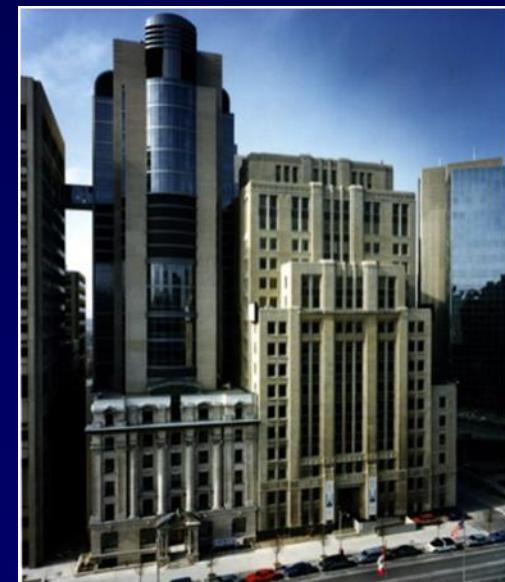
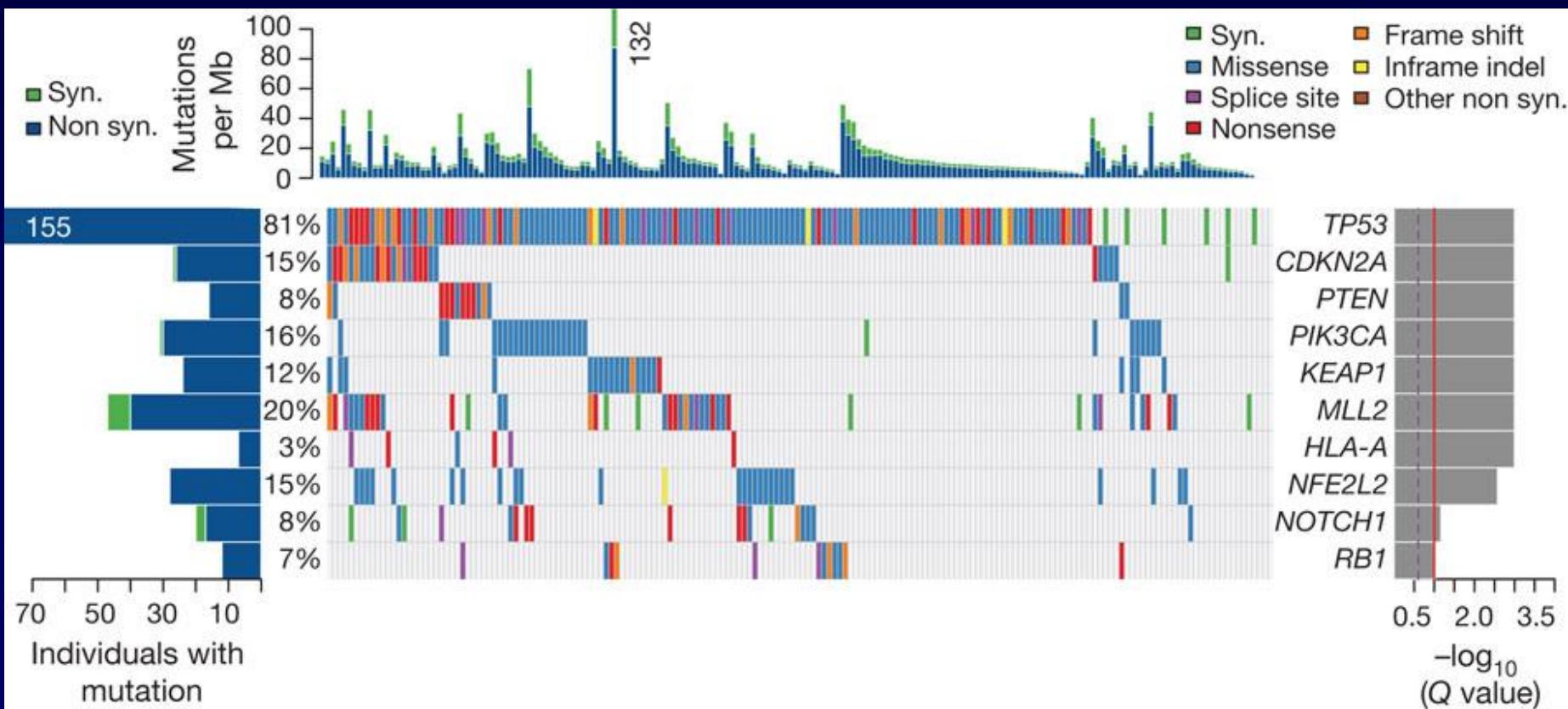
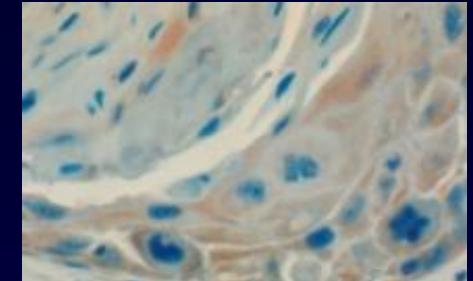


Case #5—Squamous Cell Lung Cancer: The Changing Treatment Paradigm

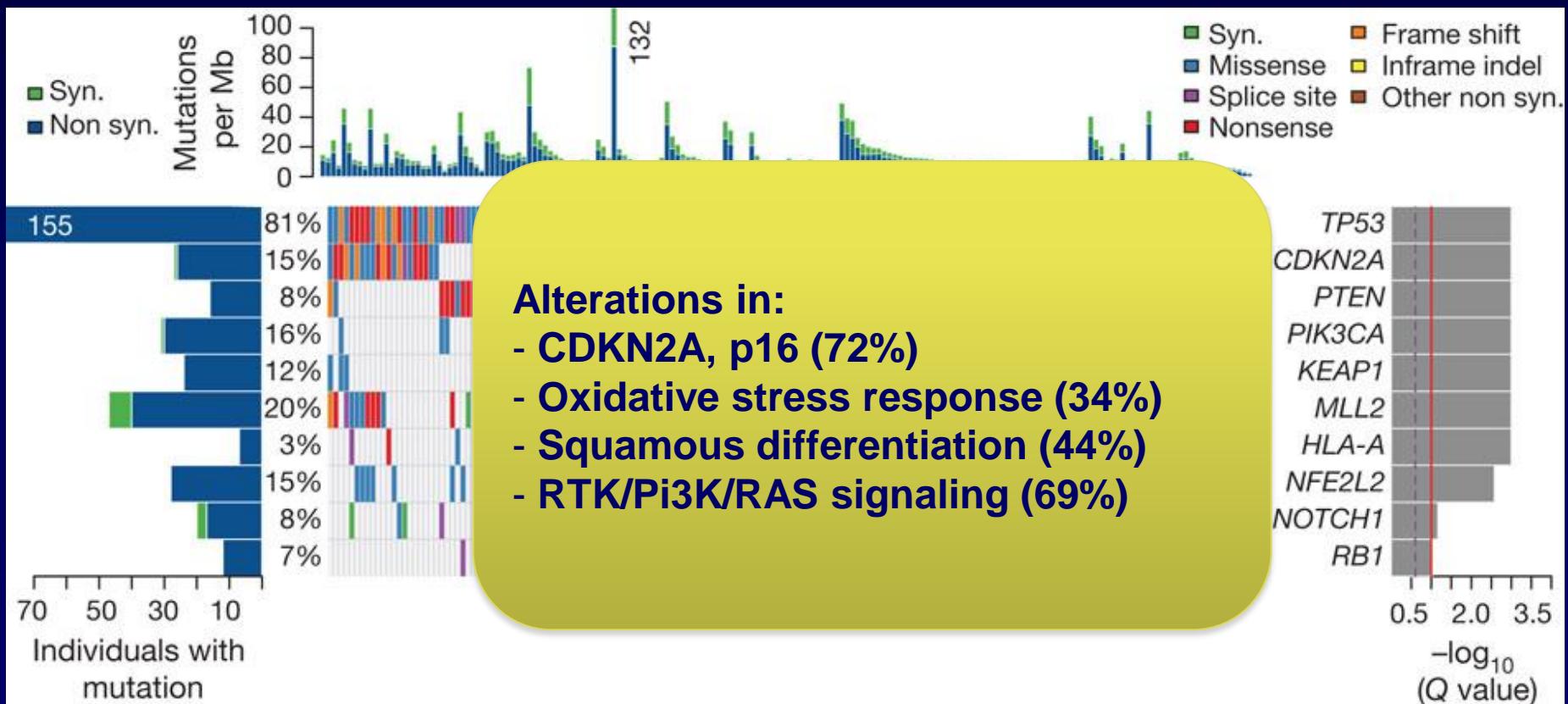
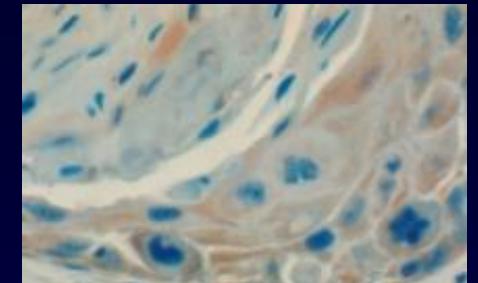
Natasha Leigh, MD, MMSc, FRCPC
Princess Margaret Hospital
Toronto, Ontario, Canada



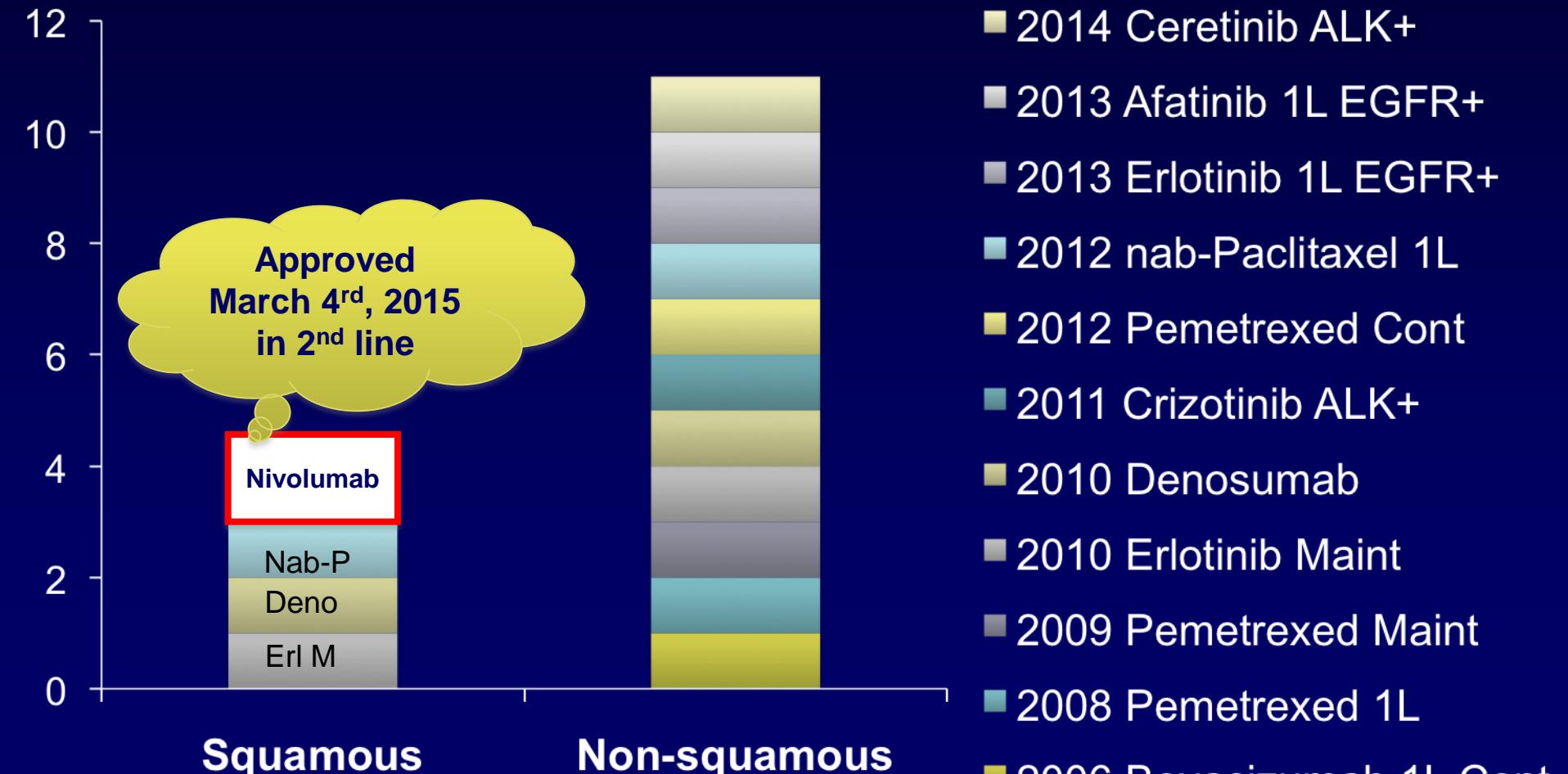
Squamous Lung Carcinoma (CK5/6+, P63/40+, CK7-)



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



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)

Current Standard Options for Advanced Squamous Lung Carcinoma

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



Future Standard Options for Advanced Squamous Lung Carcinoma

- First-line platinum doublet
(without pemetrexed)



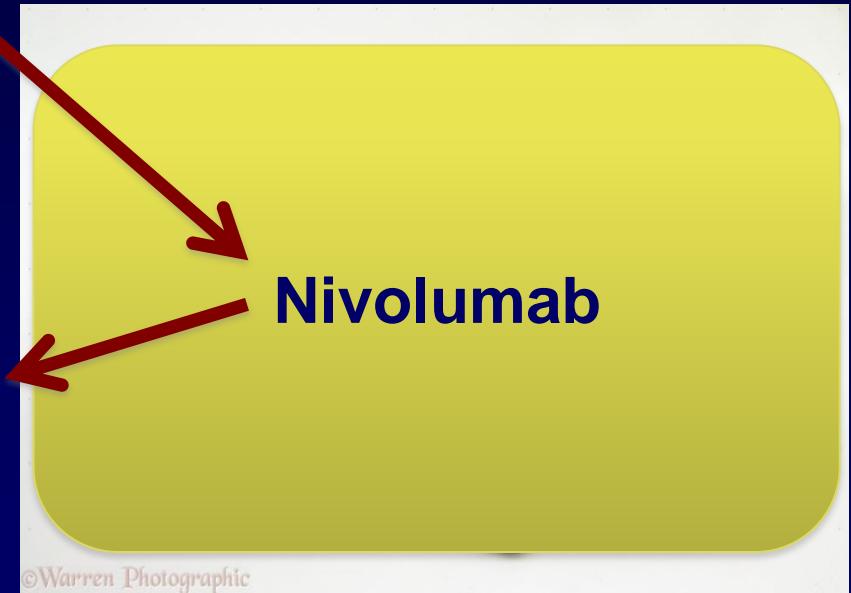
- Maintenance erlotinib



- Third-line docetaxel

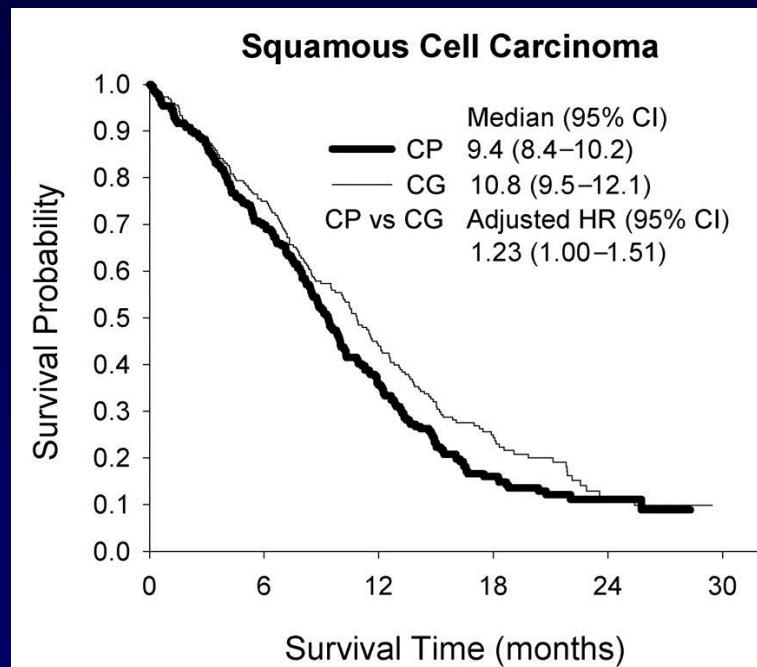


- Erlotinib
(after failure of chemotherapy)

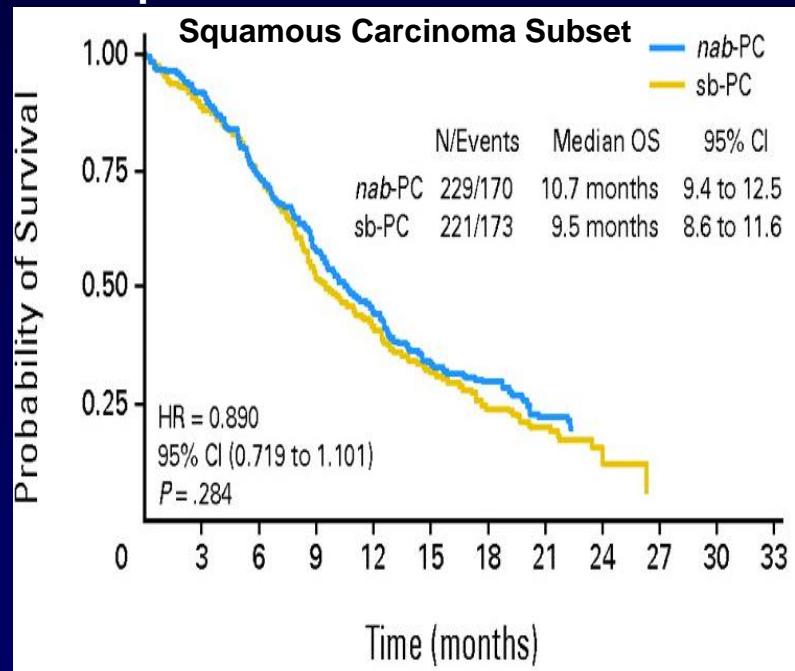


First-Line Platinum Doublet: Any Non-Pemetrexed Combination

Cisplatin + Gemcitabine vs
Cispaltin + Pemetrexed



Carboplatin + *nab*-Paclitaxel vs
Carboplatin + Paclitaxel

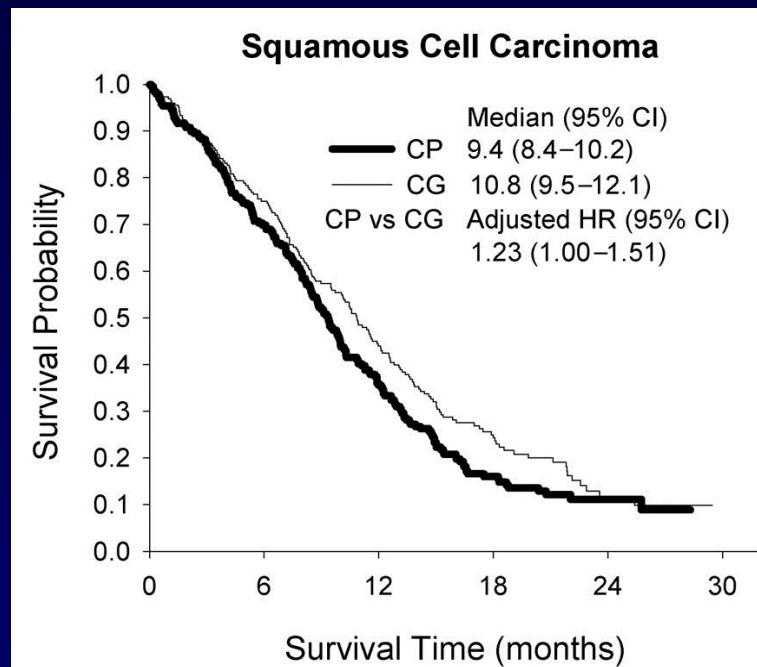


- Similar outcomes with vinorelbine-, taxane-, gemcitabine-platinum doublets in large randomized trials

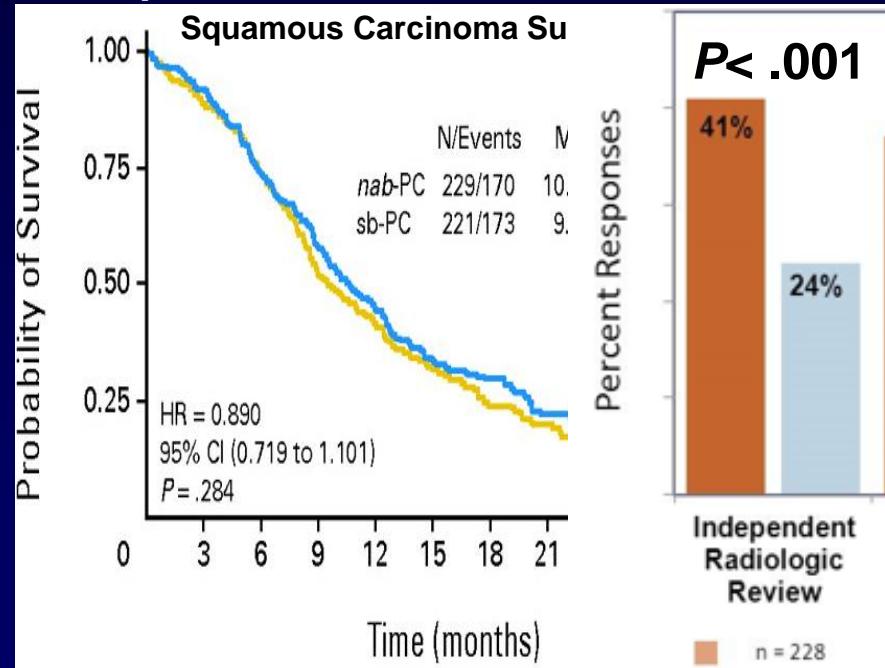
Scagliotti GV, et al. *J Thorac Oncol*. 2009;4(12):1568-1571. Socinski MA, et al. *J Clin Oncol*. 2012;30(17):2055-2062.
Kelly K, et al. *Clin Lung Cancer*. 2013;14(6):627-635. Hoang T, et al. *Lung Cancer*. 2013;81(1):47-52. Scagliotti GV, et al. *J Thorac Oncol*. 2013;8(12):1529-1537.

First-Line Platinum Doublet: Any Non-Pemetrexed Combination

Cisplatin + Gemcitabine vs
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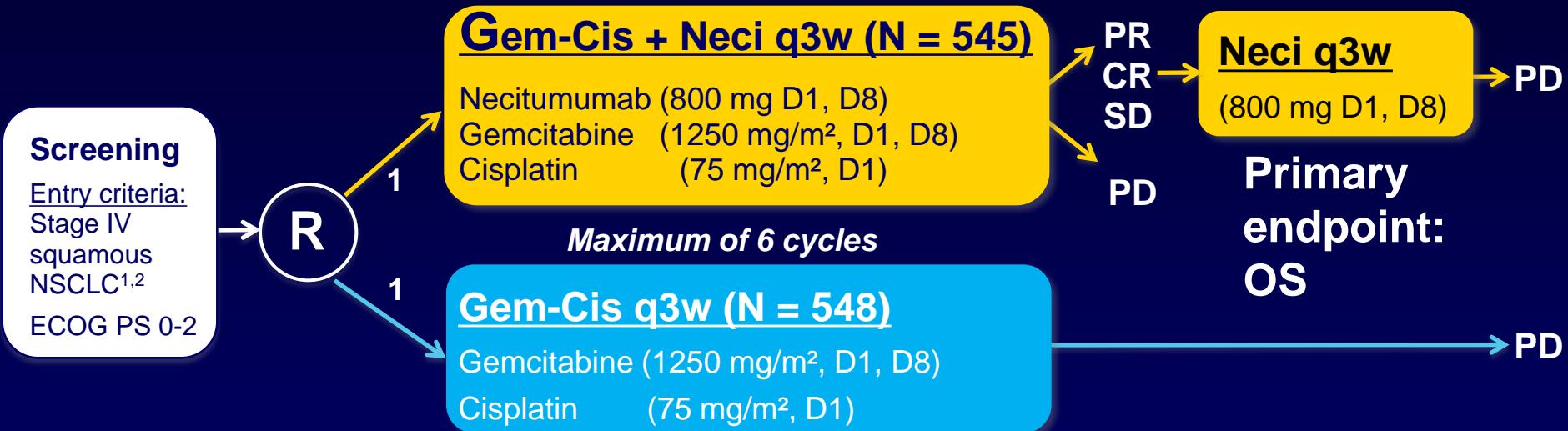
Carboplatin + *nab*-Paclitaxel vs
Carboplatin + Paclitaxel



- 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



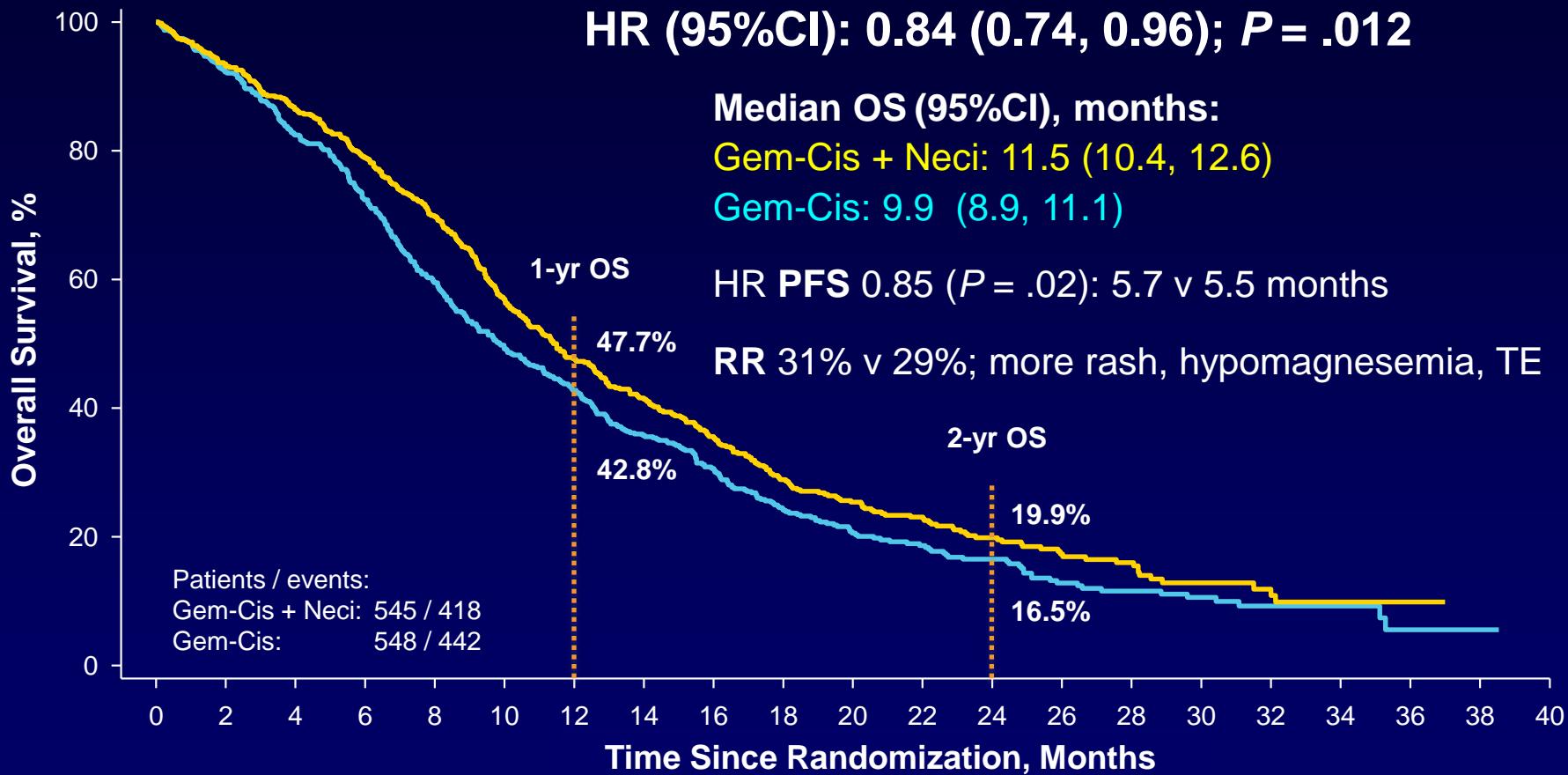
Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe, and Australia; vs South America, South Africa, and India; vs Eastern Asia)

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

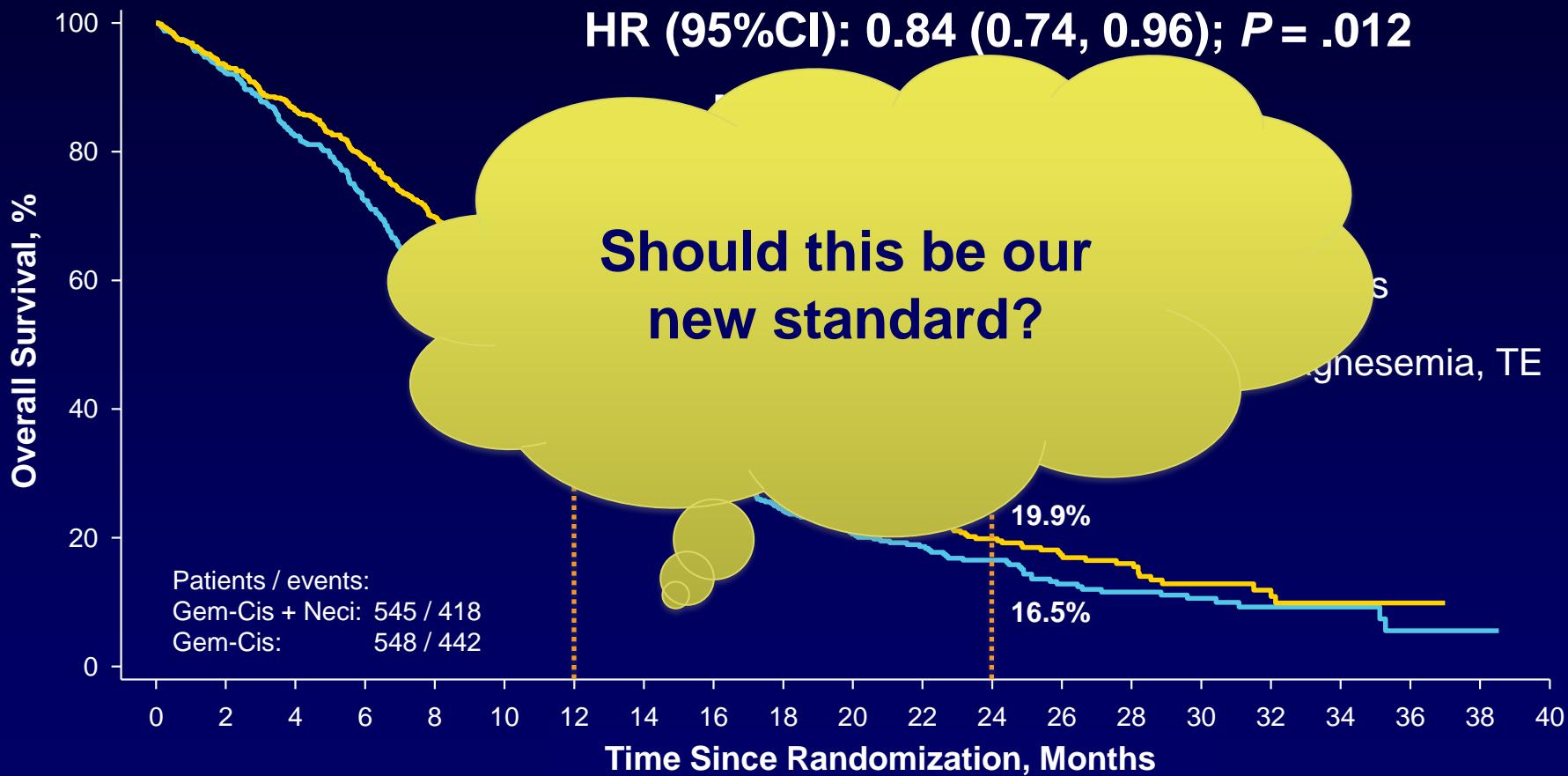
SQUIRE: Overall Survival (ITT)



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

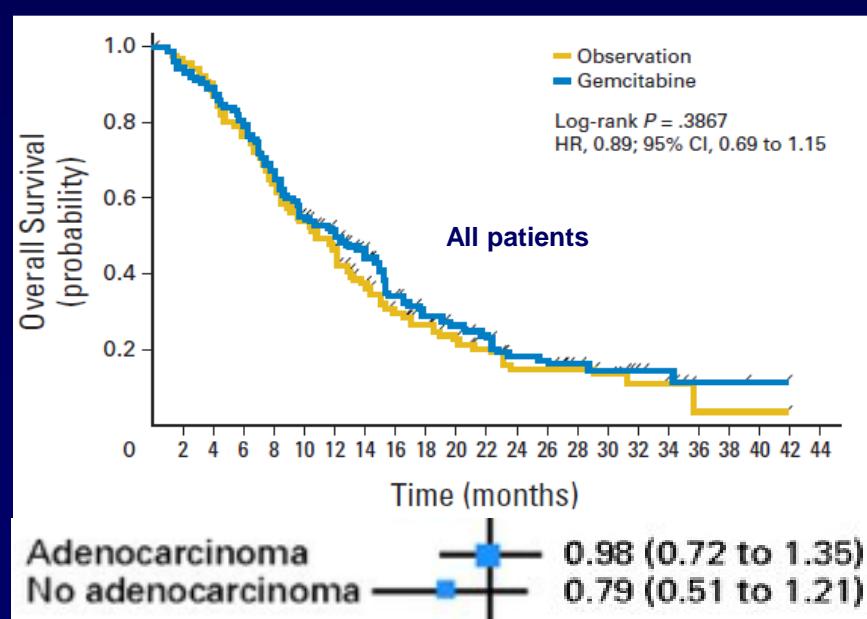
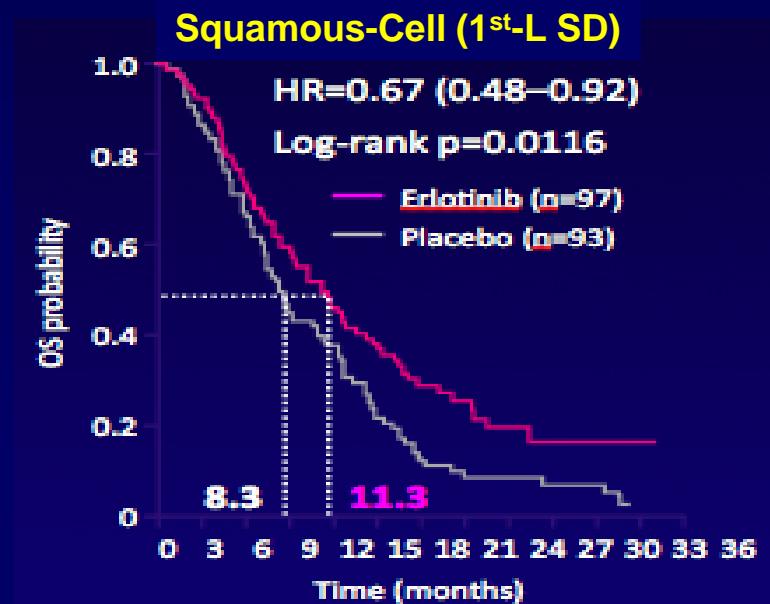
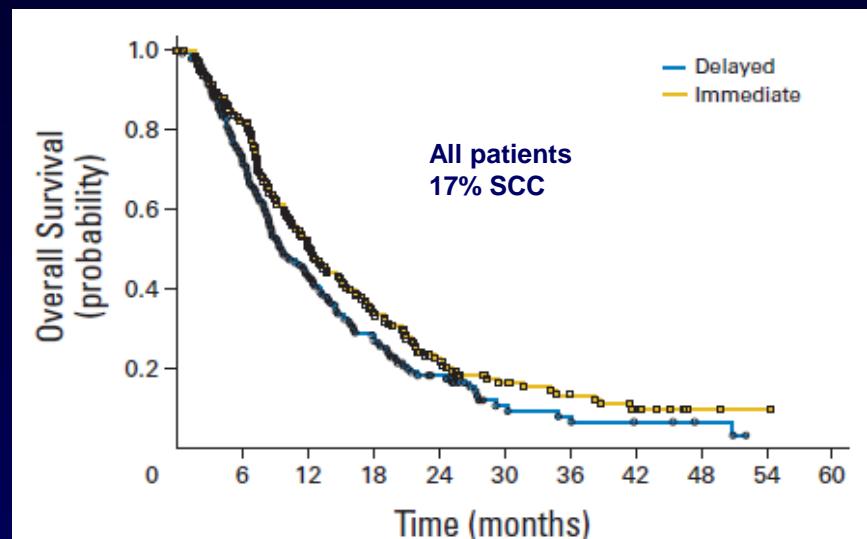
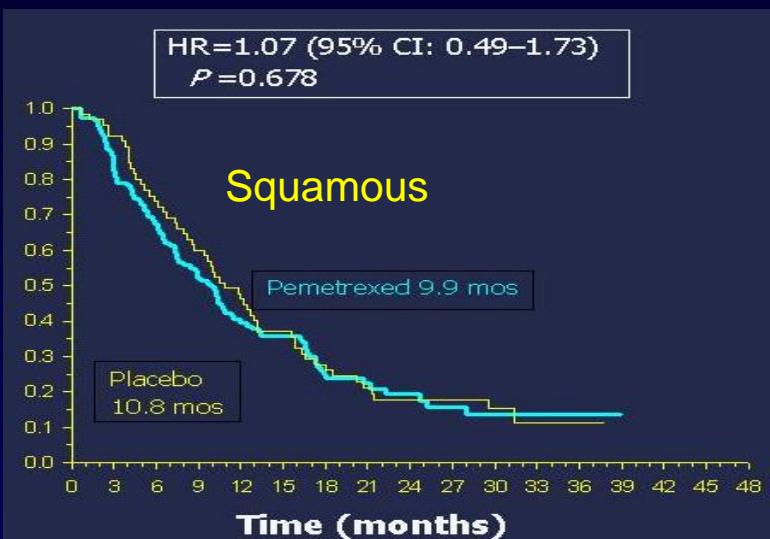
No difference by EGFR
IHC H-score

SQUIRE: Overall Survival (ITT)



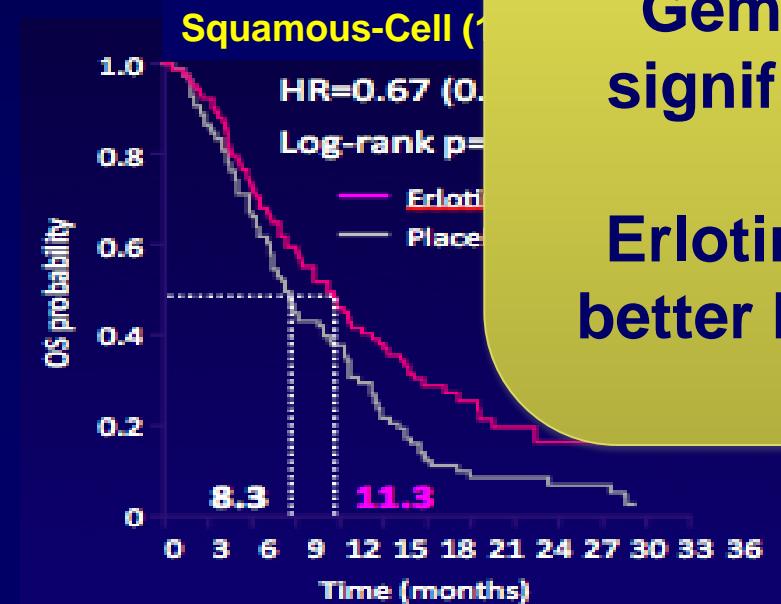
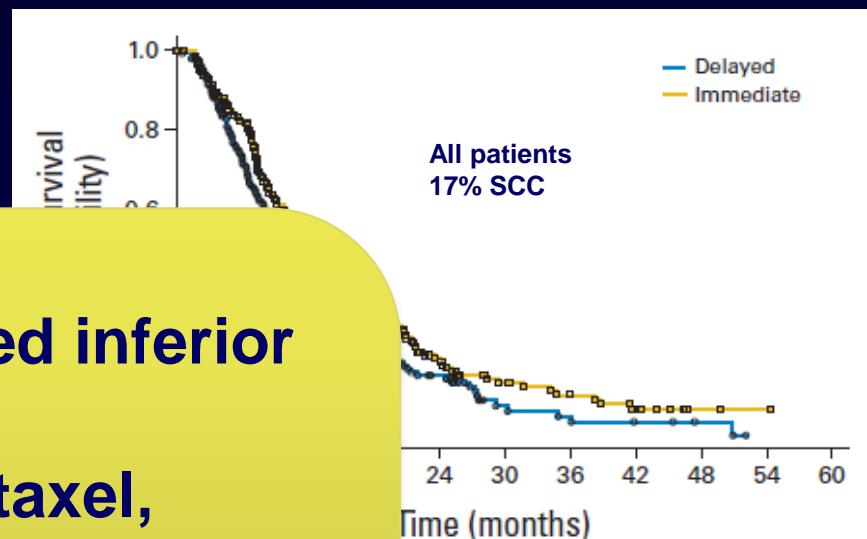
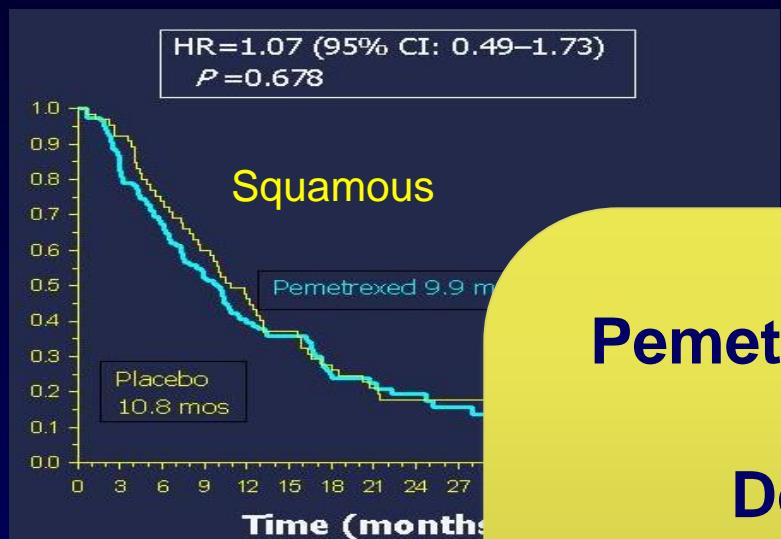
Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

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; Péröl M, et al. J Clin Oncol. 2012;30(28):3516-3524.

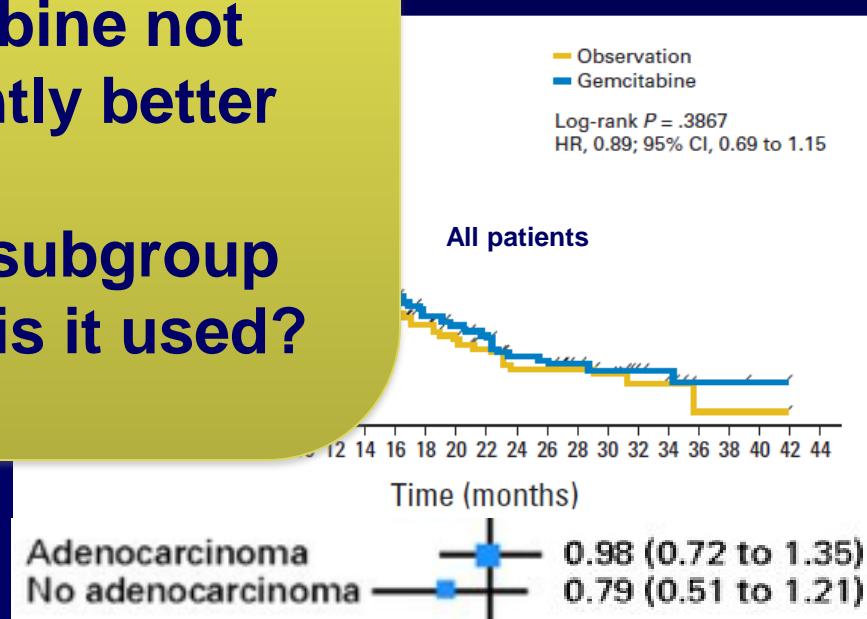
Maintenance Therapy in SCC



Pemetrexed inferior

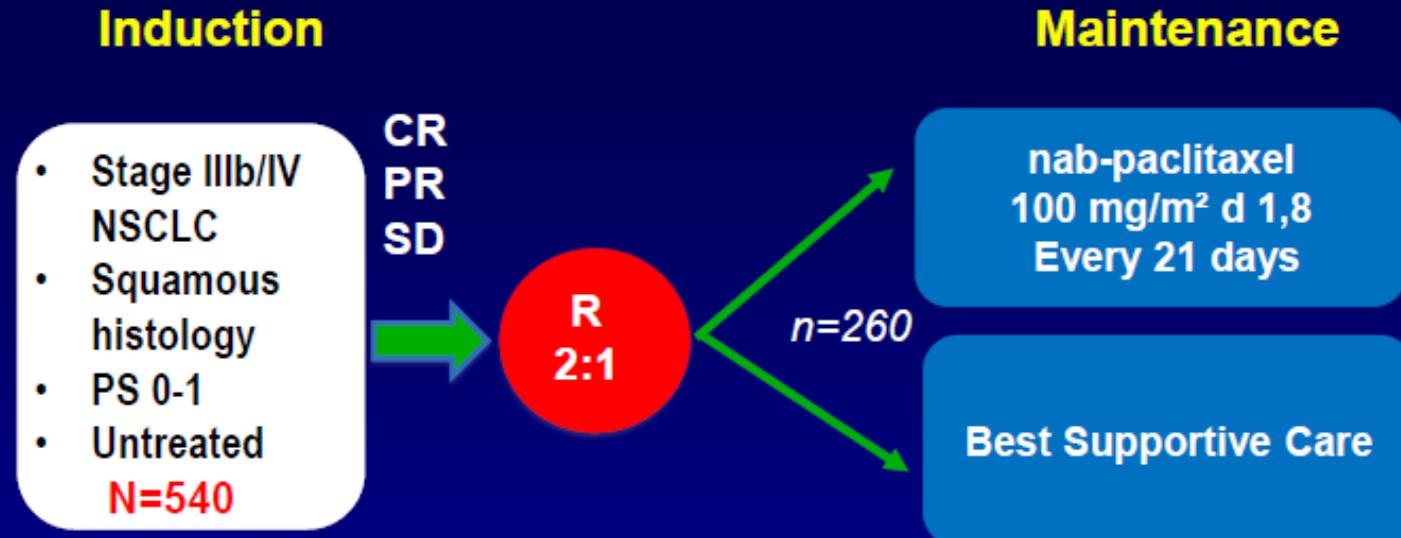
Docetaxel,
Gemcitabine not
significantly better

Erlotinib subgroup
better but is it used?



nab-Paclitaxel – ABOUND.sqm Trial

Phase III Squamous Maintenance



**nab-Paclitaxel
carboplatin
X 4 Cycles**

Primary end-point:

PFS

Secondary end-points:

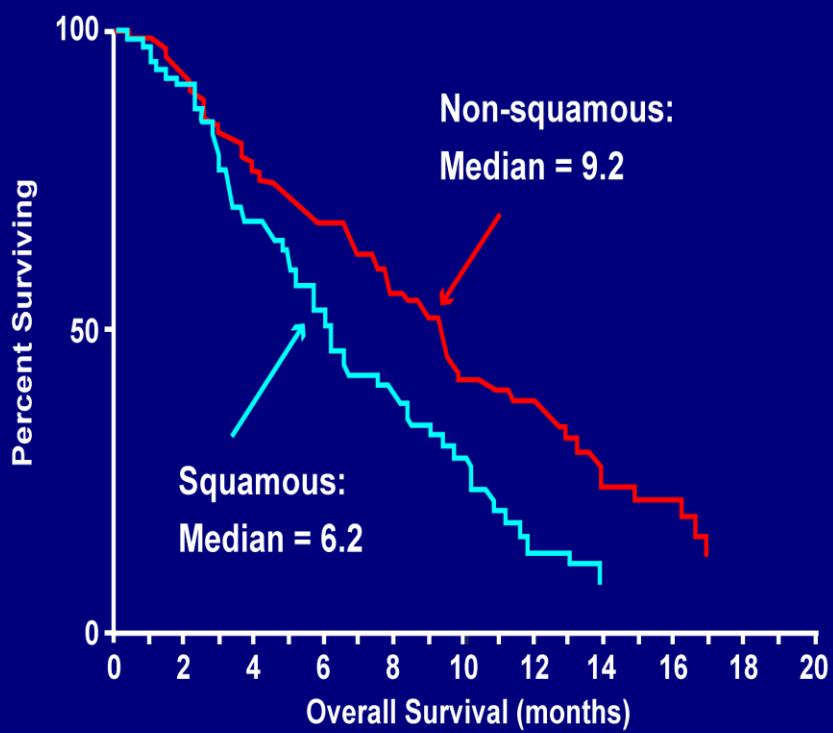
OS, ORR, safety

Exploratory:

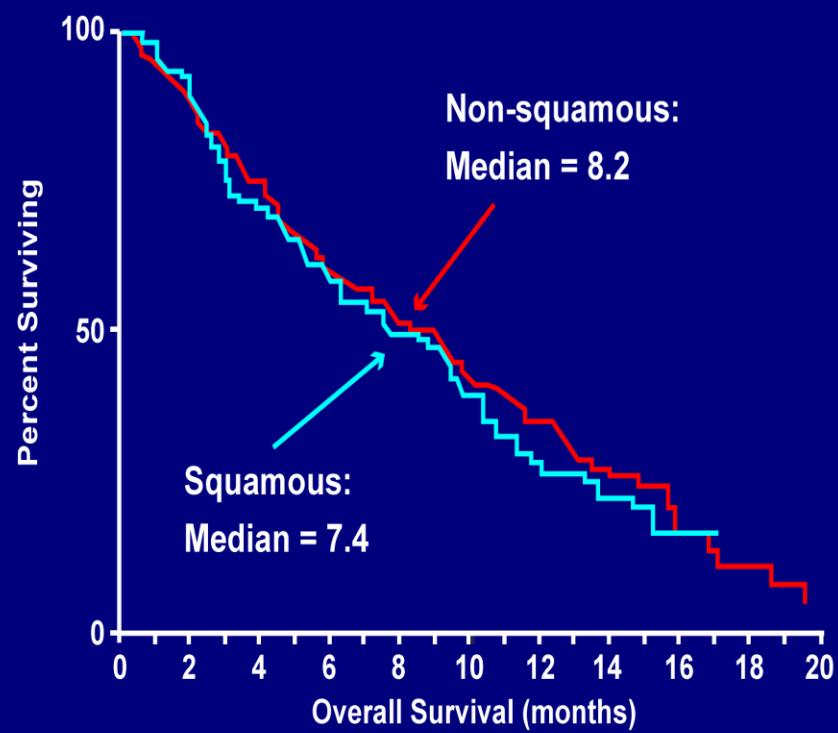
QoL, Correlative biomarkers

Docetaxel Historical Standard 2nd-line for Squamous Carcinoma

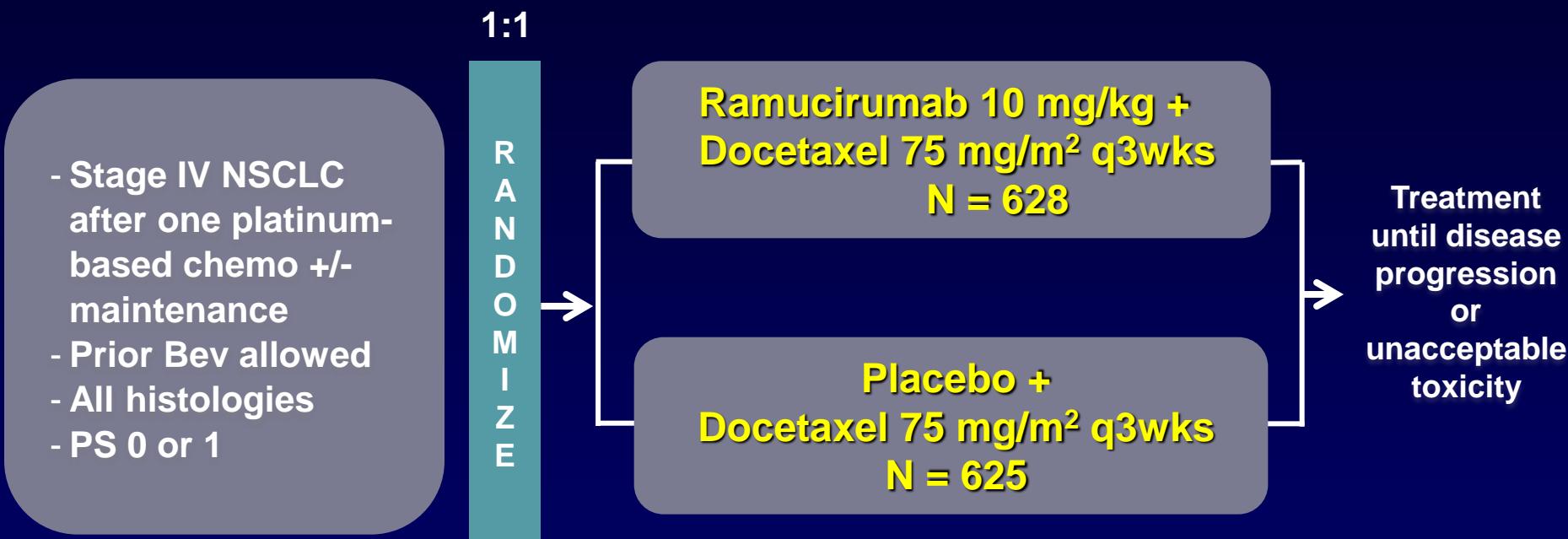
Pemetrexed



Docetaxel



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:

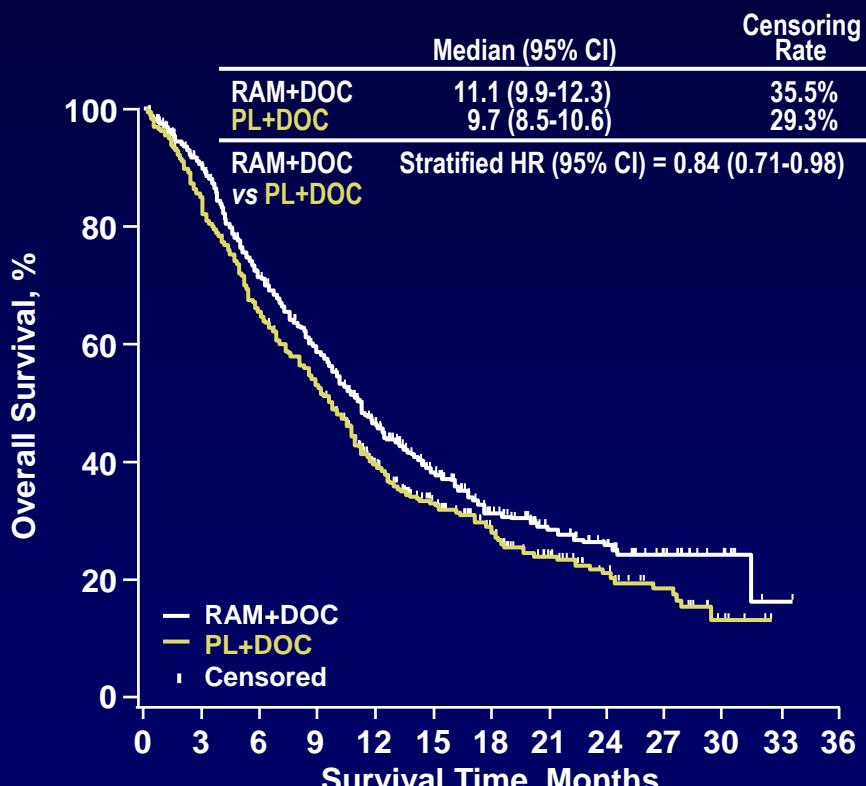
PFS, ORR, safety, patient-reported outcomes

~26% squamous

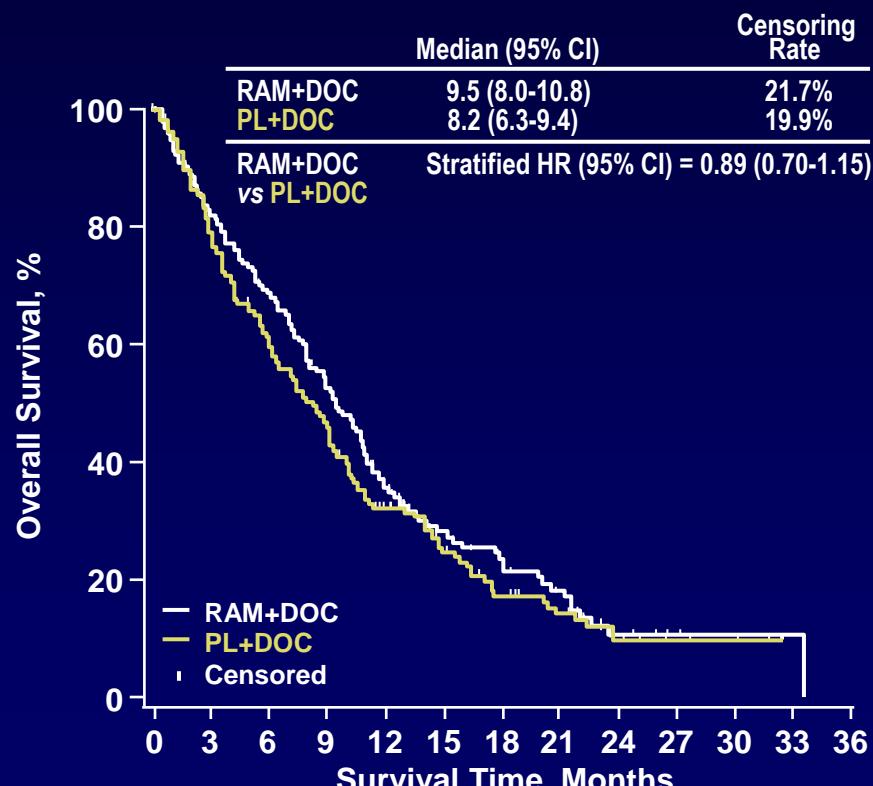
Ramucirumab Improves OS in All Histologies

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



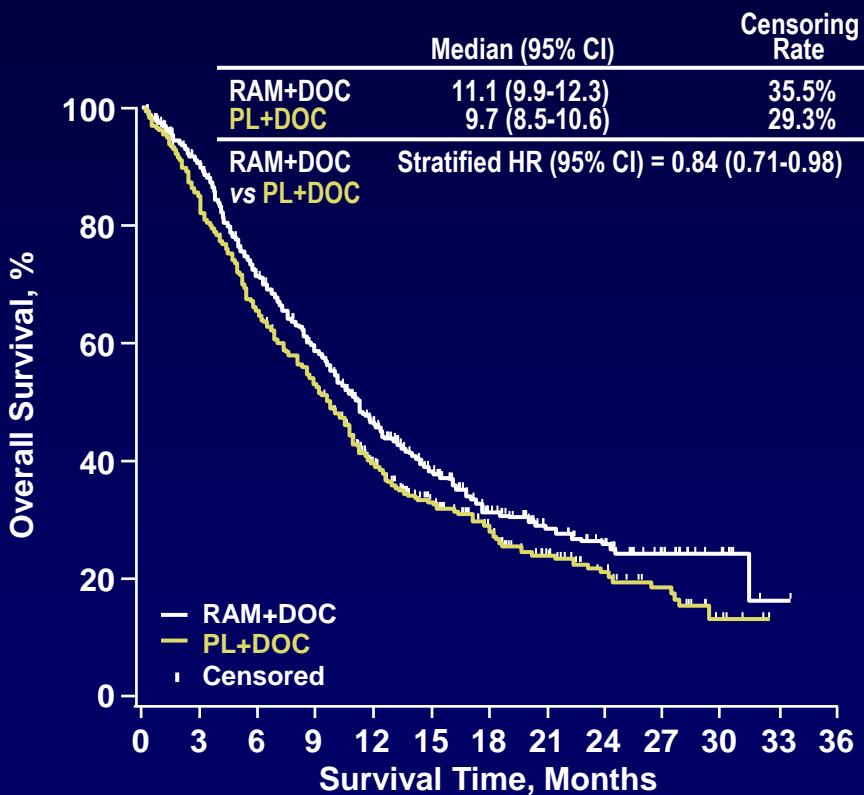
Squamous OS



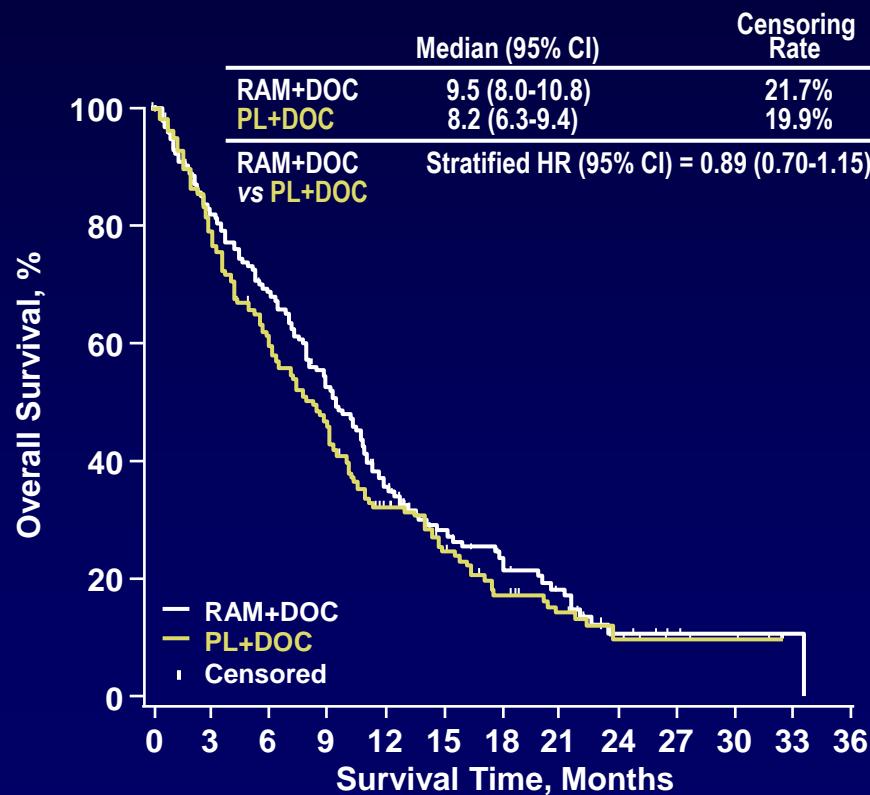
Ramucirumab Improves OS in All Histologies

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



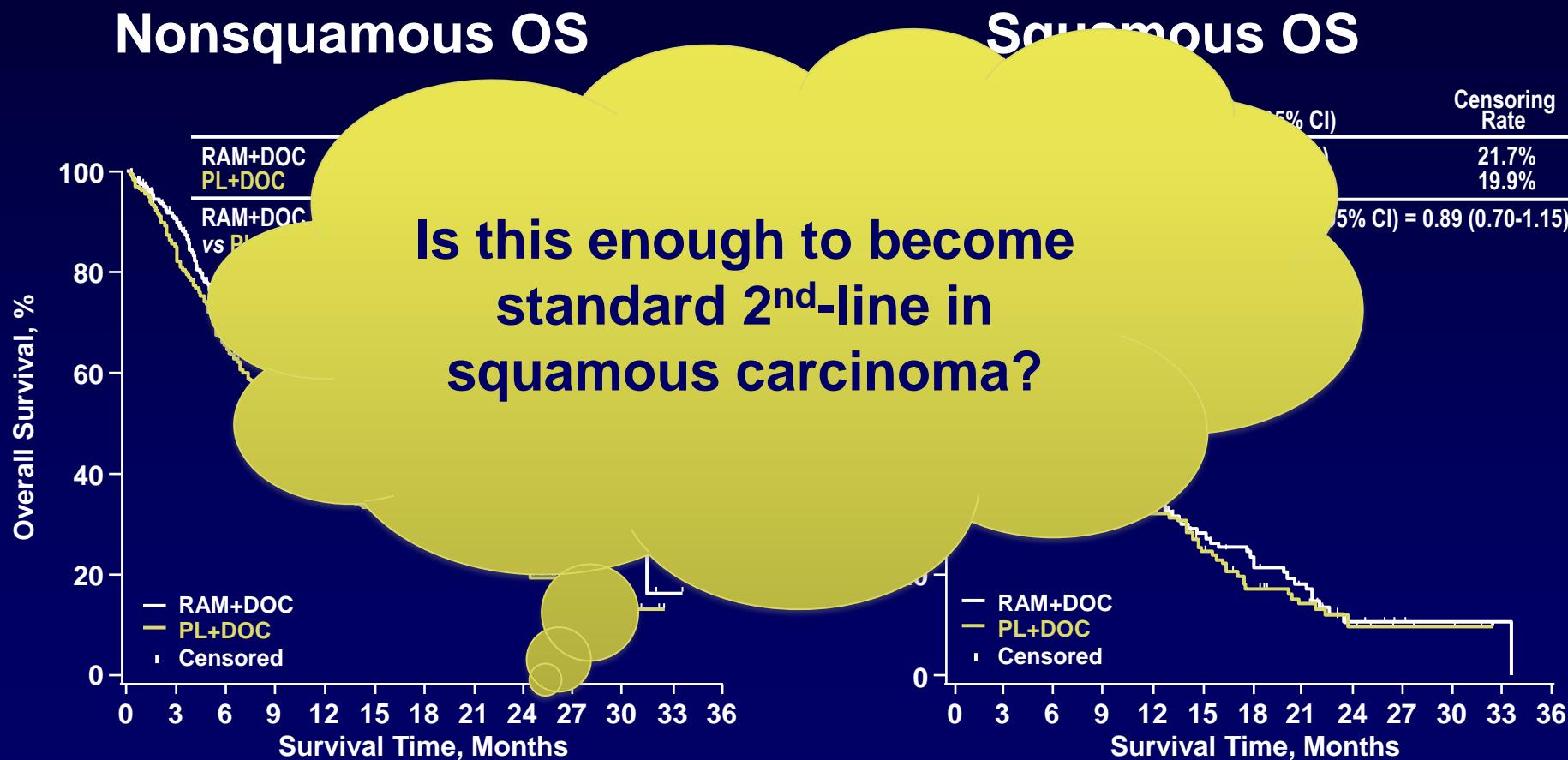
Number at risk
RAM+DOC
PL+DOC

1 1 0 0

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

Ramucirumab Improves OS in All Histologies

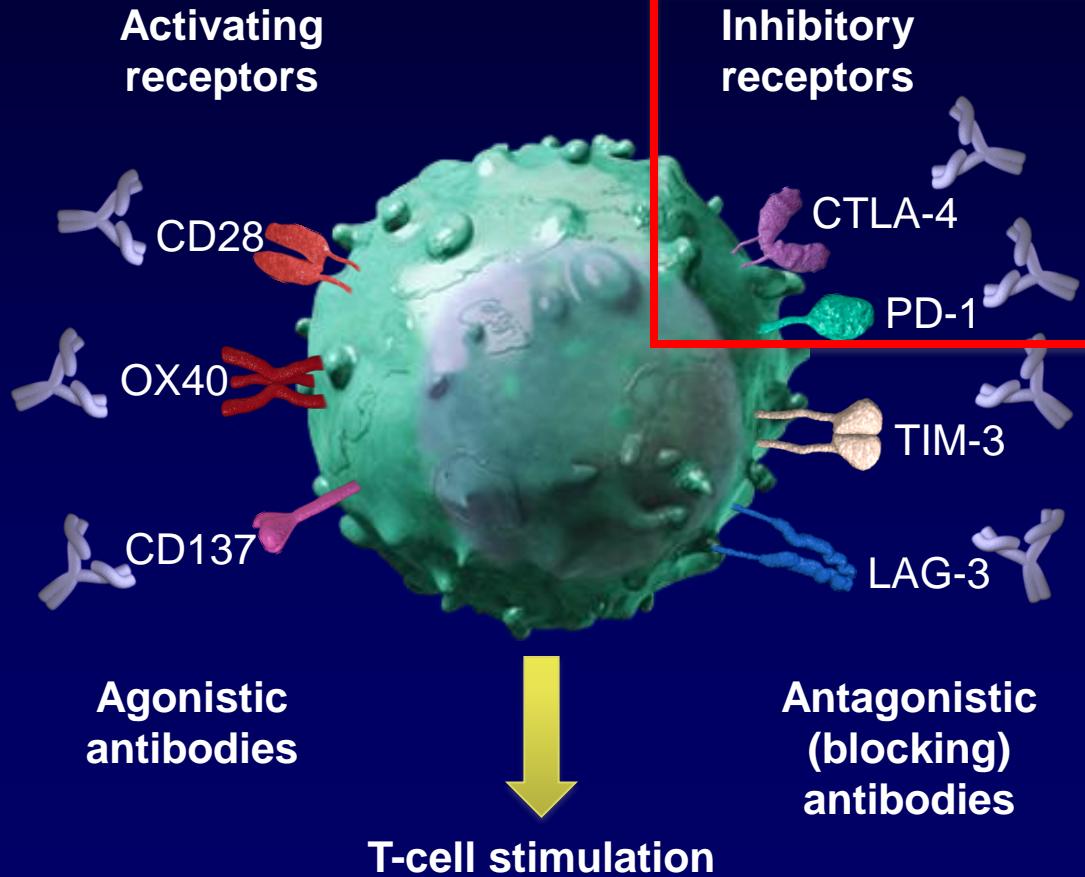
RR 23 v 14%, mPFS 4.5 v. 3.0 m, mOS 10.5 v. 9.1 m
(HR 0.857 $P = .0235$)



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

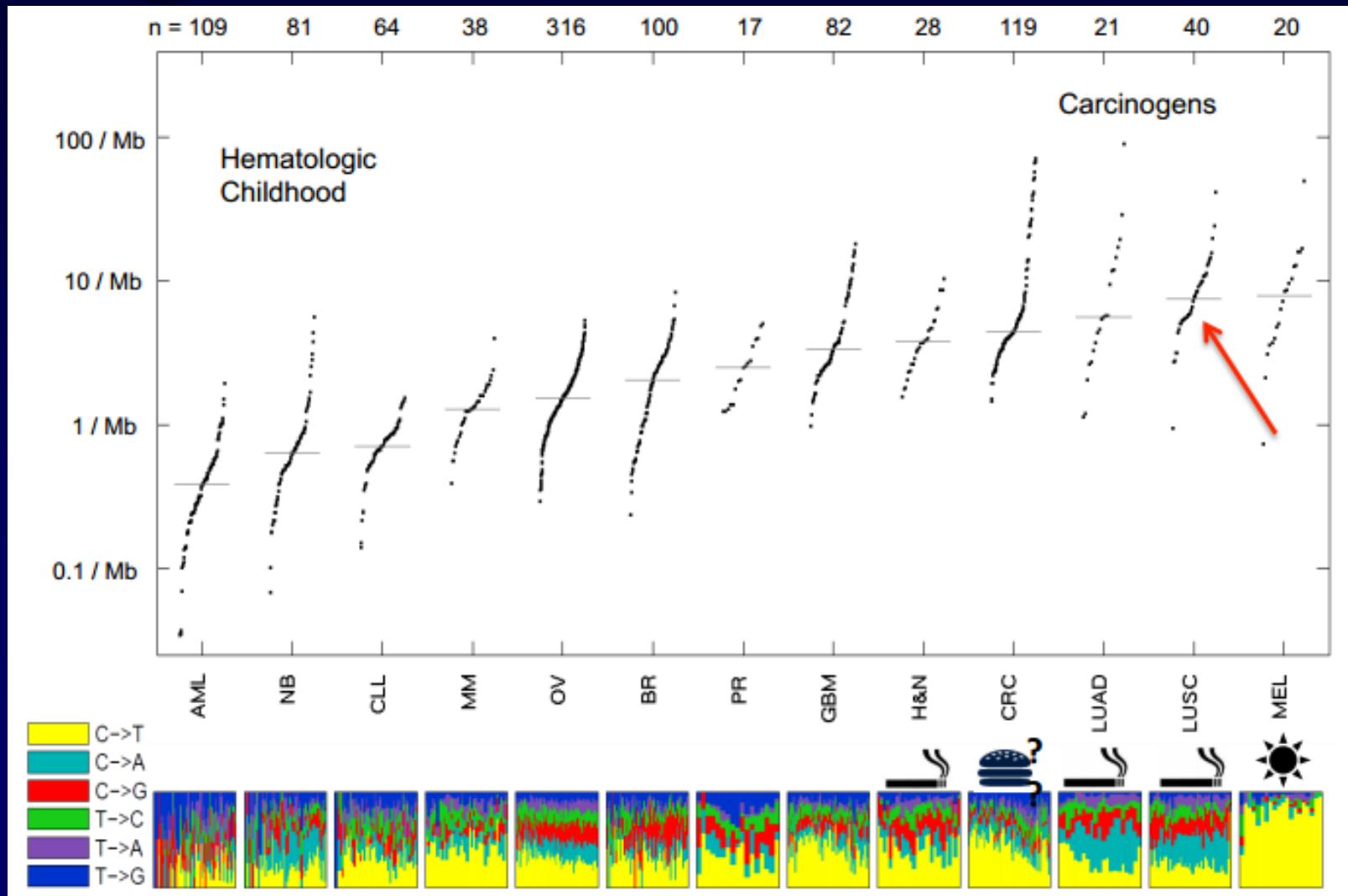
Garon

T-Cell Checkpoint Regulation

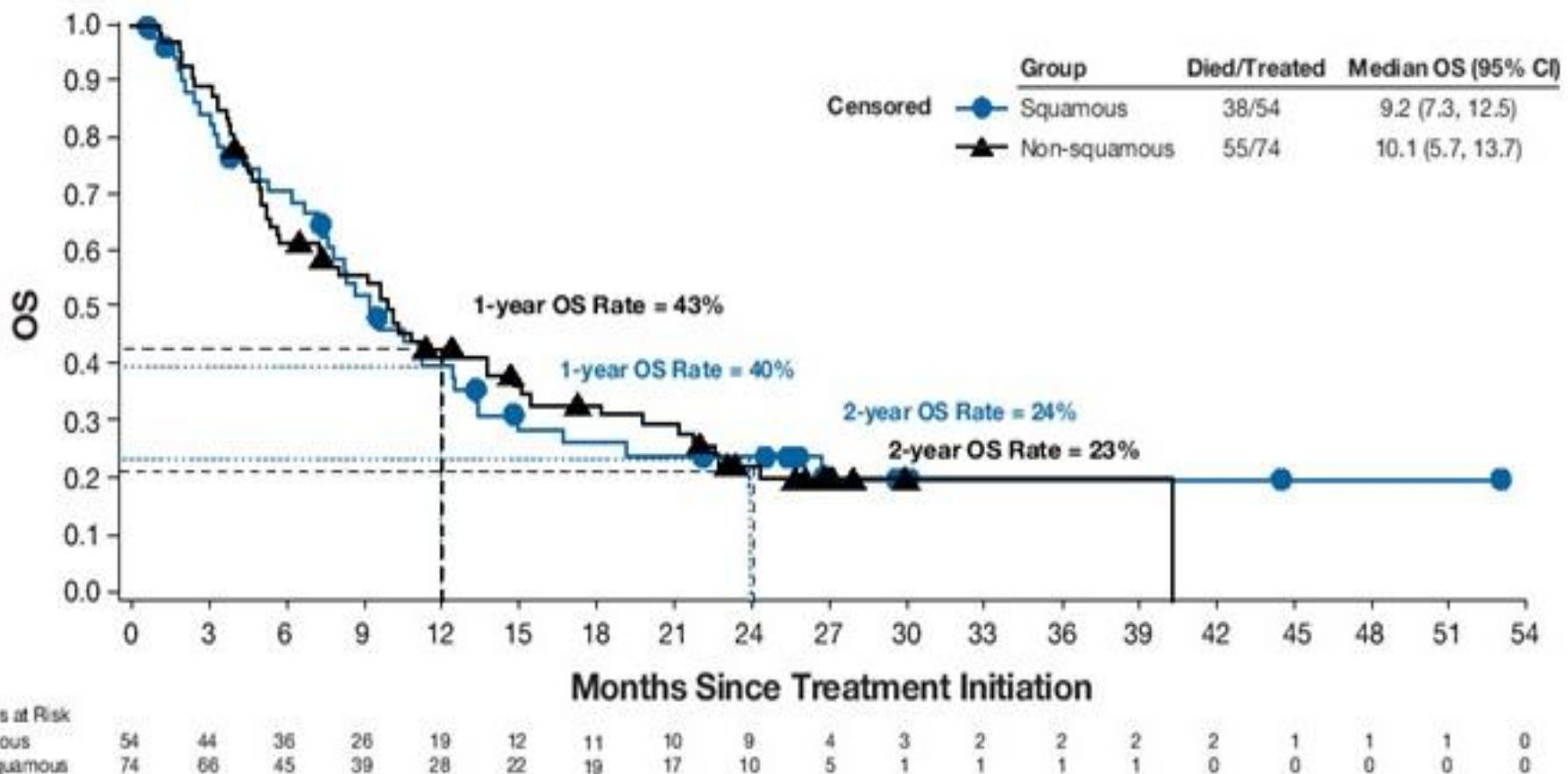


- T-cells regulated through complex balance of inhibitory (“checkpoint”) and activating signals
- Tumors can dysregulate checkpoint, activating pathways, and thus immune response
- Targeting checkpoint and activating pathways is designed to promote an immune response including PD-1 and PD-L1 inhibitors

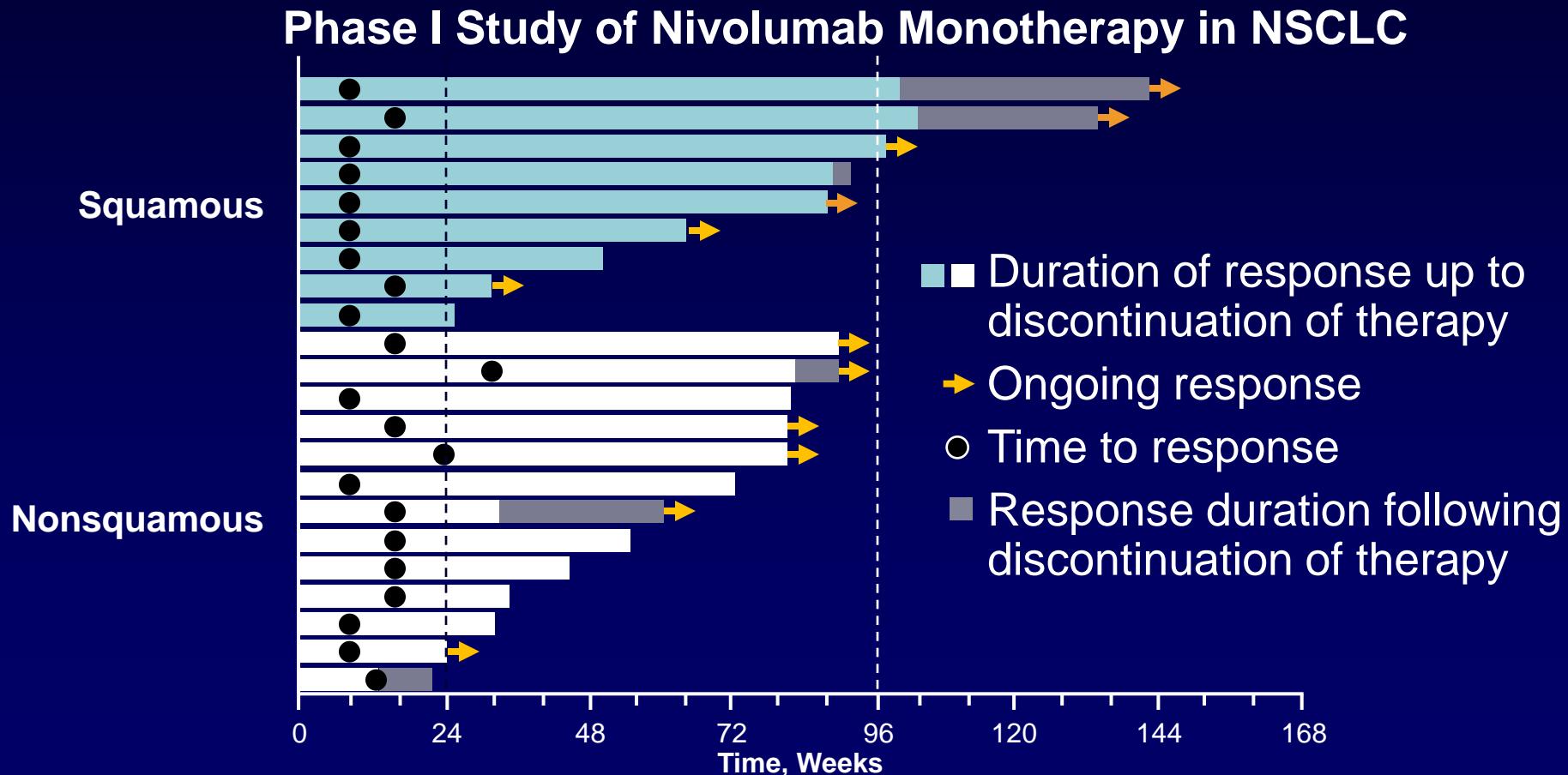
SCC is Genomically More Deranged High Rates of Somatic Mutations



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

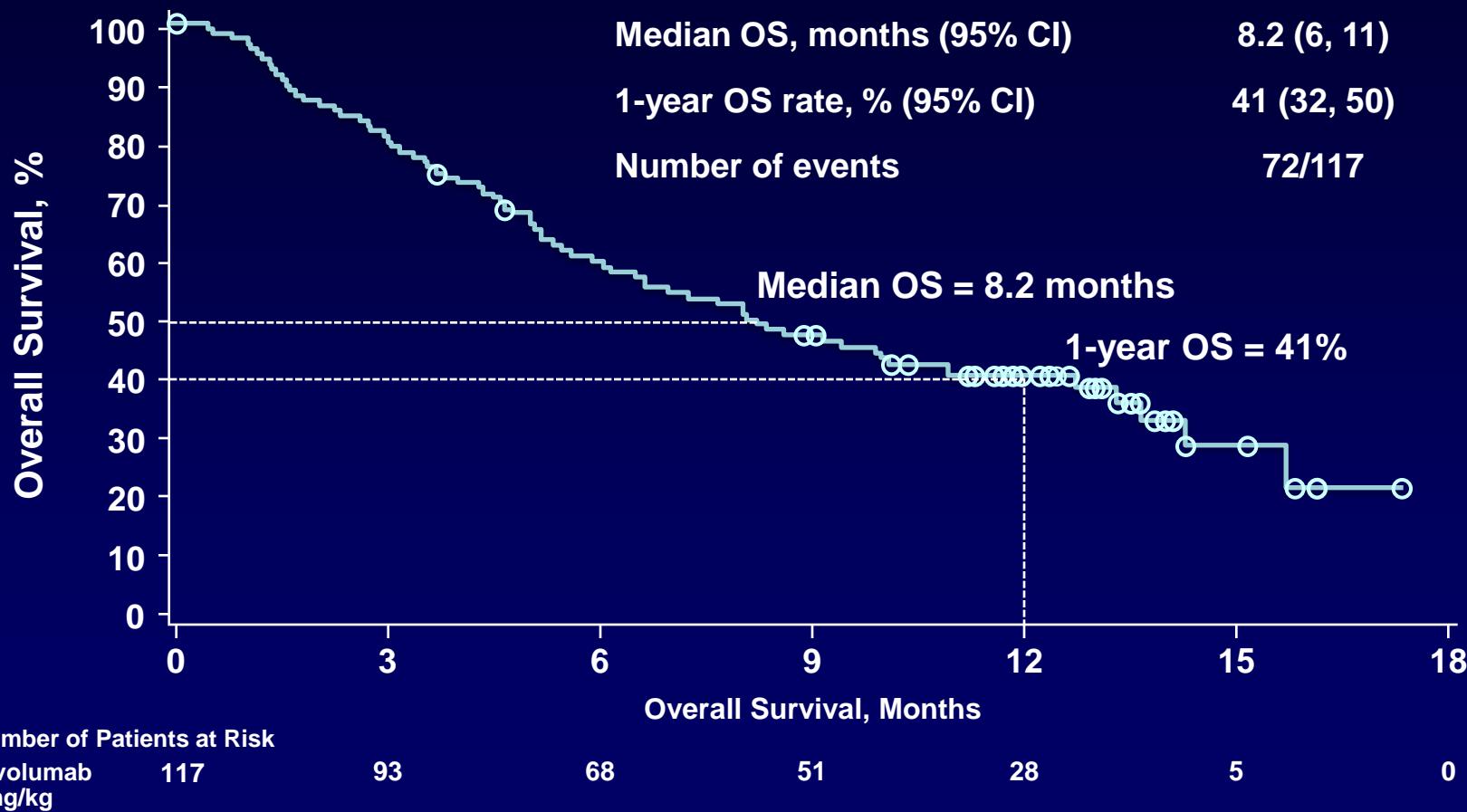


Durable Responses Seen at 8-16 Weeks and Similar Among Agents AND Histologies (Nivolumab, MK-3475, MPDL3280A)



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

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

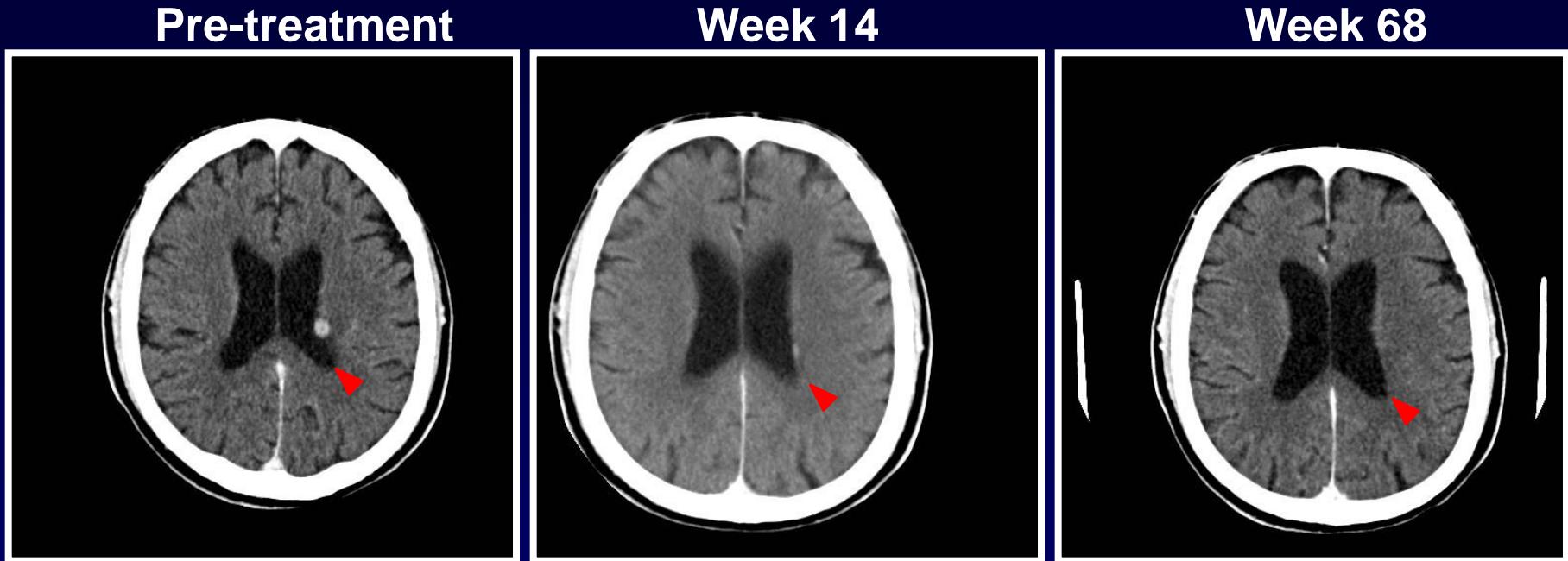


Median follow-up for survival: 8 months (range, 0–17 months)

^aBased on July 2014 DBL; Symbols represent censored observations

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

Response to Nivolumab in SQ NSCLC Brain Metastasis



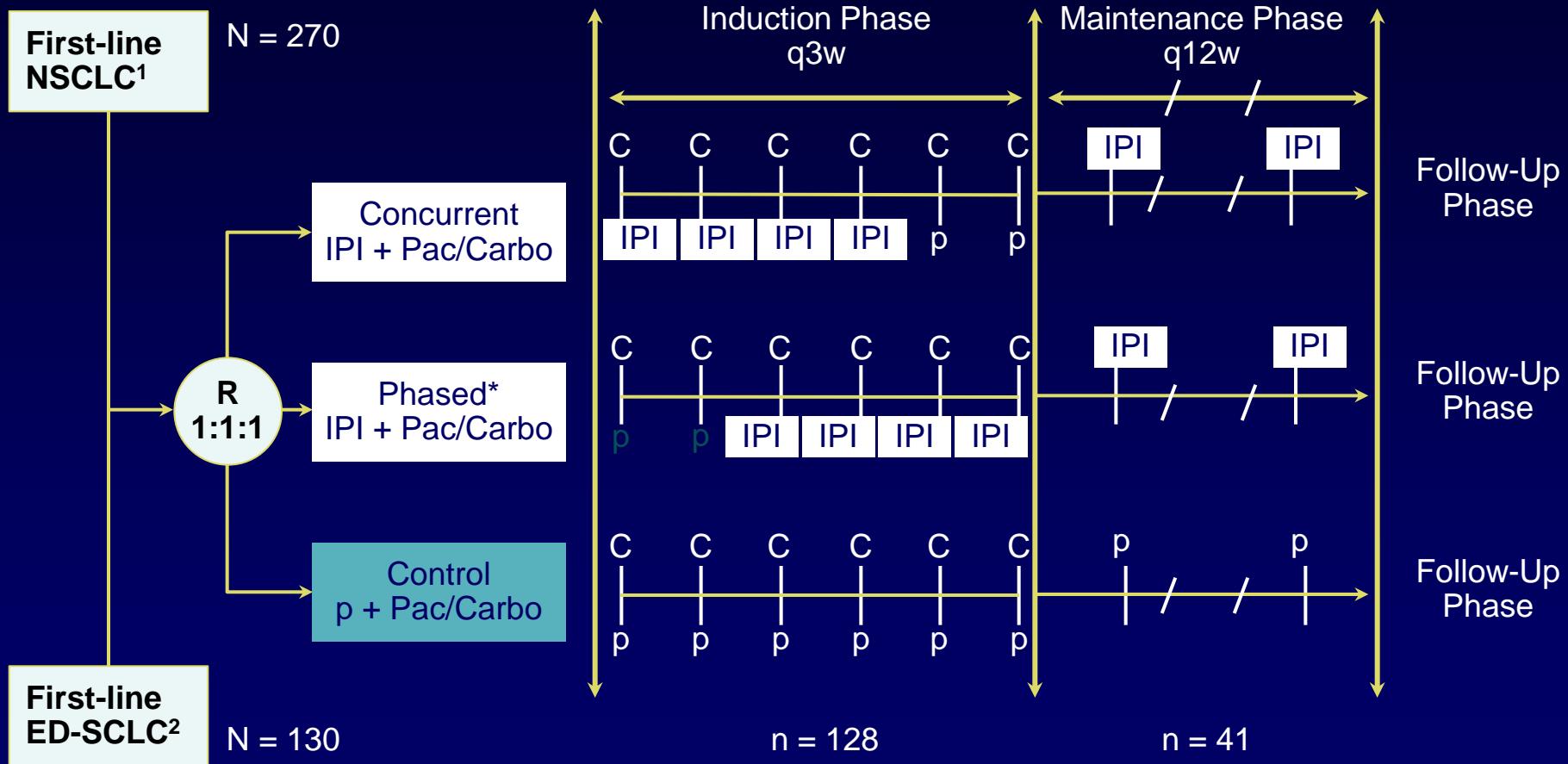
- 73 year-old male, stage IIIB, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed radiotherapy

Ramalingam, SS et al, presented at Chicago Multidisciplinary Symposium on Thoracic Oncology (CMSTO), Oct 30th- Nov 1st 2014; Oral presentation.

FDA Approves Nivolumab for Advanced (Metastatic) Squamous NSCLC

- Randomized trial of nivolumab (3 mg/kg IV q2weeks) versus docetaxel (75 mg/m² IV q3weeks)
- N = 272
- Median OS 9.2 months (7.3-13.1 mos) vs 6 months (5.1 – 7.3 mos)
- HR 0.59 (95% CI 0.44-0.79), P =.00025

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



*Phased regimen: 2 doses of paclitaxel (175 mg/m²) / carboplatin (AUC = 6) prior to start of ipilimumab.

C, chemotherapy (paclitaxel 175 mg/m² / 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.

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%)

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)

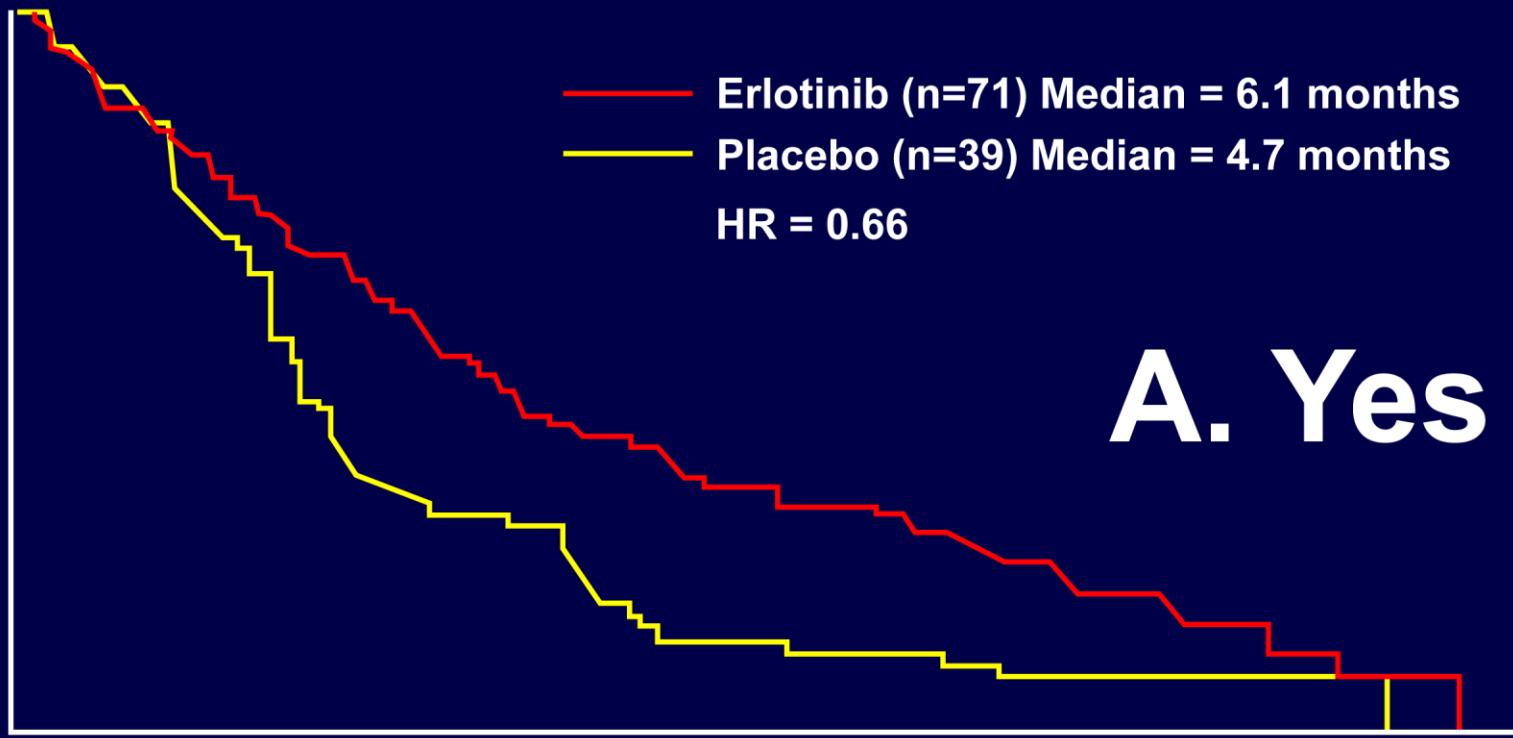
Most common related severe toxicities: pruritus (<2%), rash (<3%), and diarrhea (up to 10%)

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	To be reported
	NCT02041533/ CA209-026	III	Advanced/metastatic PD-L1 positive NSCLC, first-line	495	Investigator's choice chemotx	PFS (IRRC)	Ongoing
	NCT01905657 MK-3475-010	II/III	Previously treated PD-L1 positive NSCLC	920	Docetaxel	OS, PFS, Safety	Ongoing
MK-3745	NCT02142738 MK-3475-024	III	Metastatic NSCLC PD-L1 strong; first-line	300	Platinum-based chemotherapy	PFS	Ongoing
	NCT02031458 BilRCH	II	Locally advanced or metastatic NSCLC, PD-L1 positive	635	Single arm study	ORR	Ongoing
MPDL3280A	NCT02008227 OAK	III	Locally advanced or metastatic NSCLC, after progression on platinum-based chemo	1100	Docetaxel	OS	Ongoing
	NCT02087423 ATLANTIC	II	Third-line therapy in locally advanced or metastatic NSCLC PD-L1-positive	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		Multarm including tremi+MEDI	OS	Ongoing

Would I Offer Erlotinib After (All) Chemotherapy Failure?

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

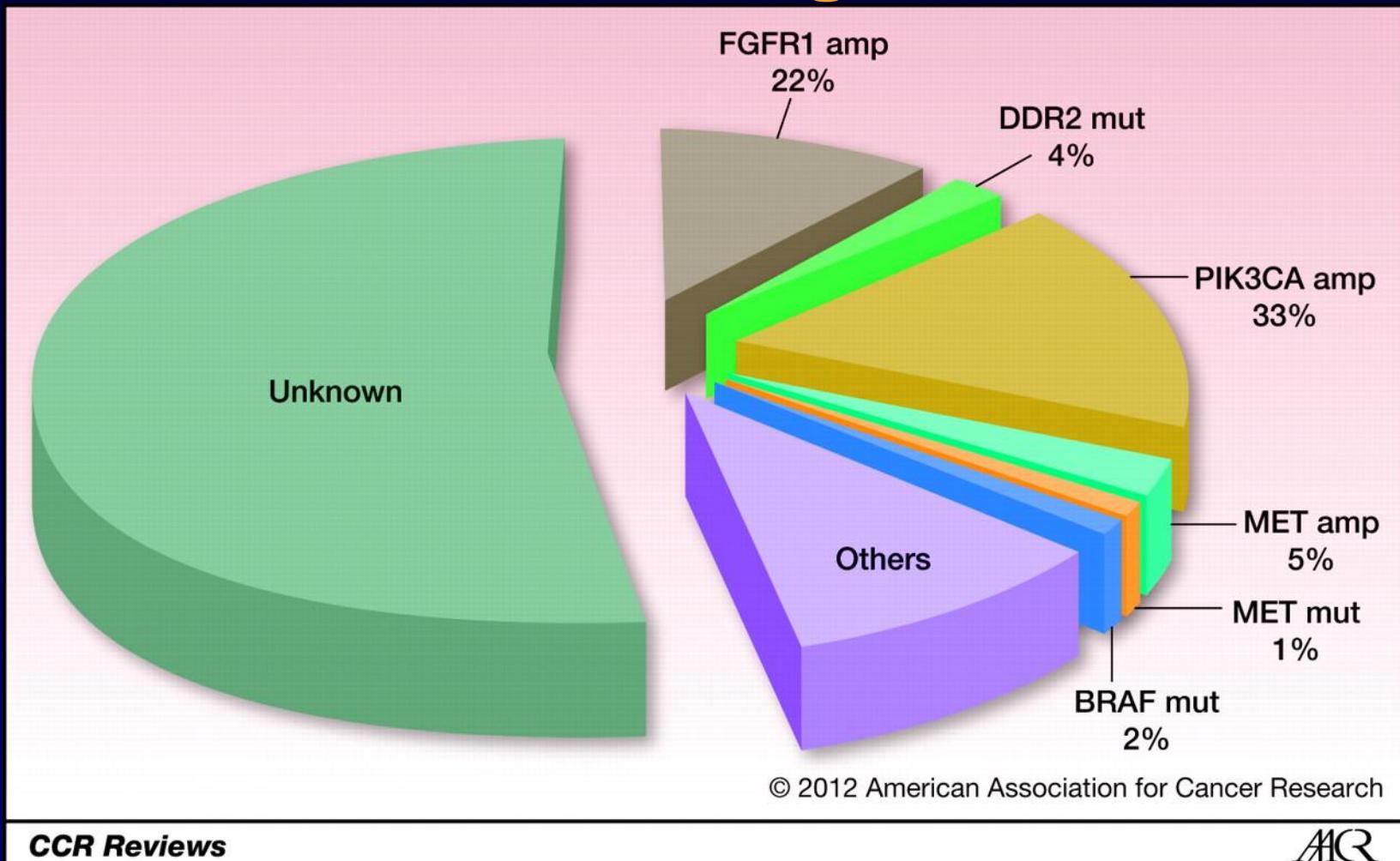


Would I Offer Erlotinib After (All) Chemotherapy Failure?

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

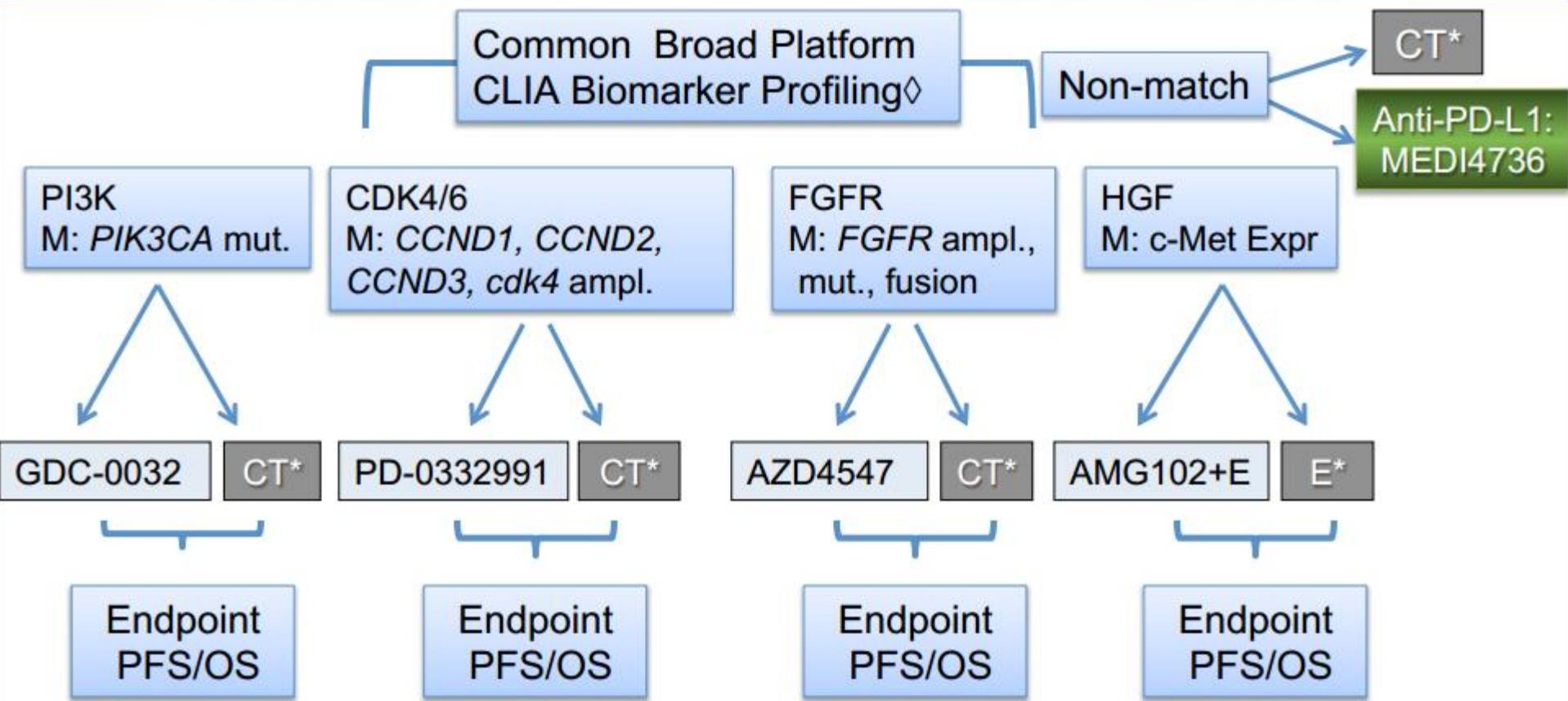
Potential Genomic Targets in SCC of Lung



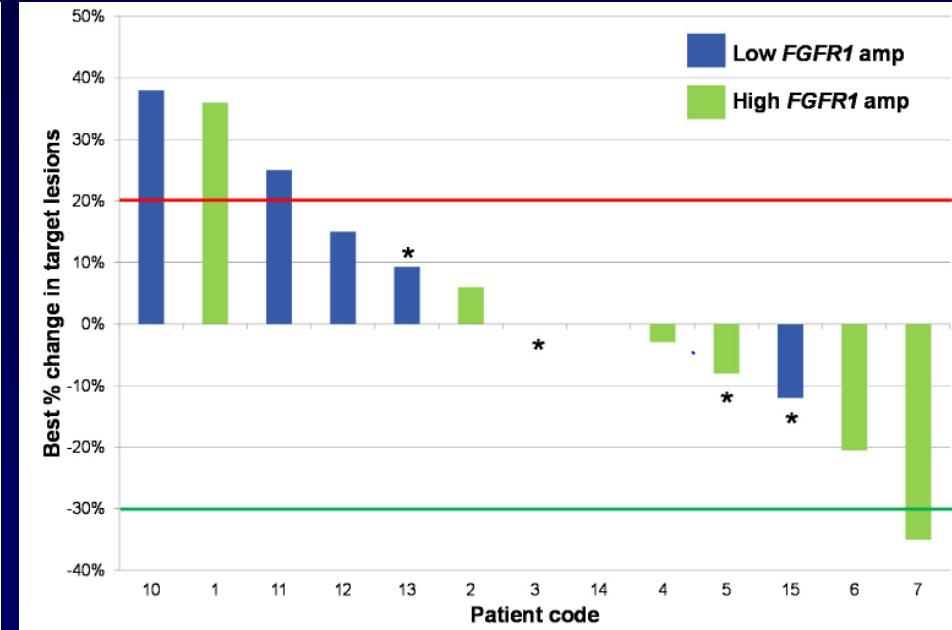
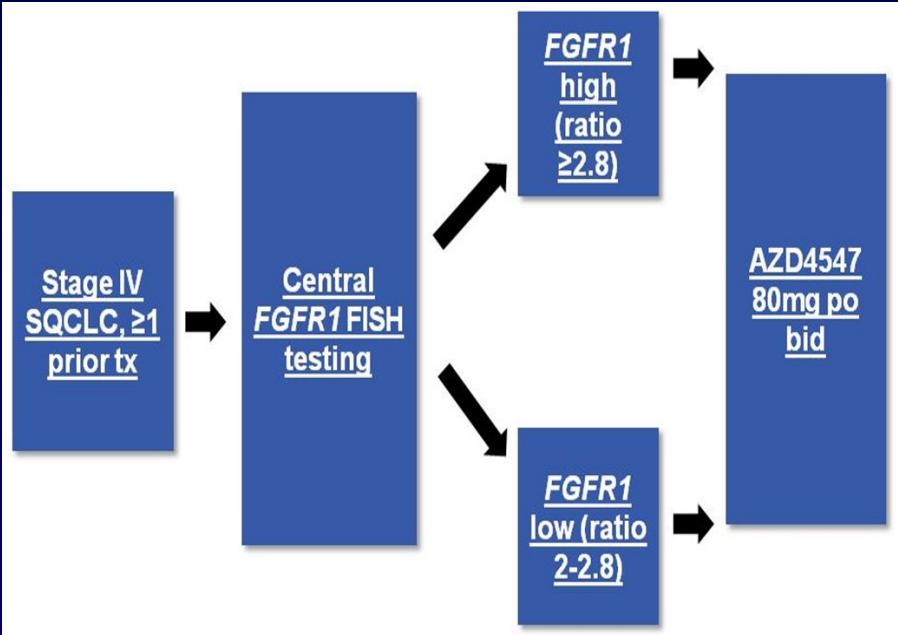


Broad genomic assessment of: Mutations, rearrangements, copy number (Foundation Medicine)

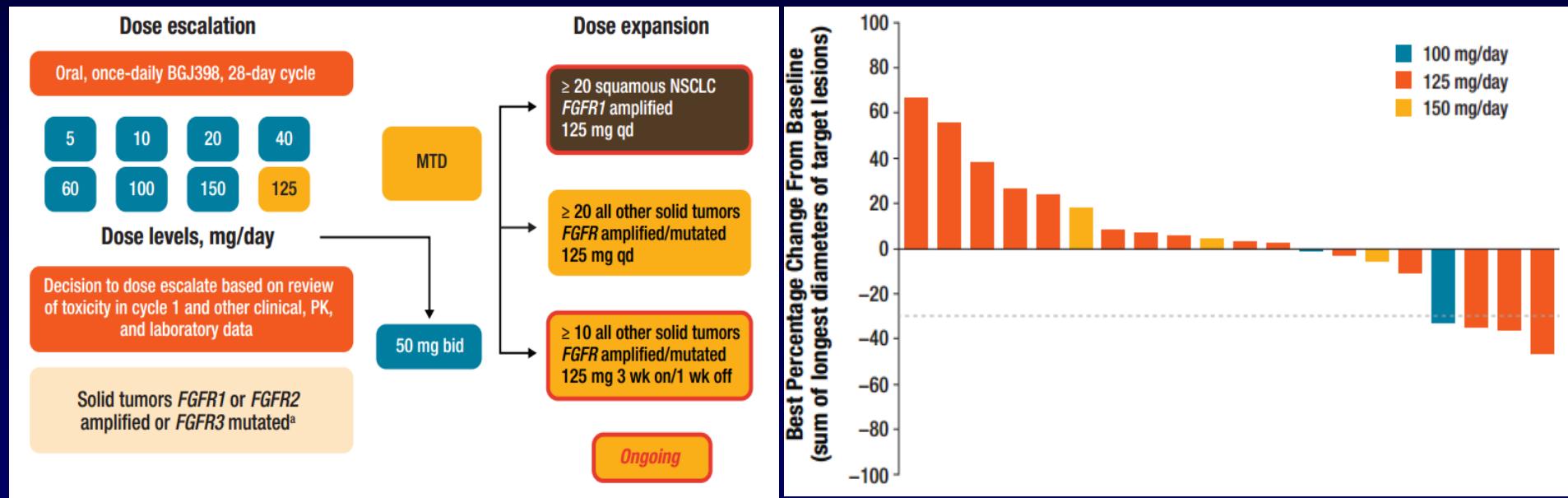
Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR N771_P772>KFP	Erlotinib Gefitinib	Cetuximab Panitumumab	Yes, see clinical trials section
CCND1 amplification	None	None	Yes, see clinical trials section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



Targeting FGFR



Targeting FGFR: BGJ398



To Conclude

- Current standards for squamous lung carcinoma:
 - First-line platinum doublet therapy (without pemetrexed)
 - Second-line docetaxel - soon to be nivolumab
 - Erlotinib after chemotherapy failure
- Promising drug development underway or arrived!
 - 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

Case #5 – What would I do?

First line Treatment

1. Platinum doublet



2. Cisplatin/pemetrexed



3. Carboplatin/*nab*-paclitaxel

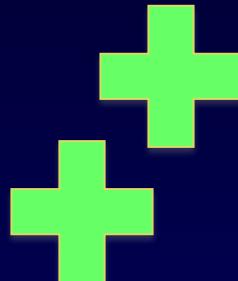


4. Cisplatin/gemcitabine/necitumumab

5. Clinical trial of immune checkpoint inhibitor
PD-1/PD-L1 inhibitor

How long to continue? Rebiopsy?

1. Break after 4 cycles



2. Two more cycles



3. Maintenance gemcitabine



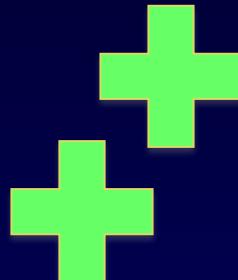
4. Maintenance erlotinib



5. Maintenance docetaxel

How long to continue? Rebiopsy?

1. Break after 4 cycles



2. Two more cycles



3. Maintenance gemcitabine



4. Maintenance erlotinib



5. Maintenance docetaxel

- Rebiopsy and molecular testing?
 - Not as standard
 - Yes for clinical trial

Case #5: 2nd-line therapy?

1. Docetaxel 
2. Erlotinib Only if no further chemotherapy
3. Afatinib 
4. Docetaxel + ramucirumab 
5. Trial with nab-paclitaxel ?
6. Trial of PD-1/PD-L1 inhibitor 