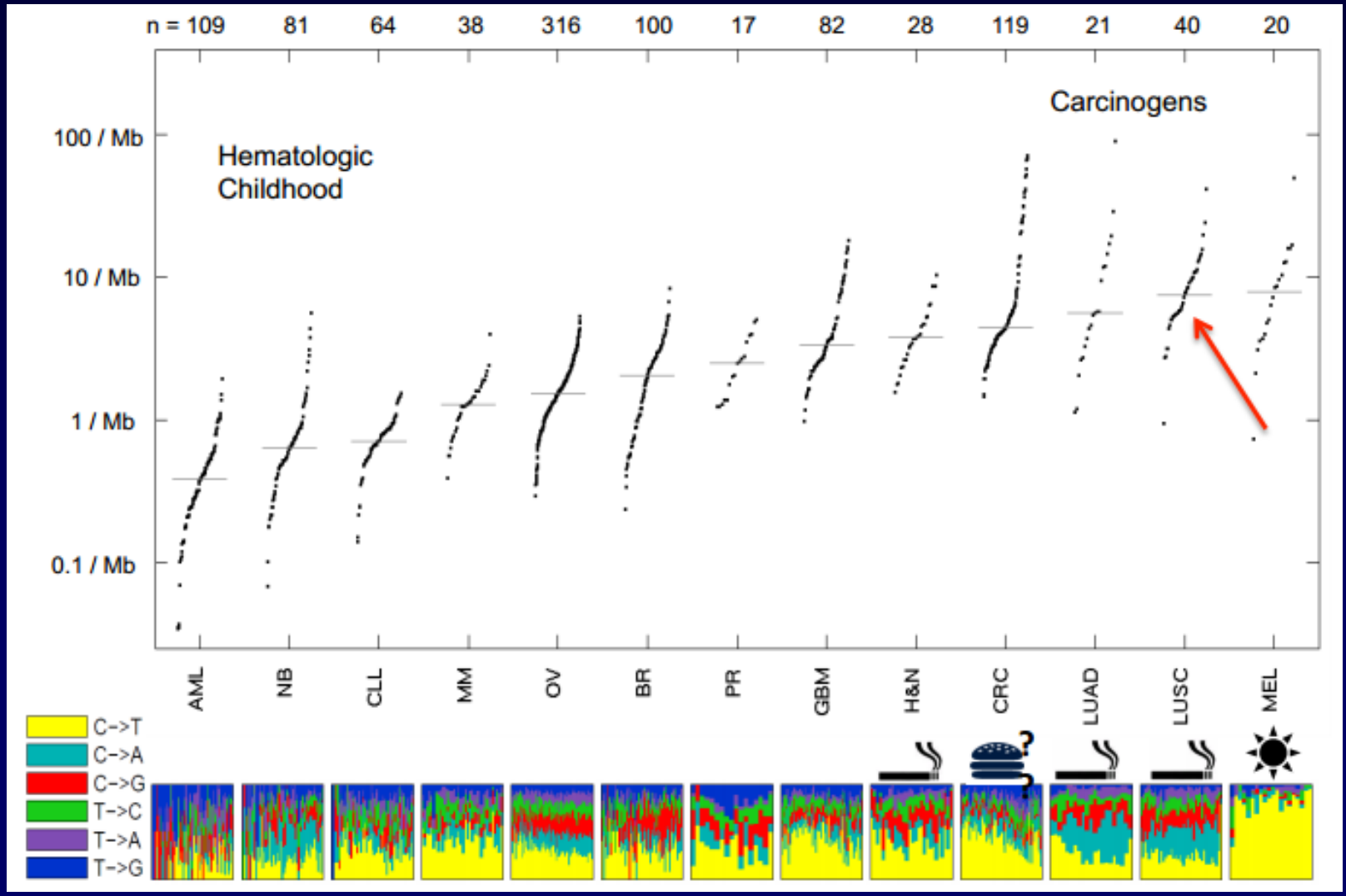
Primary endpoint PFS

No benefit in OS



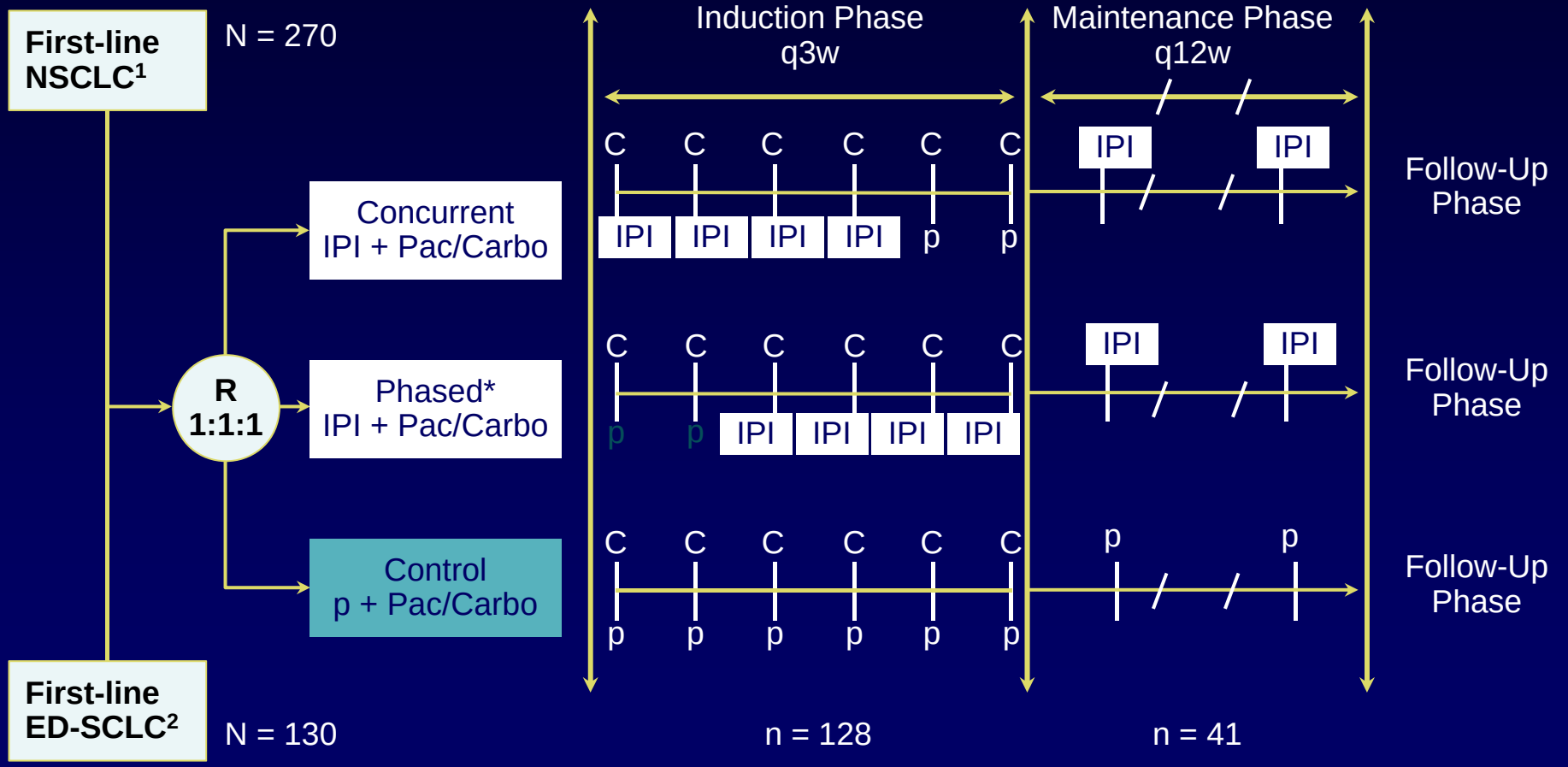
Goss G, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1222O.

SCC is Genomically More Deranged
High Rates of Somatic Mutations



Govindan R, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 7006.

Anti-CTLA4: Phase II Study of Ipilimumab and Paclitaxel/ Carboplatin in Lung Cancer



*Phased regimen: 2 doses of paclitaxel (175 mg/m^2) / carboplatin (AUC = 6) prior to start of ipilimumab.

C, chemotherapy (paclitaxel 175 mg/m^2 / carboplatin [AUC = 6]); Carbo, carboplatin; ED, extensive disease; IPI, Ipilimumab (10 mg/kg IV); NSCLC, non-small cell lung cancer; p, placebo; Pac, paclitaxel; R, randomized; SCLC, small-cell lung cancer.

Lynch TJ, et al. *J Clin Oncol*. 2012;30(17):2046-2054; Reck M, et al. *Ann Oncol*. 2013;24(1):75-83.

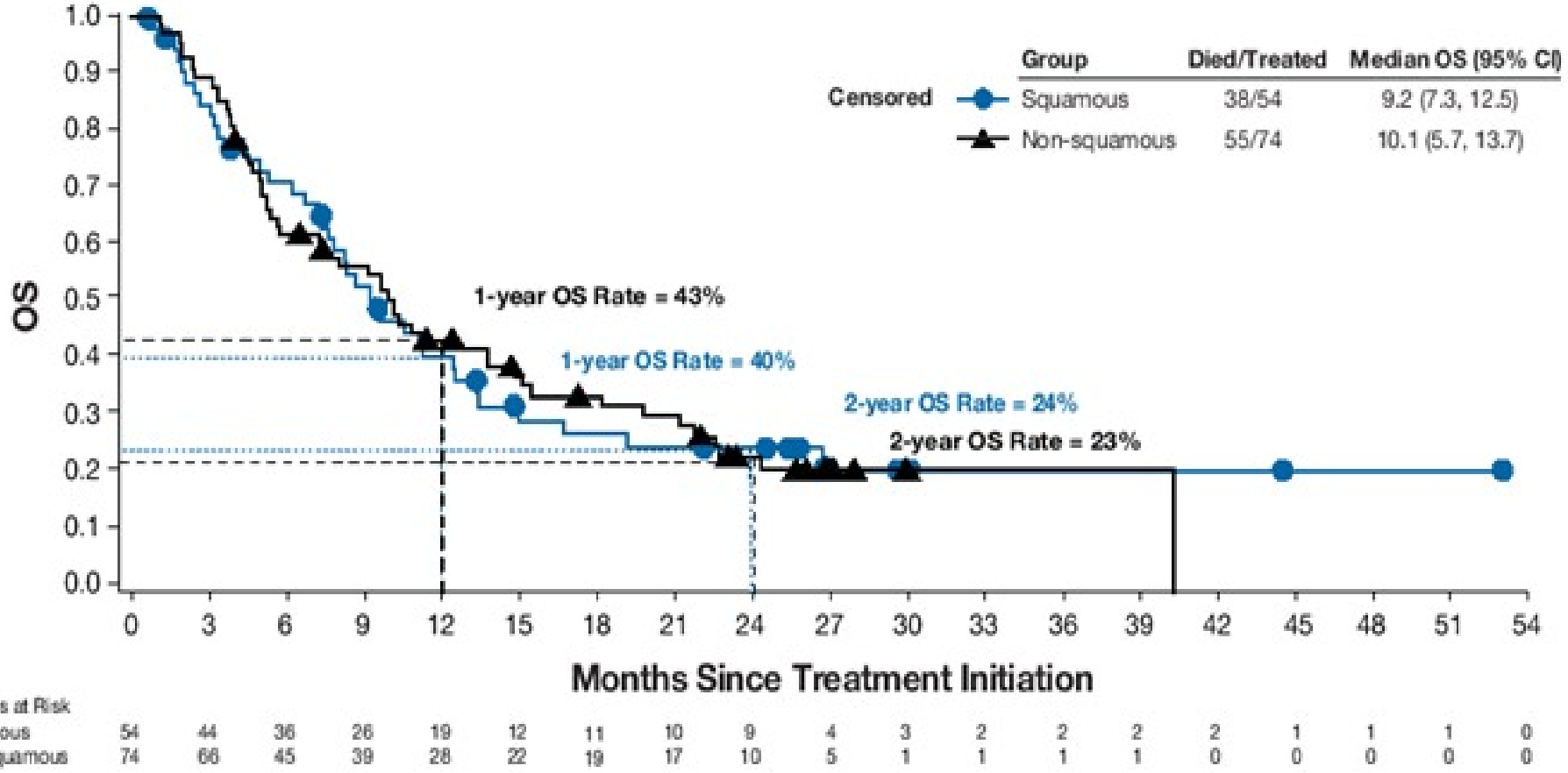
Phase II Study of Ipilimumab and Paclitaxel/ Carboplatin: OS in the NS-NSCLC & SCC Population

OS, Median Mo	Control Pbo + Chemo (n = 66)	Concurrent IPI + Chemo (n = 70)	Phased IPI + Chemo (n = 68)
Total NSCLC	**8.3**	**9.7** (HR = 0.99, *P* = .48)	**12.2** (HR = 0.87, *P* = .23)
Squamous	7.9	6.2 1.02 (0.50–2.08)	10.9 0.48 (0.22–1.03)
Nonsquamous	8.3	12.4 0.96 (0.60–1.53)	12.9 1.17 (0.74–1.86)
ED-SCLC	**9.9**	**--**	**12.9** (HR = 0.75, *P* = .13)

Most common related severe toxicities: pruritus (<2%), rash (<3%), and diarrhea (up to 10%)

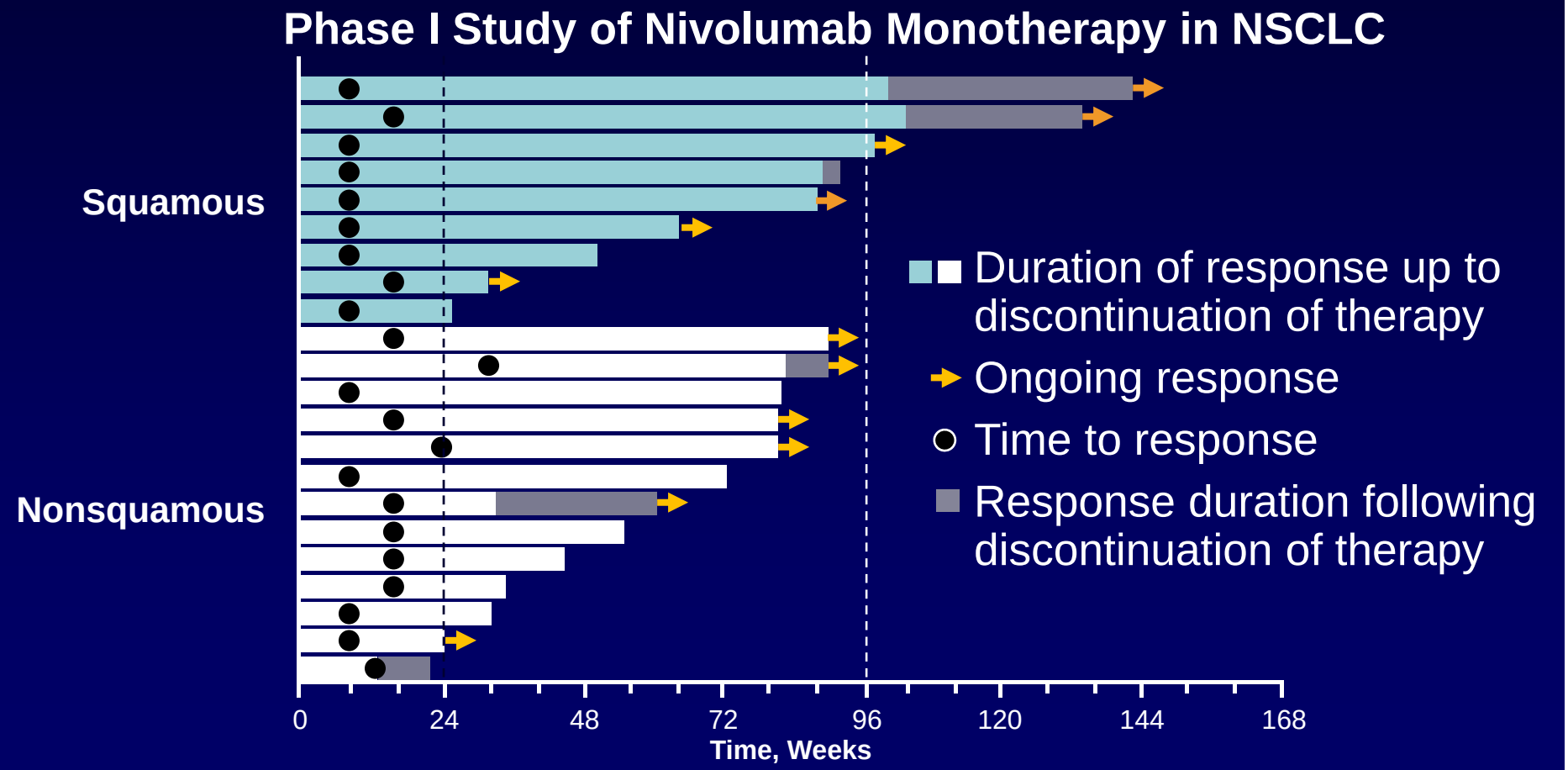
Lynch TJ et al. *J Clin Oncol*. 2012;30(17):2046-2054.

Anti PD-1: Nivolumab Phase I OS Similar Across Histologies



Brahmer JR, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8112.

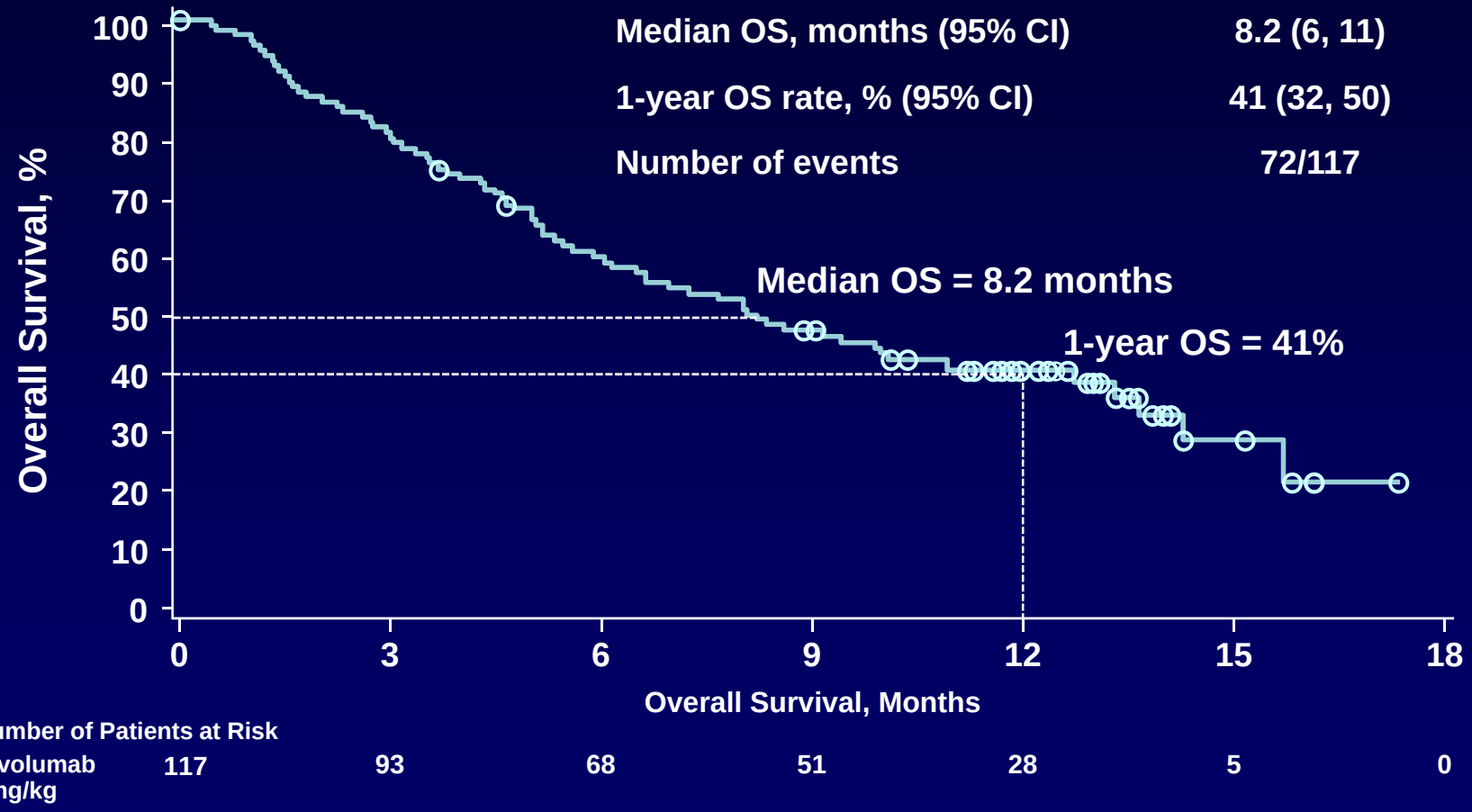
Durable Responses Seen at 8-16 Weeks and Similar Among Agents AND Histologies (Nivolumab, MK-3475, MPDL3280A)



Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy.

Brahmer JR, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 8030. .

Overall Survival (OS)
3L Squamous NSCLC Patients (Checkmate-063)



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

[a]Based on July 2014 DBL; Symbols represent censored observations

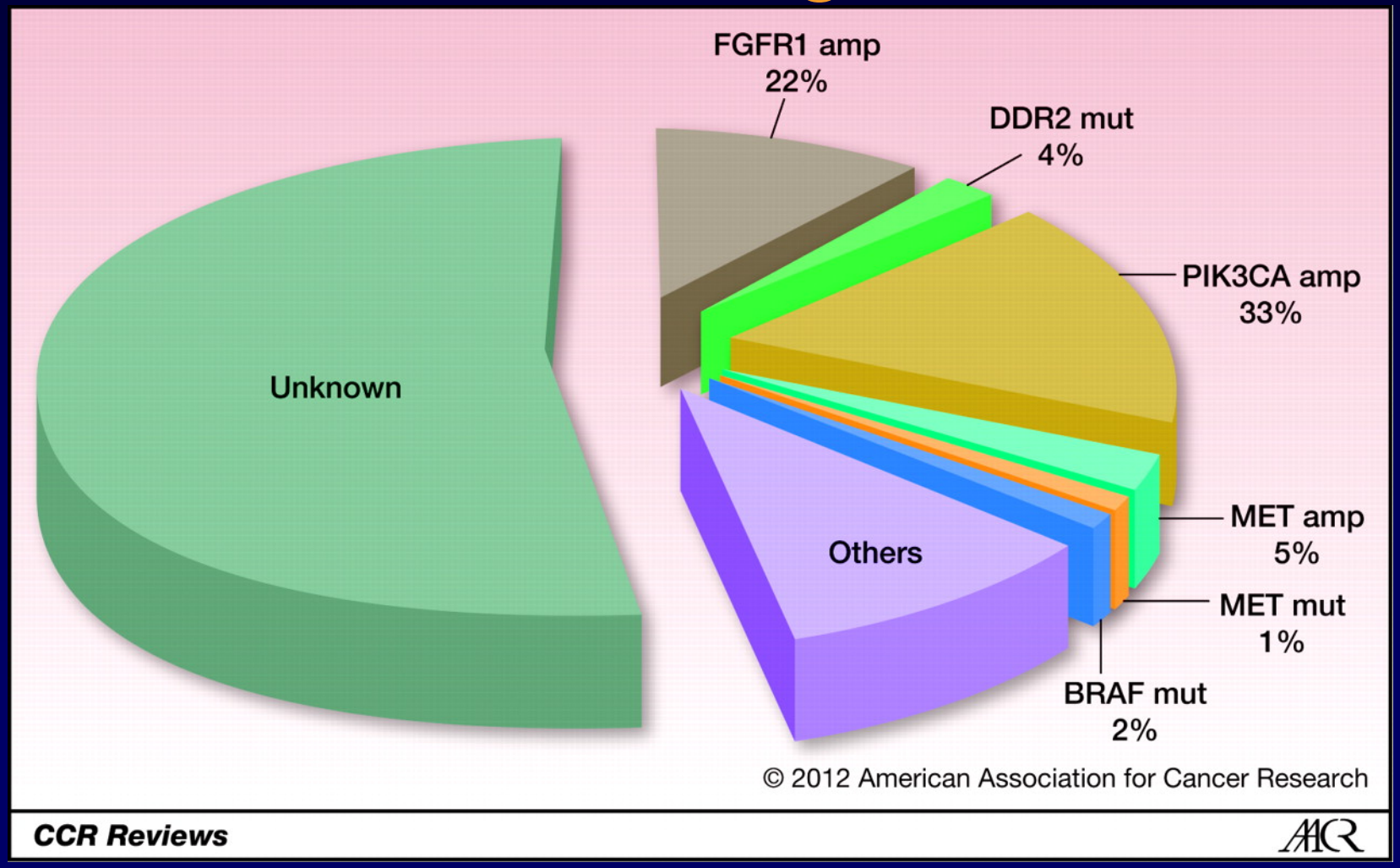
Ramalingam,SS et al. *Int J Radiat Oncol Biol Phys.* 2014;90(5 Suppl): Abstract 3462.

Selected Anti-PD1 and Anti-PDL1 Trials (SCC Eligible)

	Study No.	Phase	Indication(s)	N	Comparator	Primary Endpoint	Status
Nivolumab	NCT01642004/ CA209-017	III	Advanced/metastatic squamous NSCLC, second-line	264	Docetaxel	ORR, OS	Accrual completed
	NCT02041533/ CA209-026	III	Advanced/metastatic PD-L1 positive NSCLC, first-line	495	Investigator's choice chemotx	PFS (IRRC)	Ongoing
MK-3745	NCT01905657 MK-3475-010	II/III	Previously treated PD-L1 positive NSCLC	920	Docetaxel	OS, PFS, Safety	Ongoing
	NCT02142738 MK-3475-024	III	Metastatic NSCLC PD-L1 strong; first-line	300	Platinum-based chemotherapy	PFS	Ongoing
MPDL3280A	NCT02031458 BiIRCH	II	Locally advanced or metastatic NSCLC, PD-L1 positive	635	Single arm study	ORR	Ongoing
	NCT02008227 OAK	III	Locally advanced or metastatic NSCLC, after progression on platinum-based chemo	1100	Docetaxel	OS	Ongoing
MEDI-4736	NCT02087423 ATLANTIC	II	Third-line therapy in locally advanced or metastatic NSCLC PD-L1-positiive	184	Single arm	ORR	Ongoing
MEDI-4736	Lung-MAP	II	Advanced squamous second line		Docetaxel	PFS	Ongoing
	ATLANTIC ARCTIC	II III	Advanced NSCLC, previously treated		Multiarm including tremi+MEDI	OS	Ongoing

Clinicaltrials.gov.

Potential Genomic Targets in SCC of Lung



Perez-Moreno P, et al. *Clin Cancer Res.* 2012;18(9):2443-2451.

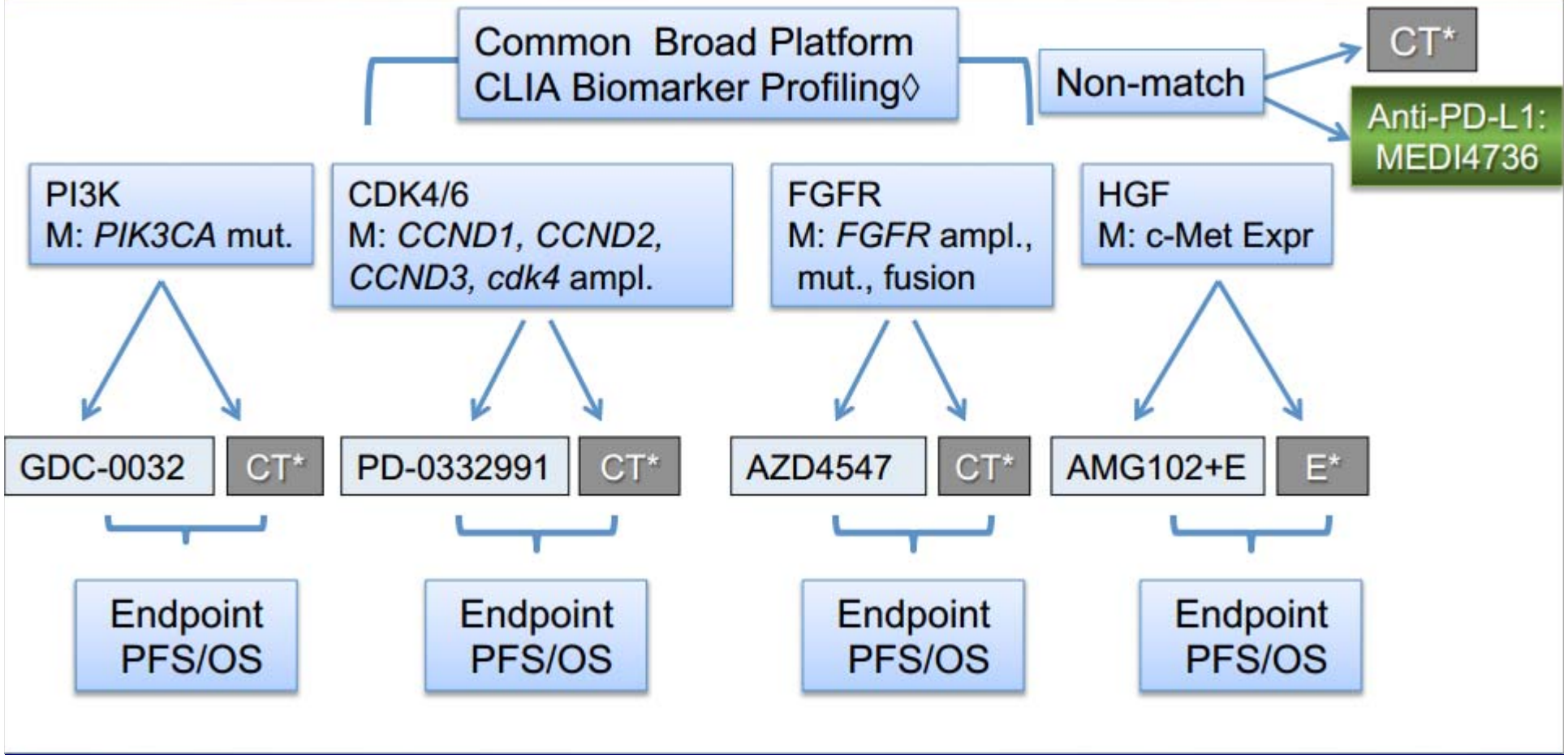
LUNG-MAP

Broad genomic assessment of: Mutations, rearrangements, copy number (Foundation Medicine)

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR N771_P772>KFP	Erlotinib Gefitinib	Cetuximab Panitumumab	Yes, see clinical trials section
CCND1 amplification	None	None	Yes, see clinical trials section
ARID1A Q633*	None	None	None

National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02154490. Accessed December 12, 2014.

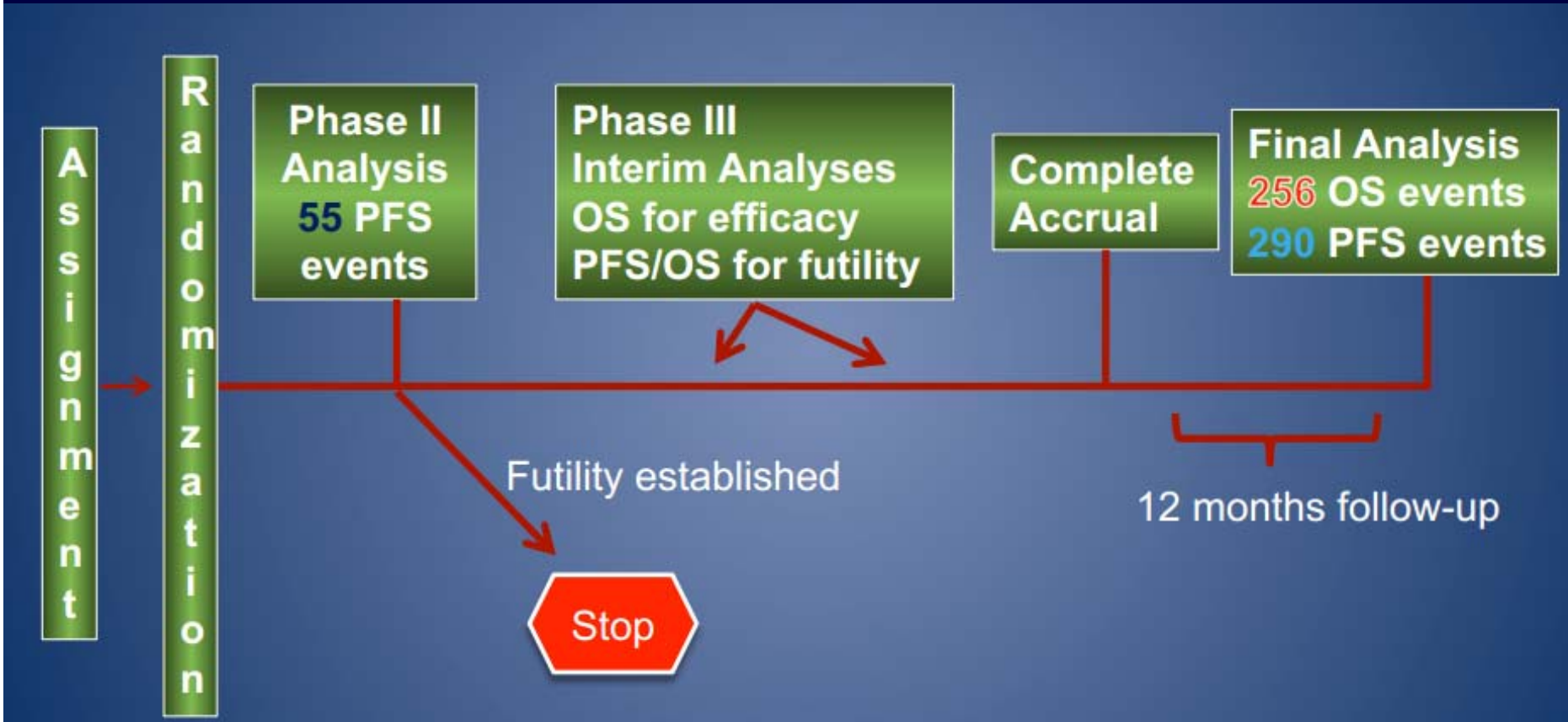
LUNG-MAP



National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02154490. Accessed December 12, 2014.

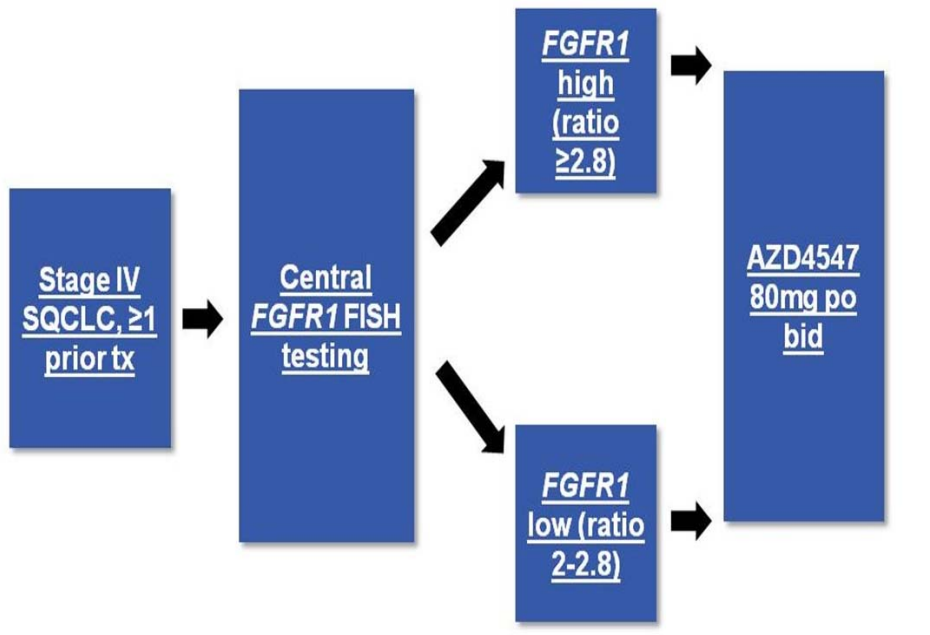
LUNG-MAP

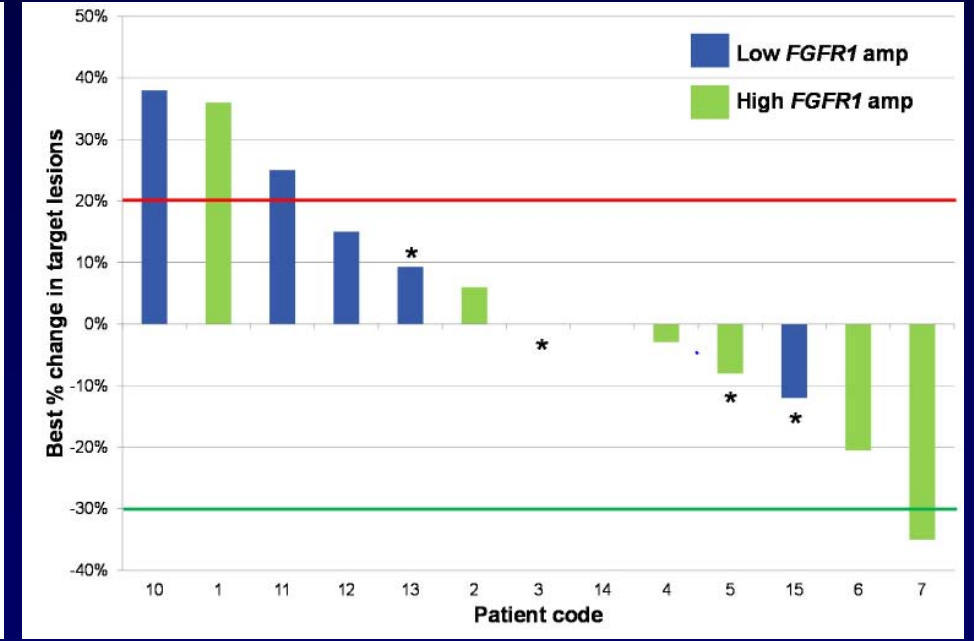
Study design within each biomarker defined subgroup



Targeting FGFR

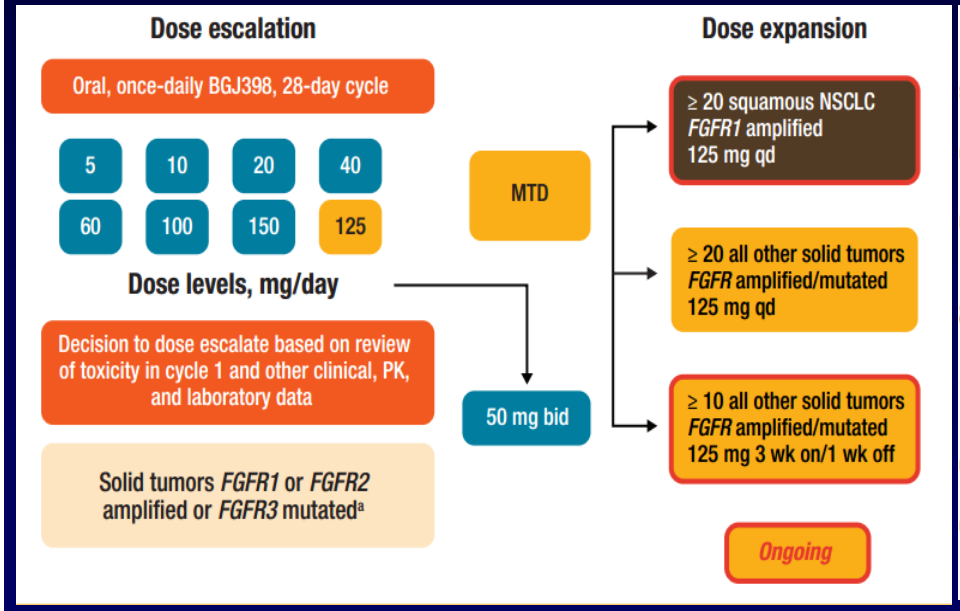
LUNG-MAP

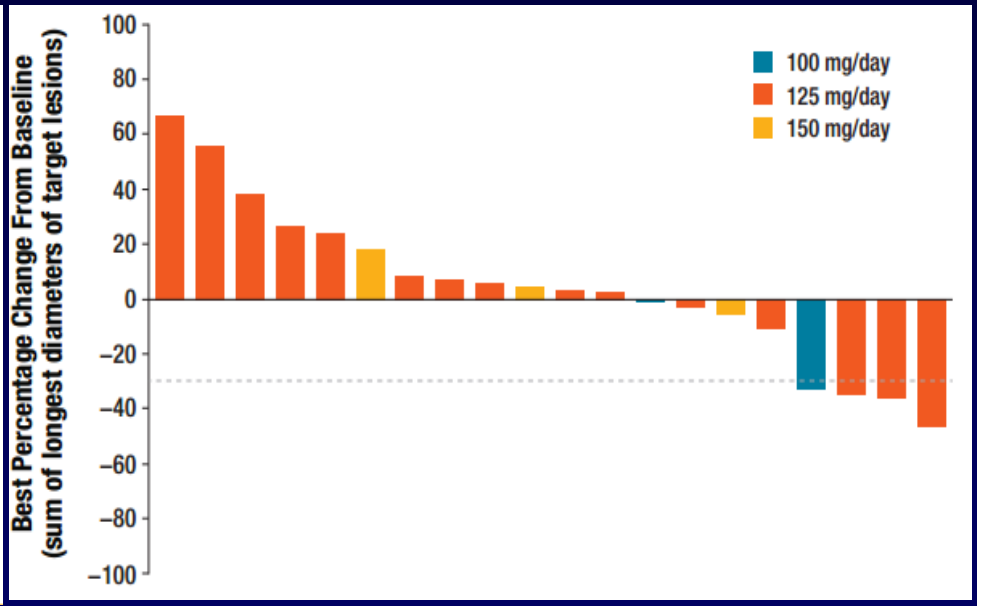




Paik et al. *J Clin Oncol.* 2014; 32(5s): Abstract 8035.

Targeting FGFR: BGJ398





Nogova L, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8034.

To Conclude

- Current standards for squamous lung carcinoma:
  - First-line platinum doublet therapy (without pemetrexed)
  - Should we add necitumumab? Can we afford it?
  - Second-line docetaxel
  - Are we ready to add ramucirumab? (not yet?)
  - Third-line erlotinib after chemotherapy failure
- Promising drug development underway:
  - PD-1/PD-L1 pathways (including combinations)
  - FGFR inhibitors, PI3K inhibitors, more
- These represent exciting potential new treatment options for our patients with squamous carcinoma