OPTIMAL FIRST LINE TREATMENT
FOR NON-ONCOGENE DRIVER NSCLC
State-of-the-Art 2015

KOSTAS N. SYRIGOS, M.D., Ph.D., FCCP

- *Professor of Medicine & Oncology, Athens Medical School, GR.*
- *Head, 3rd Department of Medicine, Sotiria General Hospital, GR.*
- *Visiting Professor of Thoracic Oncology, Yale Medical School, USA.*

15-18 April 2015, Geneva, Switzerland

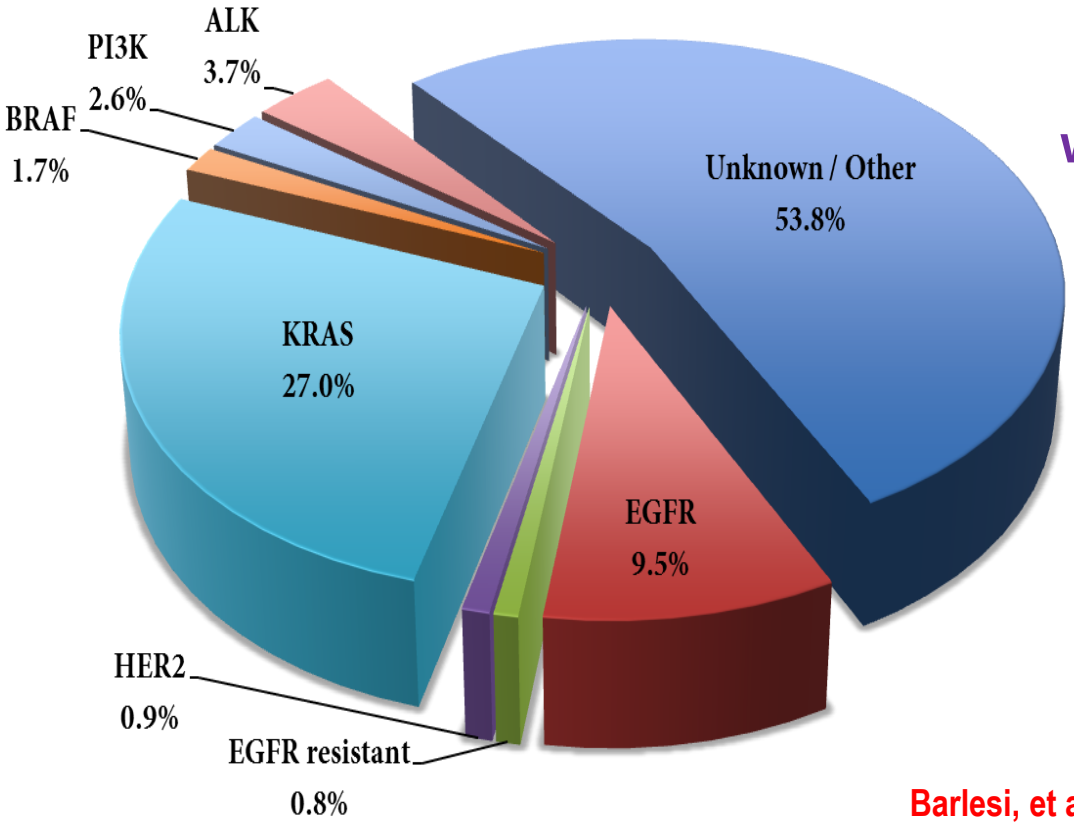
Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop Information | Research

DISCLOSURES

CONSULTING FEES: ROCHE, BRISTOL-MAYERS-SQUIB, MSD, BOEHRINGER-INGELHEIM, NOVARTIS

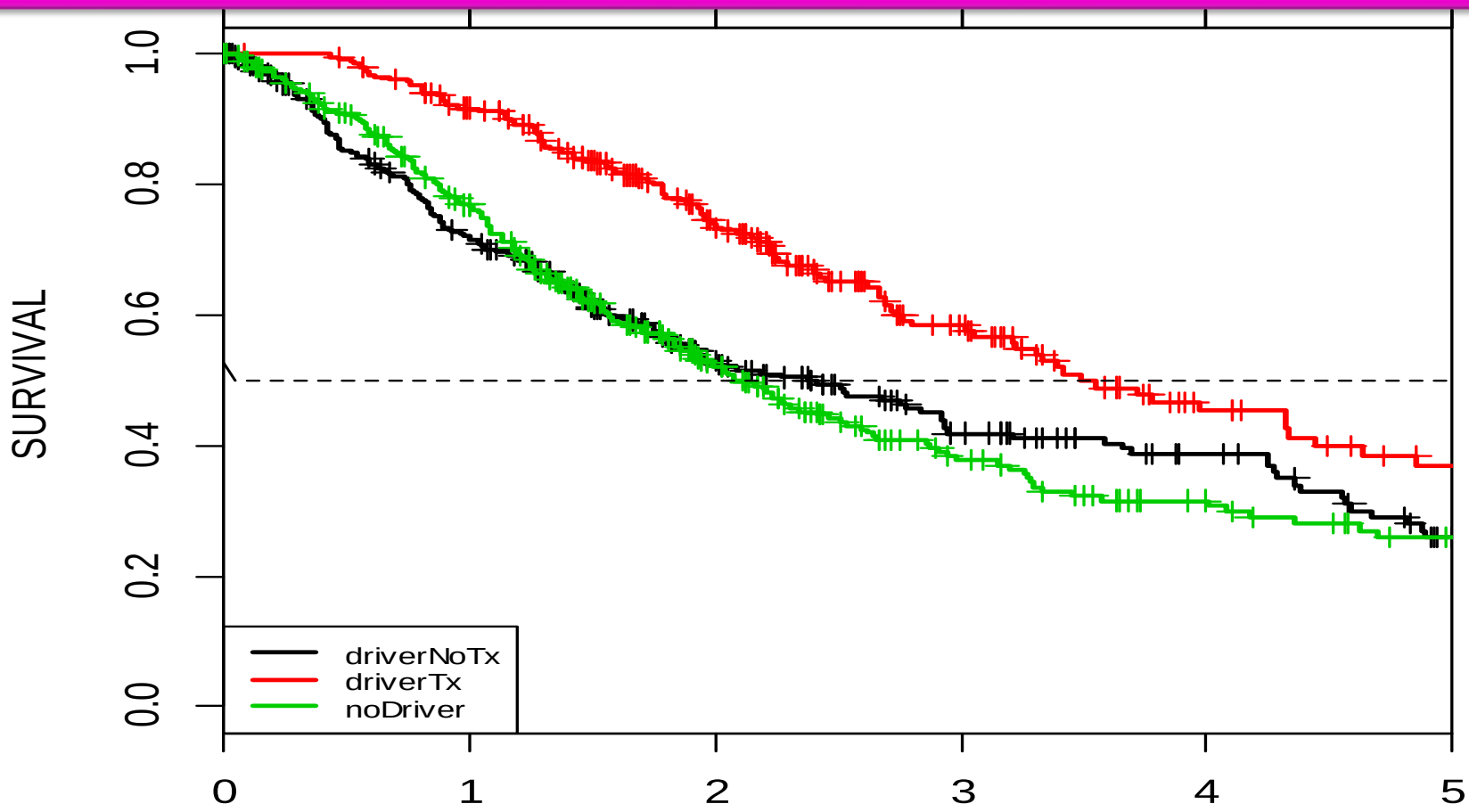
Digging in the Lung Cancer Genome



Driver mutations in 10,000 patients with non-squamous NSCLC

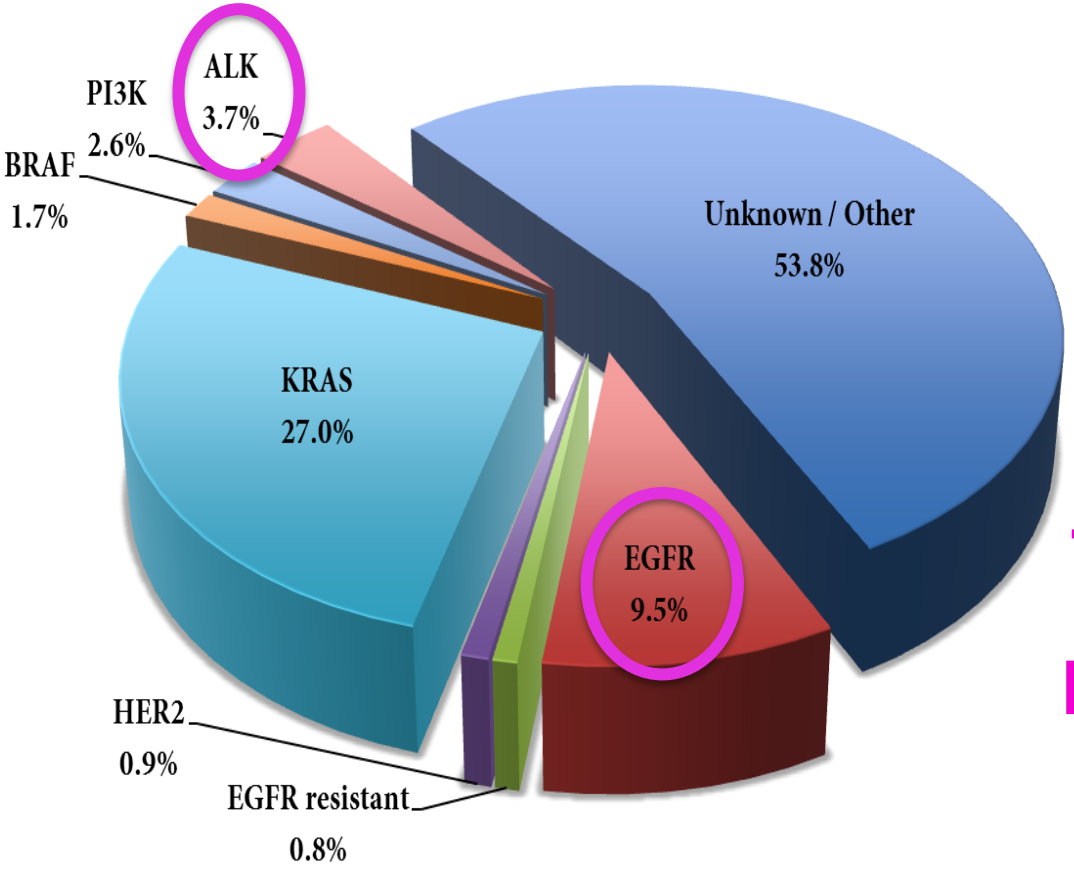
Barlesi, et al. ASCO 2013

NSCLC Survival of Patients with Drivers: Targeted vs Non-Targeted Therapies



Driver, no targeted therapy (A)	313	2.4 years (1.8 to 2.9)
No driver (B)	361	2.1 years (1.8 to 2.5)
Driver, targeted therapy (C)	264	3.5 years (3.2 to 4.6)

Digging in the Lung Cancer Genome

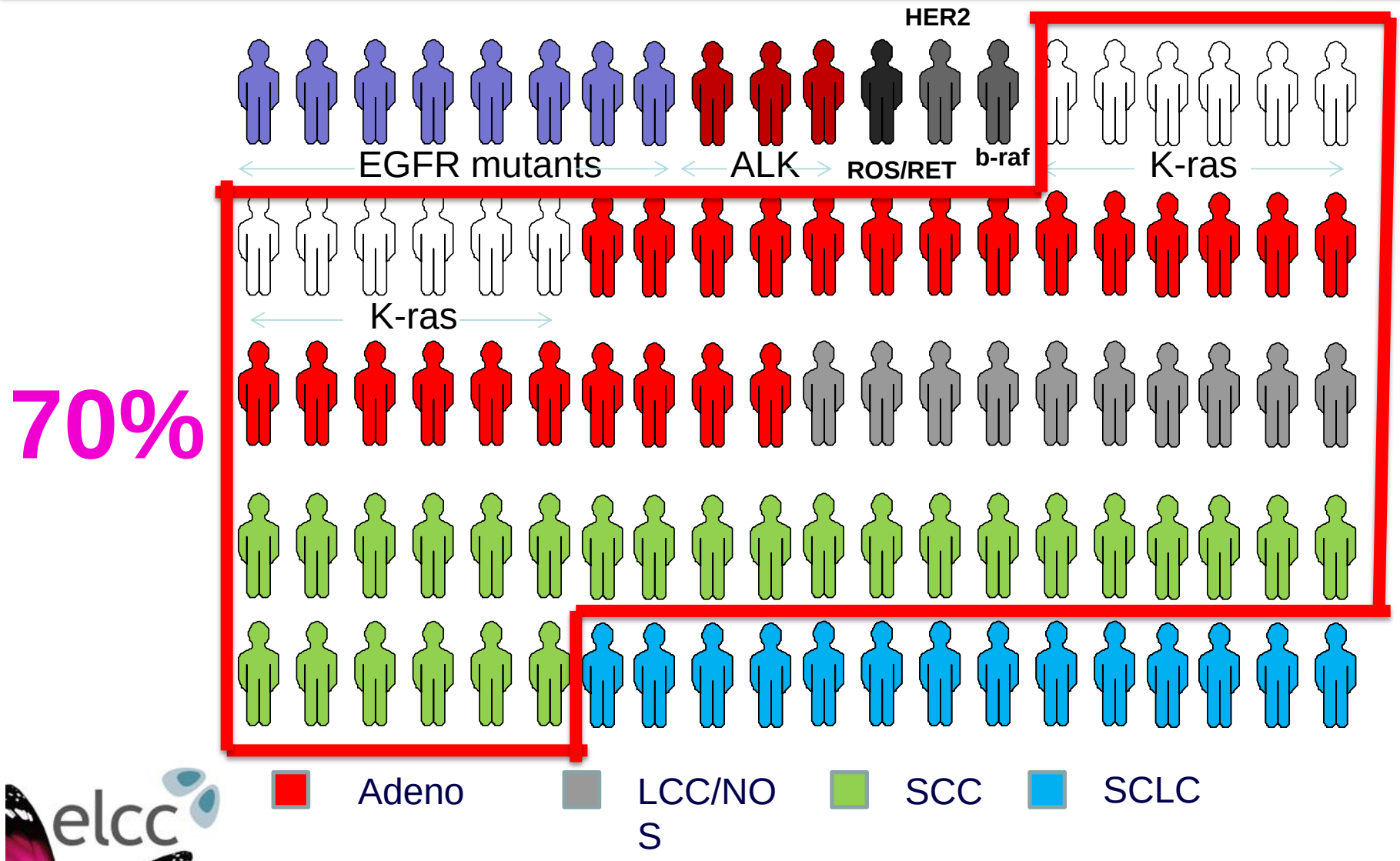


Barlesi, et al. ASCO 2013

Driver mutations in 10,000 patients with non-squamous NSCLC

The majority of NSCLC patients do not have an actionable biomarker

2015: the therapeutic landscape of advanced lung cancer



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Real Life Scenario

- Petros, male 56 yrs. old, builder, current smoker 80 p.y.
- medical history of hypertension and diabetes well controlled
- onset of dyspnea two months ago, gradually increasing
- large left apical mass 5 cm, multiple smaller lesions in both lungs, large left pleural effusion and left adrenal gland mass and multiple bone lesions.
- no brain, liver or bone disease

Real Life Scenario

- CT guided FNB: adenocarcinoma
- EGFR mutation: negative
- ALK-EML4 translocation: negative
- ROS mutation: negative
- ECOG PS:1
- He refused recruitment in our clinical trials program

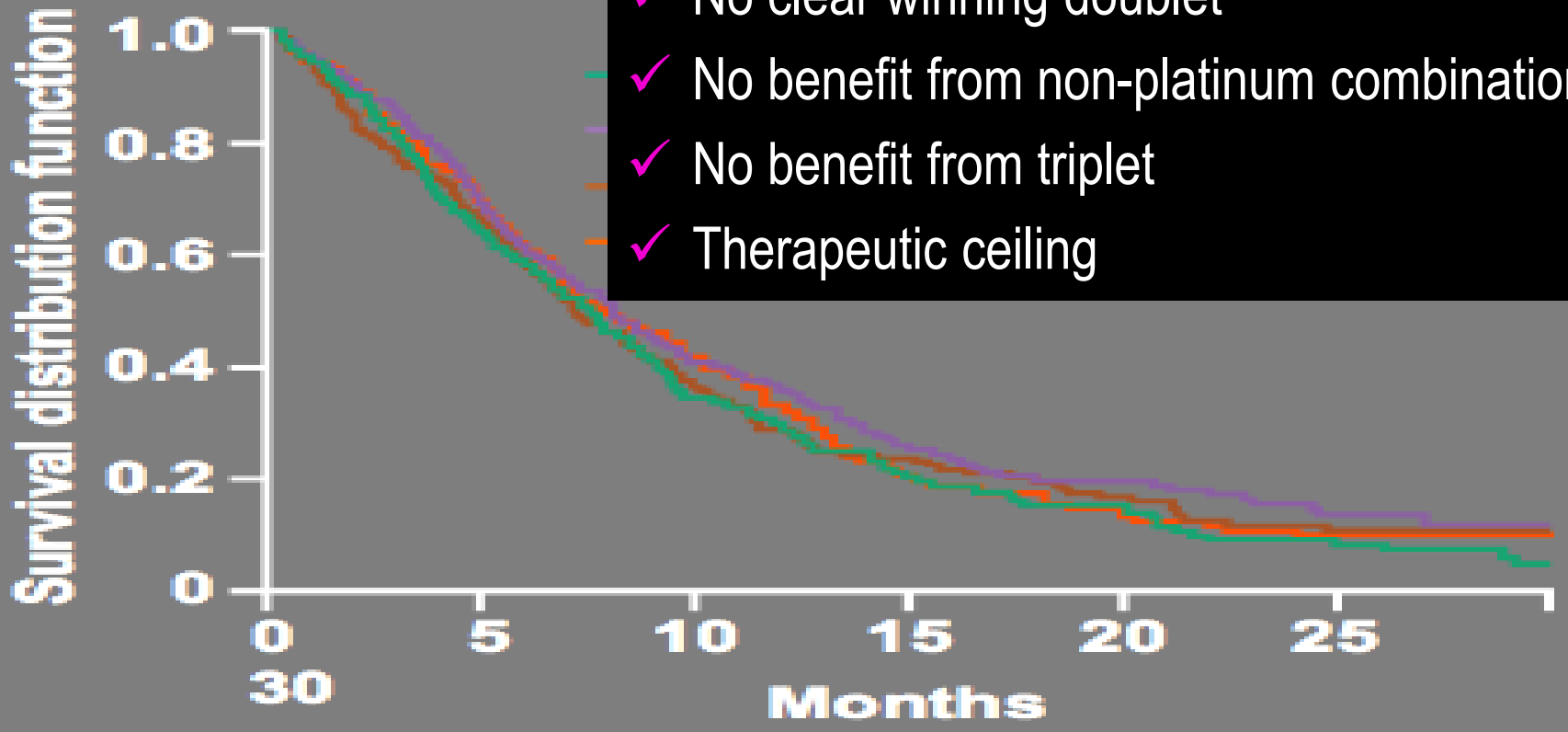
NSCLC 2002:

UNSELECTED CYTOTOXIC CHEMOTHERAPY

(ECOG 1594)

MEDIAN OVERALL SURVIVAL 6-8 MONTHS

- ✓ 1 yr survival plateau at about 35-40%
- ✓ No clear winning doublet
- ✓ No benefit from non-platinum combinations
- ✓ No benefit from triplet
- ✓ Therapeutic ceiling



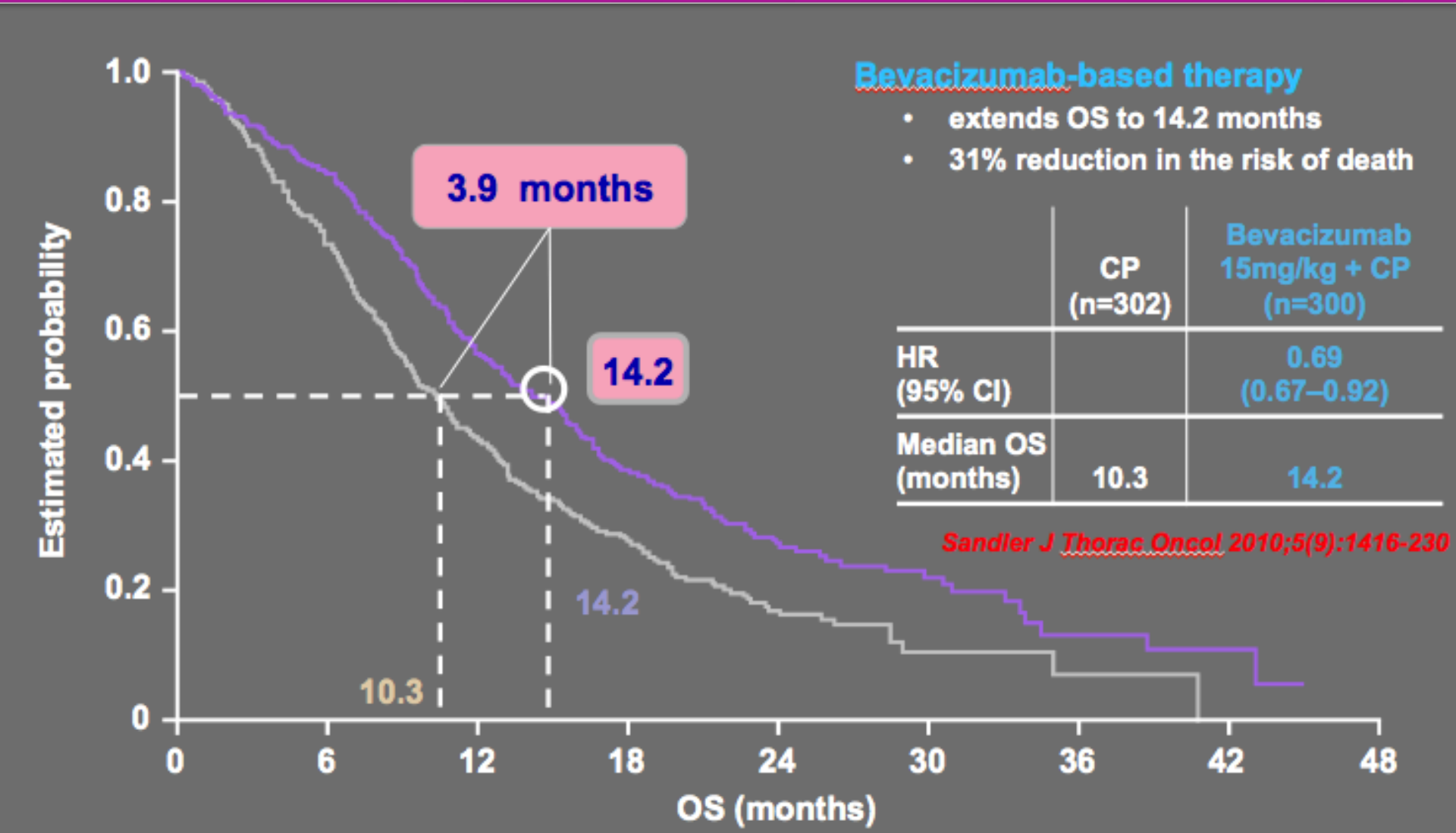
Schiller JH, et al. N Engl J Med 2002;346:92–8

NSCLC 2006: ADENOCARCINOMA

ADDITION OF BEVACIZUMAB TO CHEMOTHERAPY

OS 14 MONTHS

(E4599)



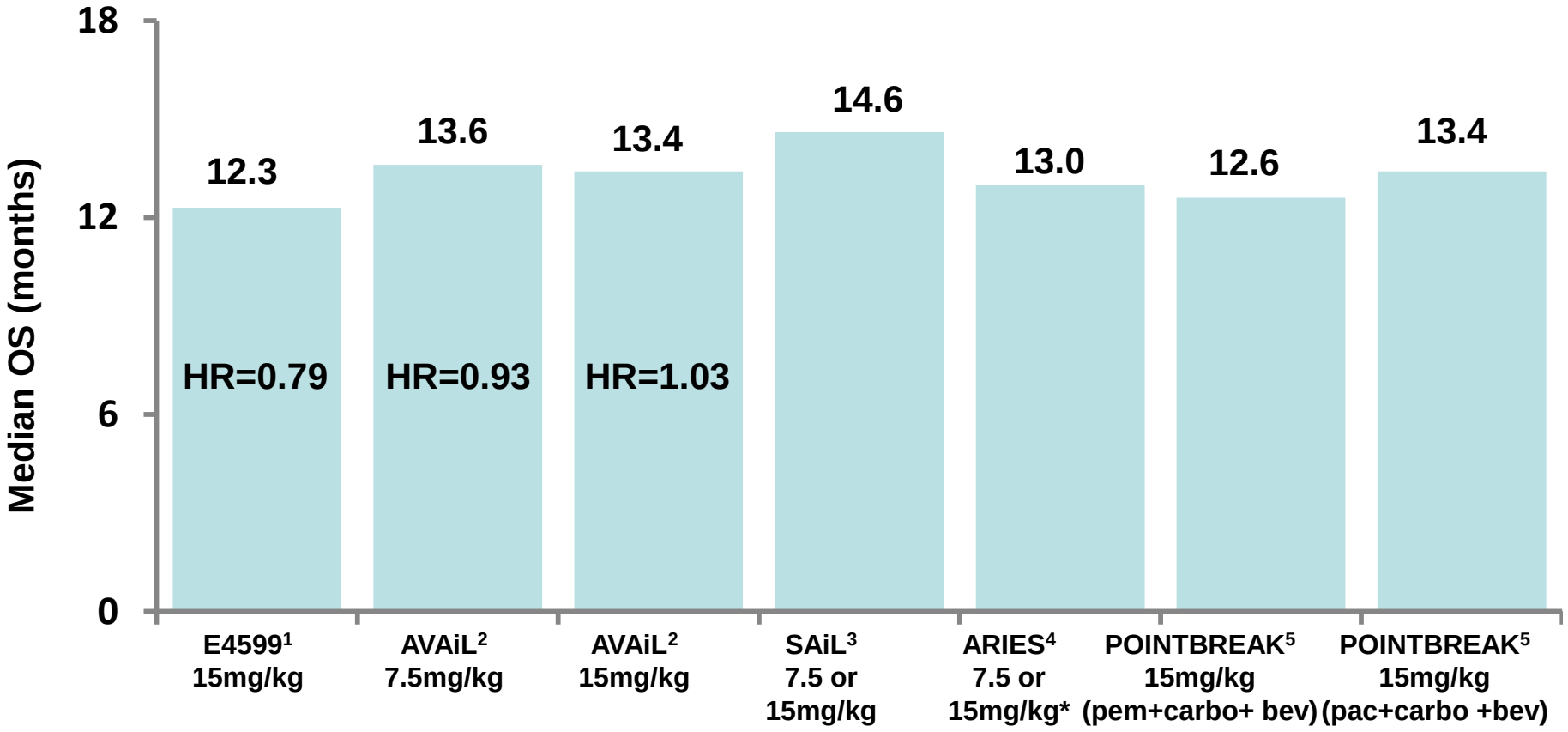
	CP (n=302)	Bevacizumab 15mg/kg + CP (n=300)
HR (95% CI)		0.69 (0.67–0.92)
Median OS (months)	10.3	14.2

Sandler J Thorac Oncol 2010;5(9):1416-230

Bevacizumab 1st Line Adeno NSCLC Randomized Trials

	E4599[1]		AVAiL[2,3]			JO19907[4]	
Outcome	PAC-CP-BEV	PAC-CP	CP-GEM (7.5)	CP-GEM (15)	PAC	PAC-CP-BEV	PAC-CP
ORR, %	35	15	34.1	30.4	20.1	60.7	31.0
	P <.001					0.001	
HR for PFS	0.66 (*P* <.001)		0.75 (*P* = .003)	0.82 (*P* = .03)		0.61 (*P* = .009)	
Median PFS, months	6.2	4.5	6.7	6.5	6.1	6.9	5.9
HR for OS	0.79 (*P* = .003)		0.93 (NS)	1.03 (NS)		0.99 (*P* = .95)	
Median OS, months	12.3	10.3	13.6	13.4	13.1	22.8	23.4

Bevacizumab: consistent OS >1 year in NSCLC



*At Investigators discretion

1. Sandler, et al. NEJM 2006
2. Reck, et al. Ann Oncol 2010
3. Crinò, et al. Lancet Oncol 2010
4. Lynch, et al. J Thorac Oncol 2014
5. Patel, et al. JCO 2013

Angiogenesis inhibitors
Status April 2015

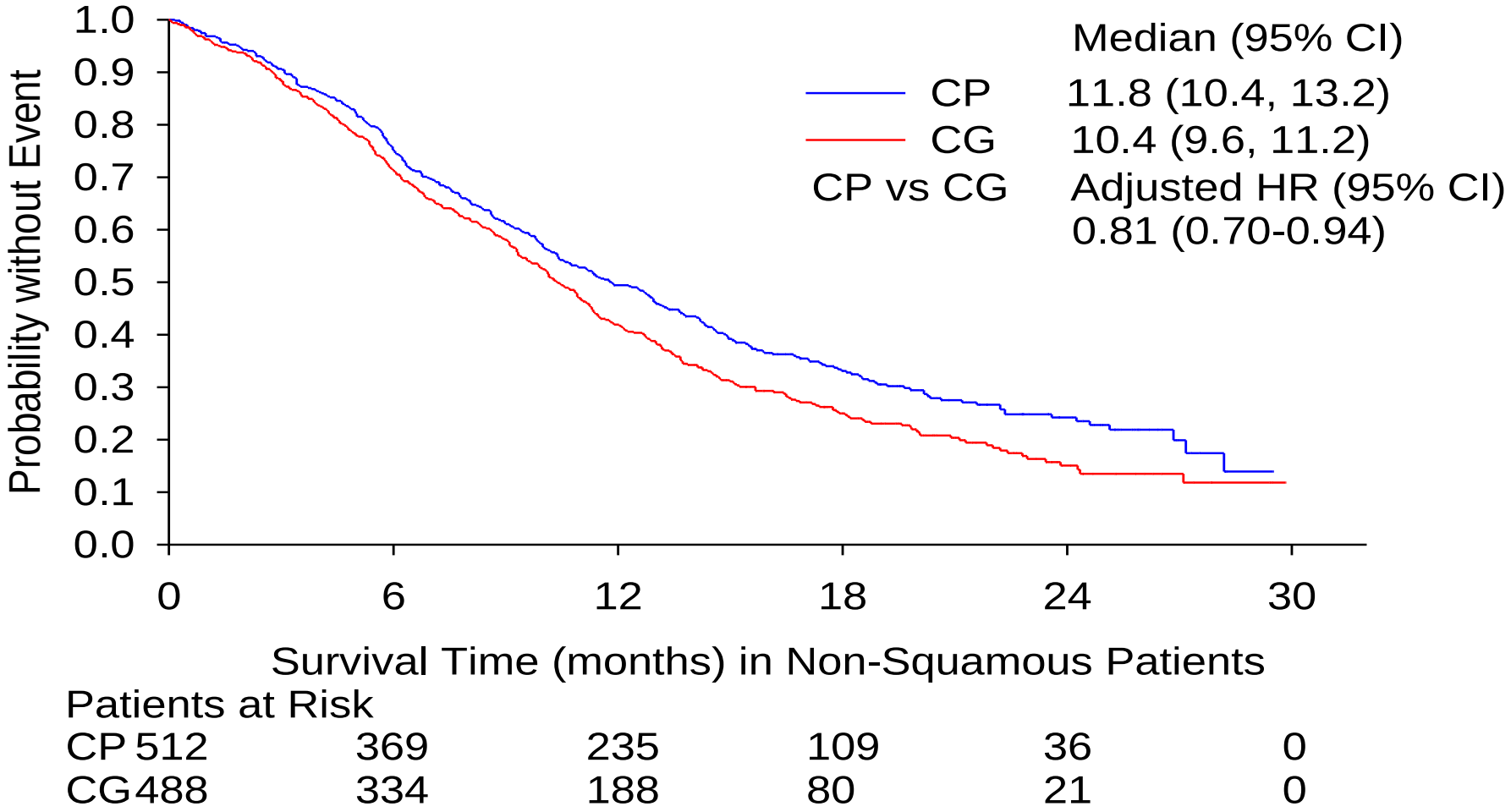
- **Bevacizumab shows efficacy in non-squamous NSCLC**
  - Dose & duration ? Biomarker ? Type of chemotherapy ?
- **Bleedings in squamous NSCLC**
- **Failures of TKIs**

First-line treatment	Second-line treatment
Sorafenib	Vandetanib
Cediranib	Aflibercept
Motesanib	
Vadimezan	

- **Nindetanib plus chemotherapy (LUME-Lung 1 & 2)**
- **Ramucirumab plus docetaxel (REVEL)**
- **Combinations with Immunotherapy**
- **Angiogenesis is one of many factors that affect outcome.**

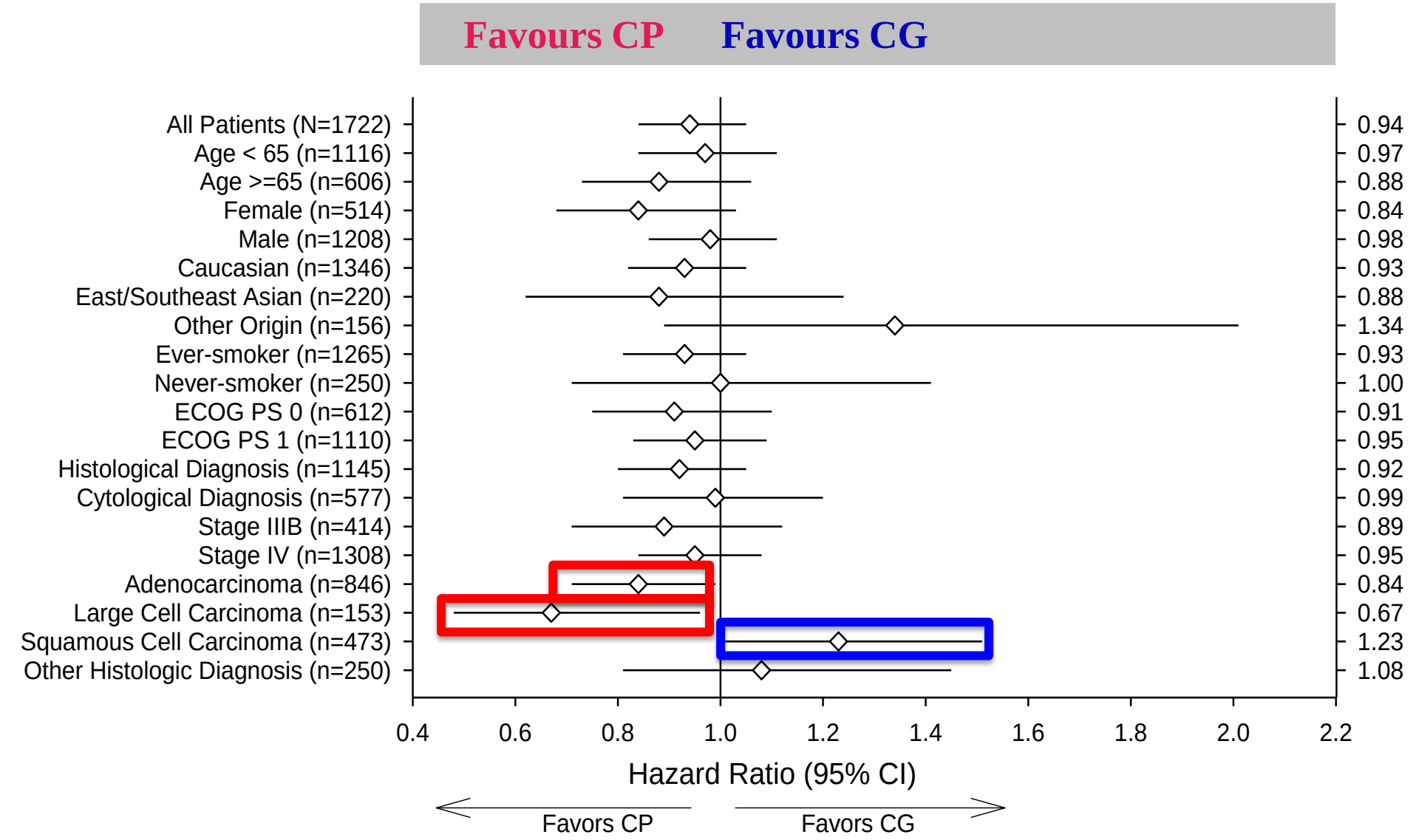
NSCLC 2009: ADENOCARCINOMA

(JMDB Trial) PEMETREXED OS 13 MONTHS

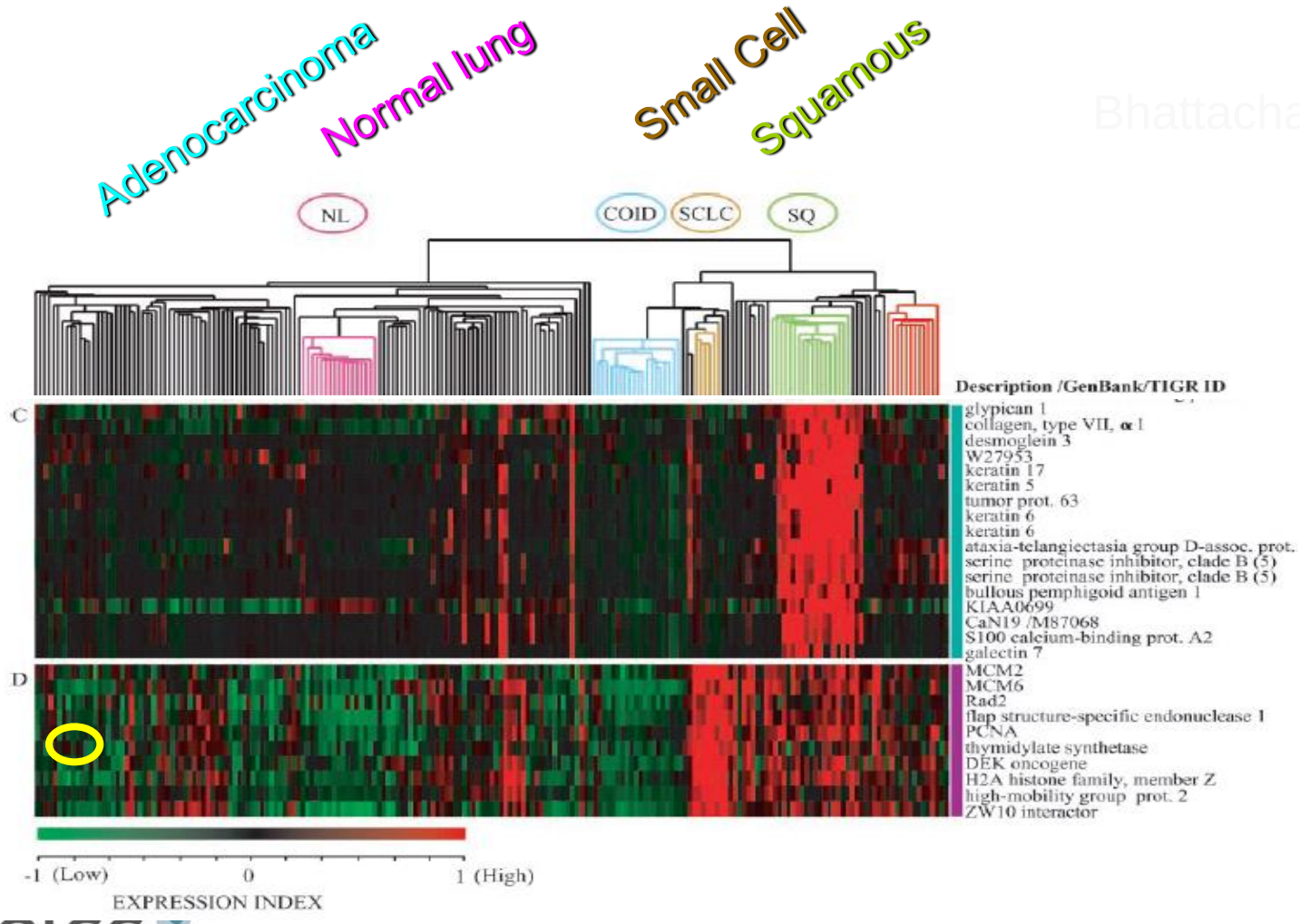


NSCLC 2009: ADENOCARCINOMA PEMETREXED TARGETS TS

(JMDB Trial)



Thymidylate Synthtase Expression in Lung Cancer



TS

Bhattacharjee PNAS 2001

- SCLC – High TS
- Squamous – High TS
- Adeno – Low TS

Histological classification is mandatory for decision making in advanced NSCLC

- Cisplatin superior to carboplatin in adenocarcinoma **Ardizzoni, JNCI 2007**
- Benefit of bevacizumab added to 1st L chemo in non-squamous NSCLC
  Sandler, JCO 2006; Reck, JCO 2009
- Differential effect of pemetrexed in non-squamous vs. squamous NSCLC
  Scagliotti, JCO 2008
- Histology will help decision making about molecular analysis

The diagnosis of "non-small cell lung cancer" is no longer acceptable

Real Life Scenario

- Adenocarcinoma
- No hemoptysis
- No brain mets
- No heart-related comorbidities
- Well controlled BP

The patient is eligible for Pemetrexed

The patient is eligible for Bevacisumab

WHAT IS THE OPTIMAL 1ST LINE REGIMEN IN BEVACISUMAB ELIGIBLE PTS?

- ✓ Platinum based Bevacisumab containing regimen?
- ✓ Platinum based Pemetrexed containing regimen?
- ✓ Platinum based combination of both?

Maintenance

- Believer or Not
- Continuation vs. Switch Maintenance
- Cytotoxic vs. Targeted Agent
- Patient's preferences

Overall goals of therapy

Prolong overall survival (OS) with good quality of life (QoL)

Diagnosis → **1st Line Therapy** → **Maintenance**

Goals of 1st L. Therapy

- ❑ Control symptoms
- ❑ Prevent early progression (during induction)
- ❑ Prolong OS
- ❑ Safety and reasonable toxicity

Overall goals of therapy

Prolong overall survival (OS) with good quality of life (QoL)

Diagnosis → **1st Line Therapy** → **Maintenance**

Goals of maintenance

- ❑ Maintain benefit obtained during induction
- ❑ Further delay of the progression
- ❑ Good tolerability during maintenance

Maintenance therapy: Phase III trials

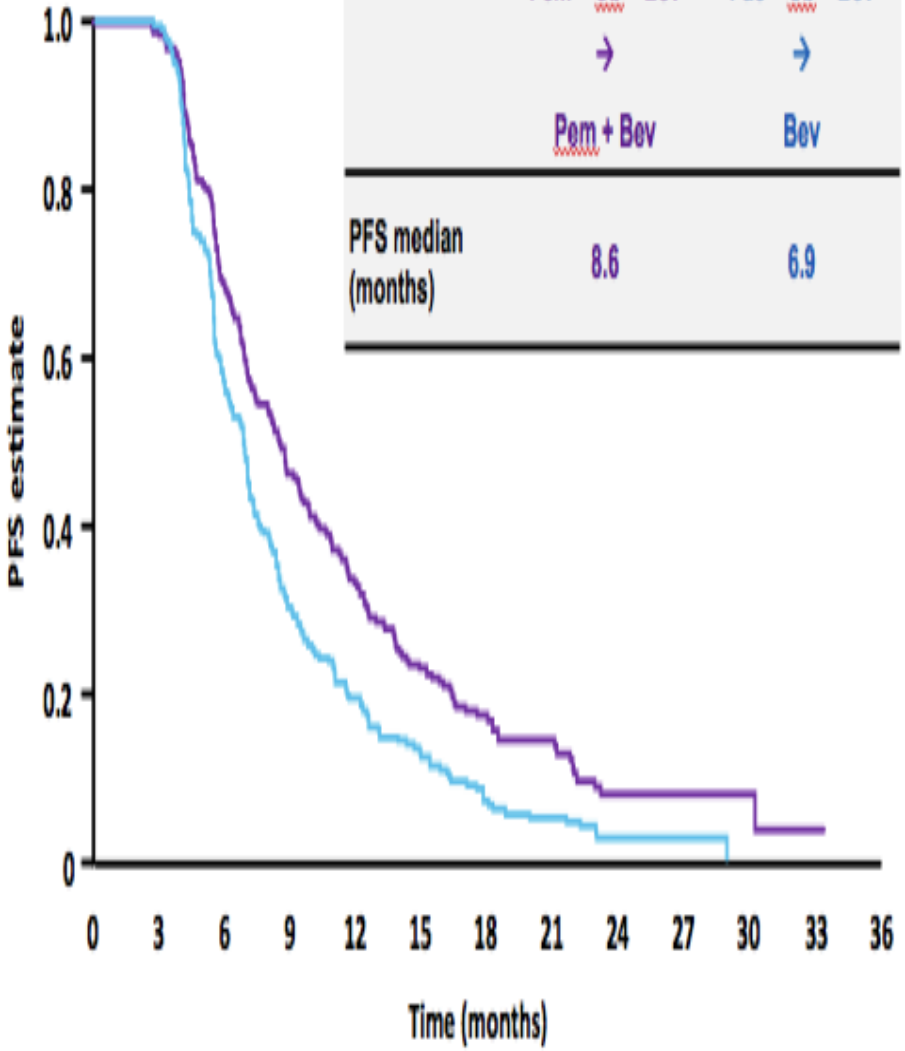
- **Vinorelbin** — *Westeel V et al. JCNI 2005, 97, 499*
- **Gemcitabine**
  - CECOG — *Brodowicz T et al. Lung Cancer 2006, 52, 155*
  - US-Studie — *Belani CP et al. JCO 2010, 28, 15s (Abstr 7506)*
  - IFCT-GFPC — *Perol M et al. J Clin Oncol 2012, 30, 3516*
- **Pemetrexed**
  - JMEN — *Ciuleanu T et al. Lancet 2010, 374, 1432*
  - PARAMOUNT — *Paz-Ares L et al. Lancet Oncol 2012, 13, 247*
  - AVAPERL — *Barlesi F et al. JCO 2013 & Ann Oncol2014, 25, 1044*
- **Erlotinib**
  - SATURN — *Cappuzzo F et al. Lancet Oncol 2010, 11, 521*
  - IFCT-GFPC — *Perol M et al. J Clin Oncol 2012, 30, 3516*
- **Beva + Erlo** (ATLAS) — *Johnson BE et al. JCO 2013, 31, 3926*
- **Gefitinib** (INFORM) — *Zhang L et al. Lancet Oncol 2012, 13, 466*

PointBreak: 1st L Best Chemo with Bev.

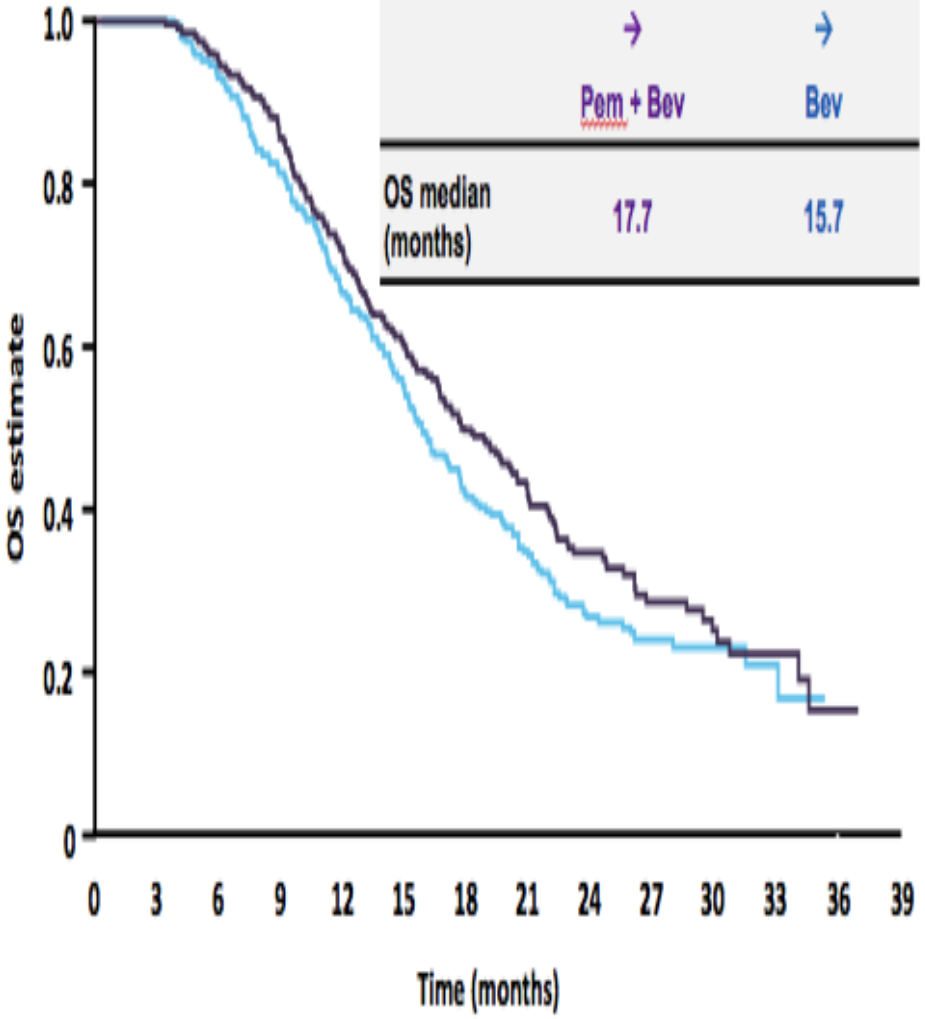
(Patel et al JCO 2013)

maintenance population (exploratory)

	Pem + Cb + Bev → Pem + Bev	Pac + Cb + Bev → Bev
PFS median (months)	8.6	6.9



	Pem + Cb + Bev → Pem + Bev	Pac + Cb + Bev → Bev
OS median (months)	17.7	15.7



PointBreak:

(Patel et al 2012)

1st L Best Chemo with Bev. Toxicity Profile

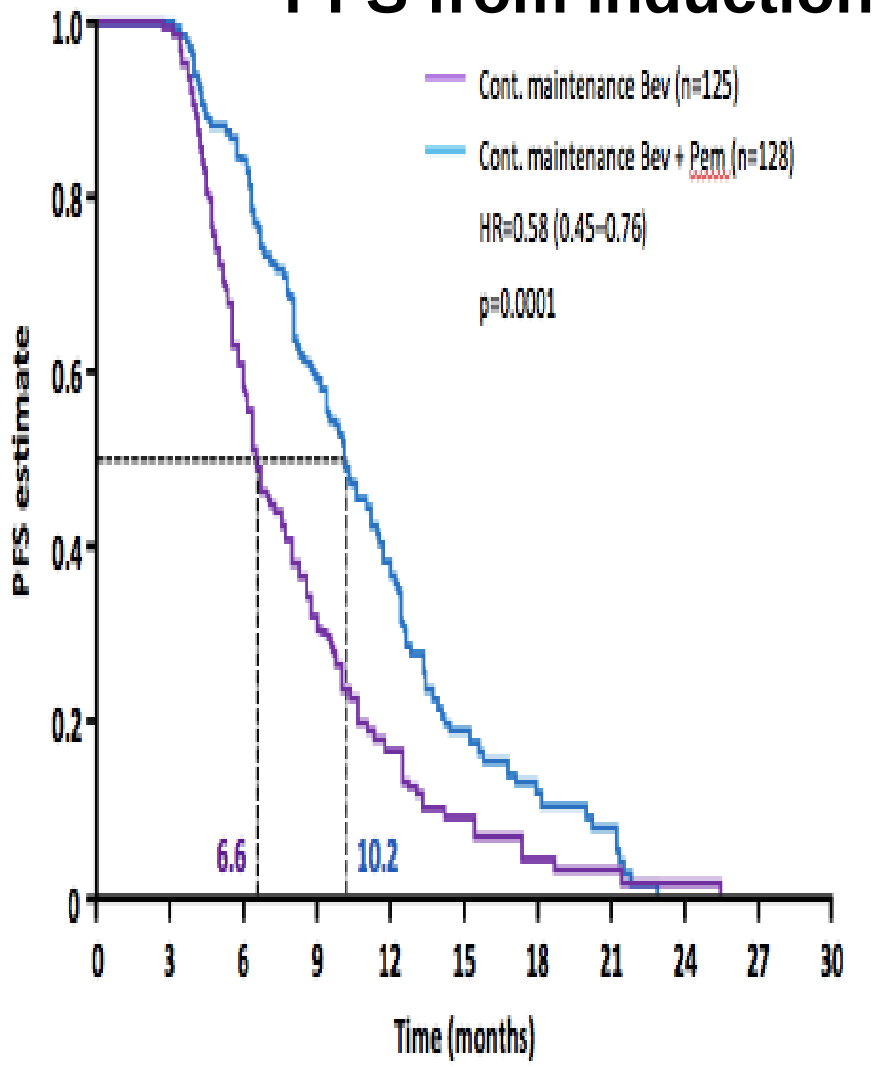
	PEM + CP + BEV (N = 442) %	PAC + CP + BEV (N = 443) %	PEM + CP + BEV (N = 442) %	PAC + CP + BEV (N = 443) %
	Grade 1/2	Grade 1/2	Grade 3/4 (5)	Grade 3/4 (5)
Anemia†	31.0	24.4	14.5	2.7
Thrombocytopenia†	17.9	17.2	23.3	5.6
Neutropenia†	14.7	8.4	25.8	40.6
Febrile neutropenia†	0.2	0.2	1.4	4.1
Fatigue†	42.1	39.5	10.9	5.0
Hemorrhage GI/pulmonary	3.6	3.8	1.8 (0.5)	0.5 (0.7)
Thromboembolic event	0.5	0.2	3.2	2.0
Neuropathy/sensory†	11.8	35.7	0.0	4.1
Alopecia*	6.6	36.8	-	-
Other grade 5 events (PEM Arm/PAC Arm %)	Includes: CNS ischemia (0.2/0.7); cardiac events (0.2/0.7); ARDS (0.5/0); infection (0.2/0); other hemorrhage (0.2/0.2)			

†Significant difference between arms, for grade 3/4 toxicities *Maximum grade is grade 2.

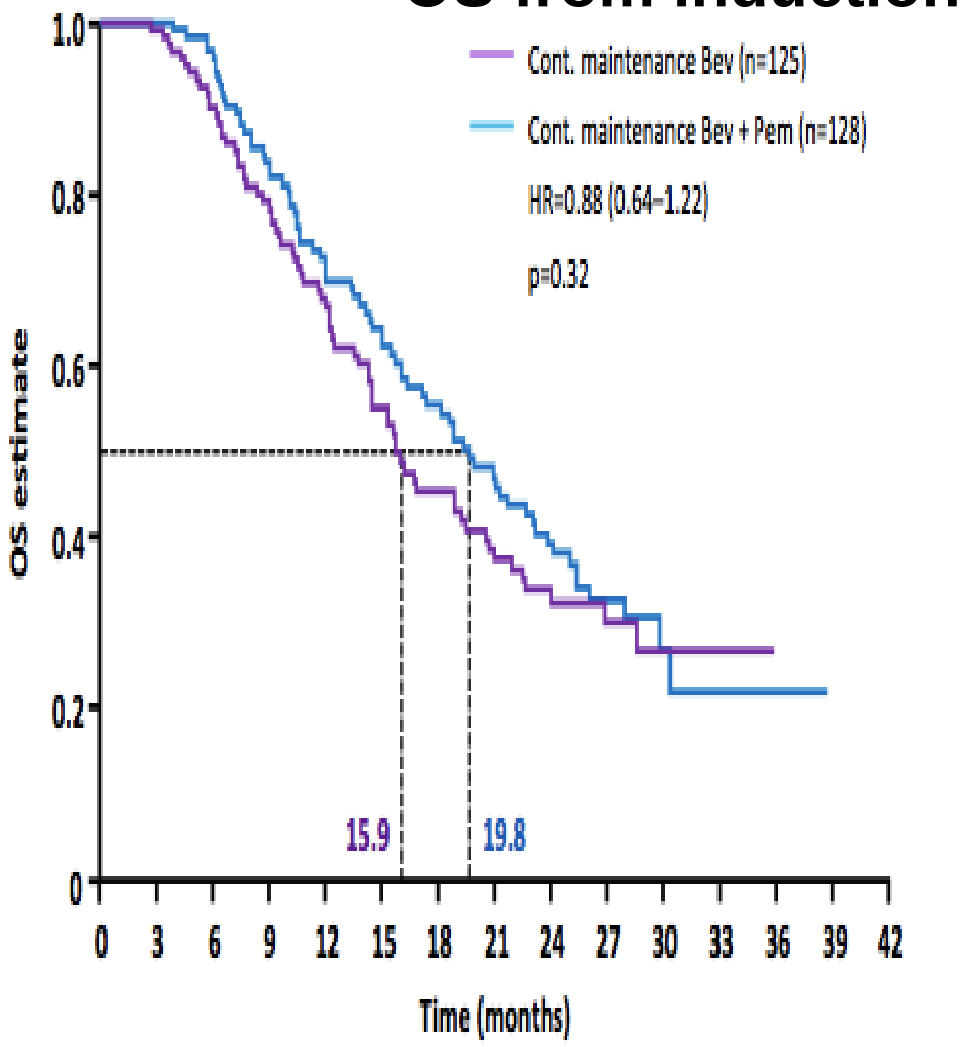
AVAPERL: Bev maint ± Pem

Barlesi et al Ann Oncol 2014

PFS from induction



OS from induction



CONTINUATION MAINTENANCE TREATMENT OS

- ✓ Different trials with different design
- ✓ Improvement of PFS for maintenance with both Bev & Pem
- ✓ No impact on OS
- ✓ Combination more toxic (*Zhang et al meta-analysis*)
- ✓ No Impact in the QoL

ONGOING MAINTENANCE TRIALS

ECOG 5508 NCT01107626	Carboplatin Paclitaxel Bevacizumab X 4 cycles	Bevacizumab vs. Pemetrexed vs. Bevacizumab/Pemetrexed
CALGB 30607 NCT00693992	Platinum-based Therapy (± Bevacizumab) X 4 cycles	Sunitinib vs. Placebo
S130 NCT00948675	Carboplatin Paclitaxel Bevacizumab vs. Carboplatin Pemetrexed X 4 cycles	Bevacizumab vs. Pemetrexed

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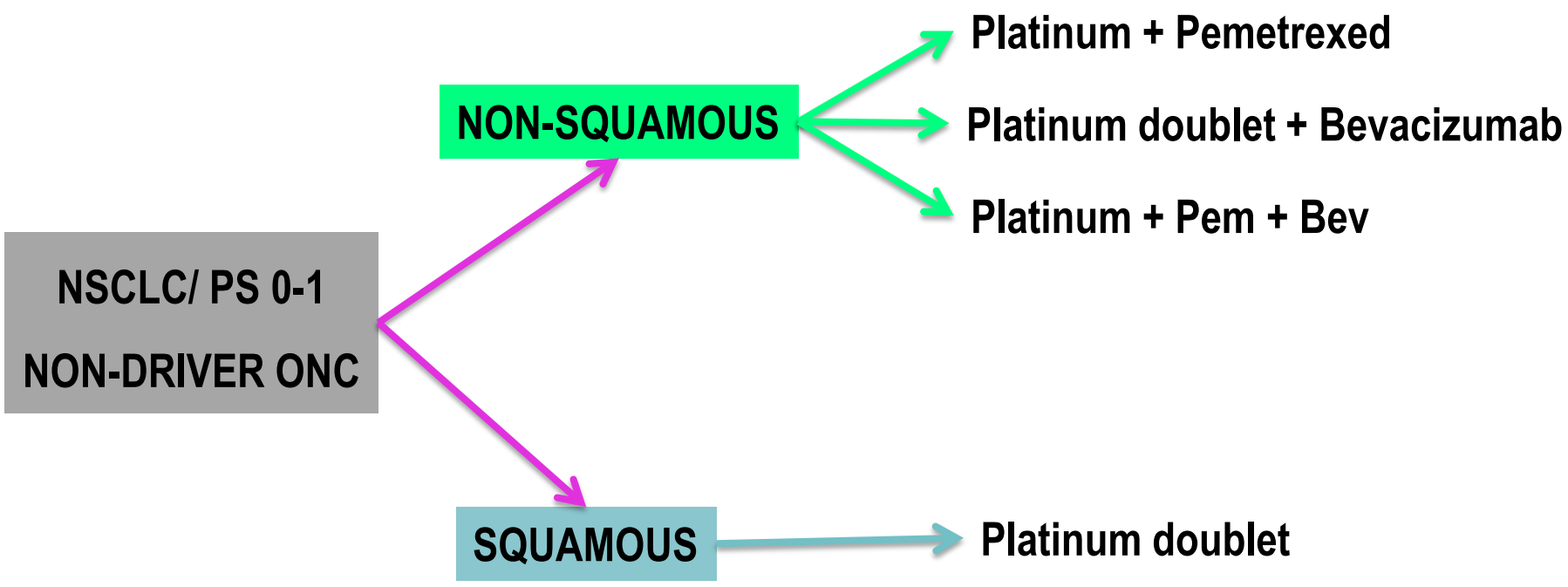

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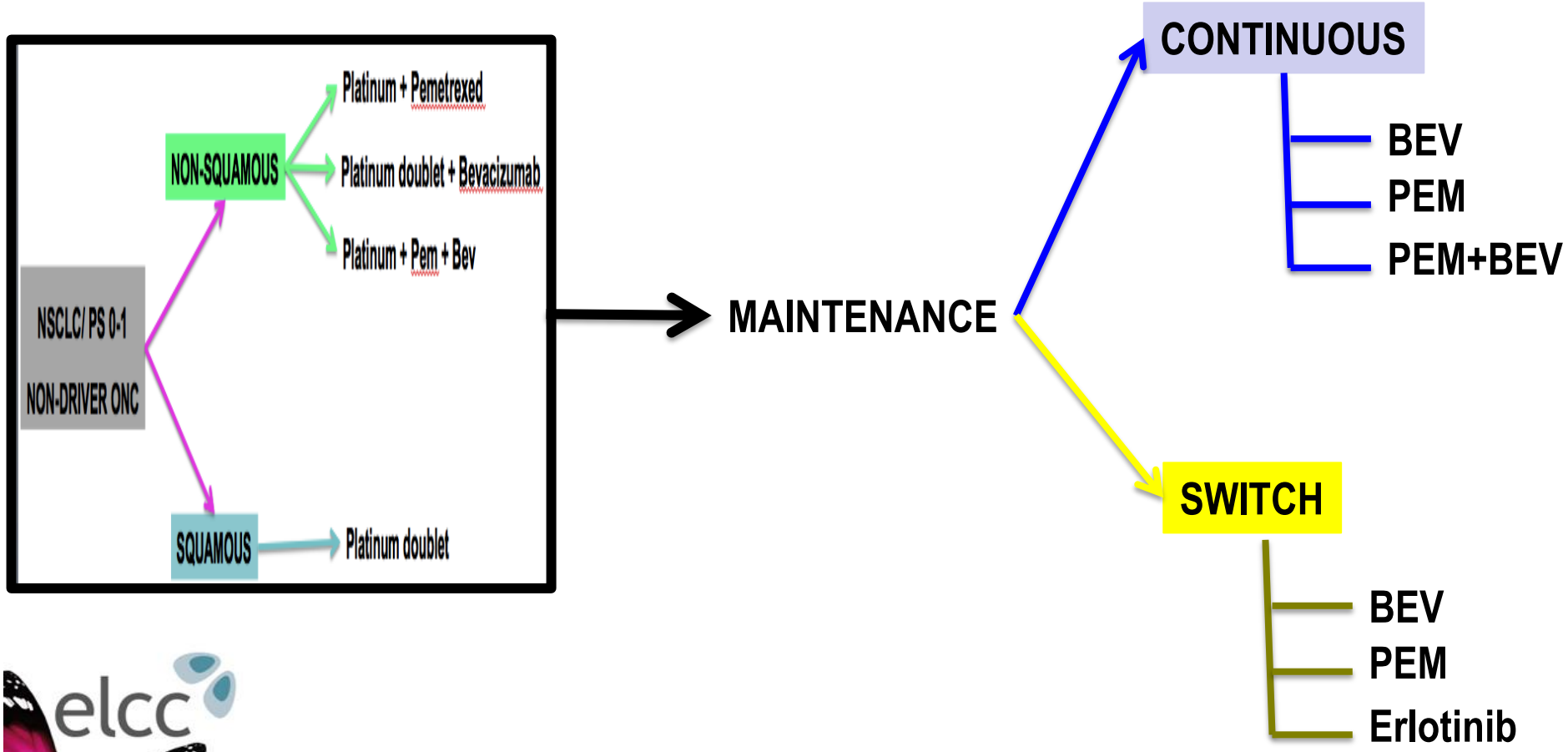

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European Society of Thoracic Surgeons 1993

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Real Life Scenario

- ✓ Cisplatin + Pemetrexed 4 cycles
- ✓ PR / PS:0
- ✓ Regimen well tolerated
- ✓ Pem maintenance therapy for 9 months
- ✓ Disease Progression

15-18 April 2015, Geneva, Switzerland

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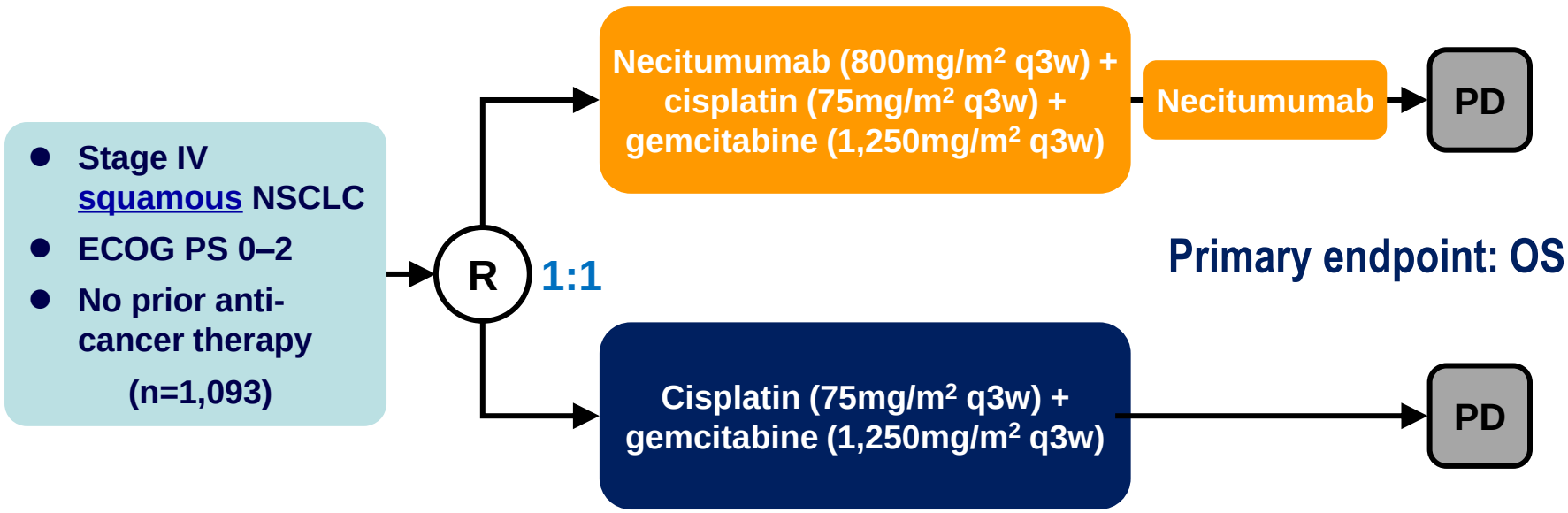
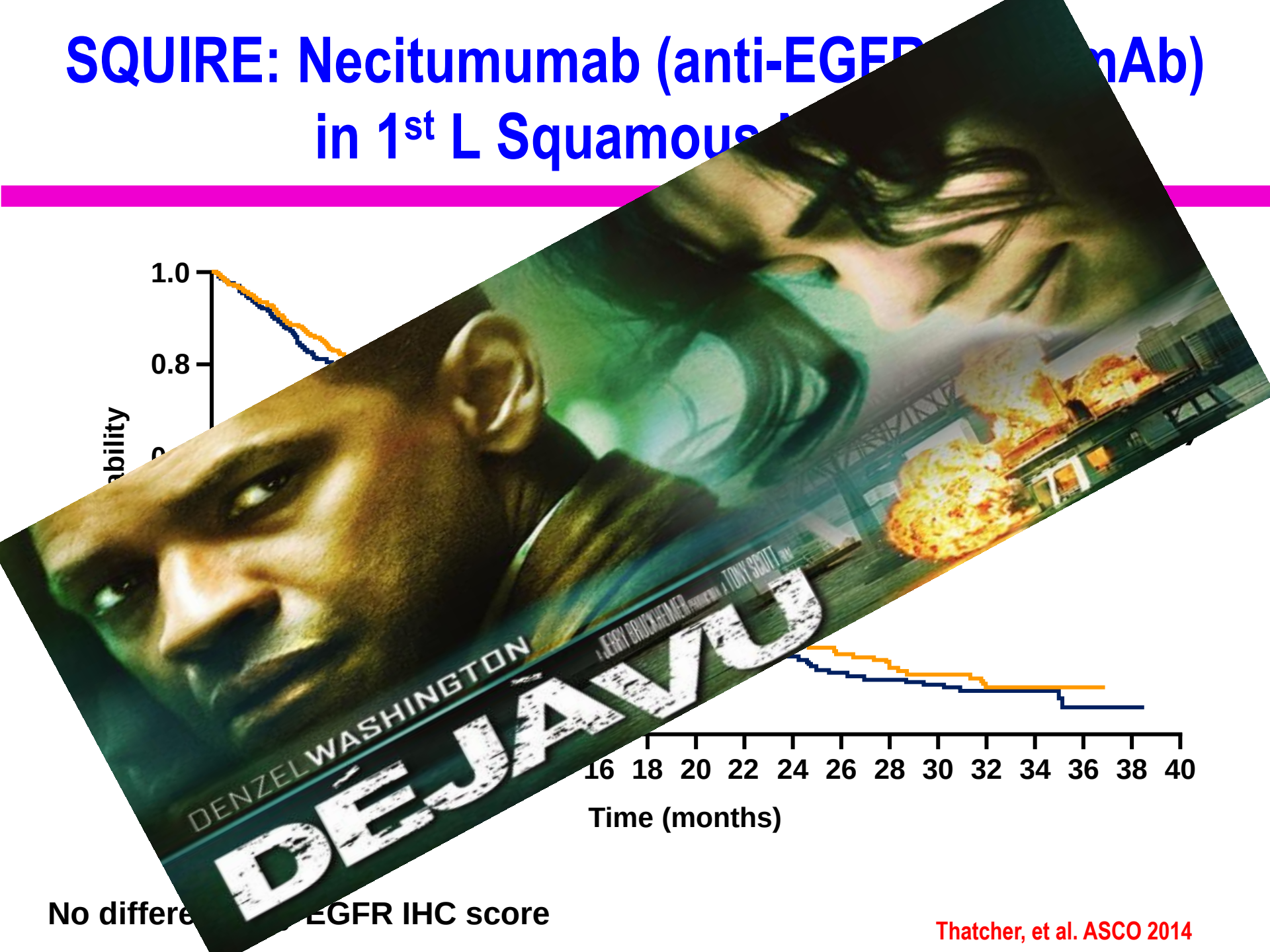
SQUIRE: Necitumumab (anti-EGFR IgG1 mAb) in 1st L Squamous NSCLC



Patients selection NOT based on EGFR protein expression

NCT00981058
Thatcher, et al. ASCO 2014

SQUIRE: Necitumumab (anti-EGFR mAb) in 1st L Squamous



No differe EGFR IHC score

Thatcher, et al. ASCO 2014

Carboplatin and Paclitaxel ± Veliparib in Previously Untreated Advanced NSCLC

Phase II trial

Metastatic or advanced NSCLC
(N = 158; ~ 50 sites, 8 countries)

→ Carboplatin/Paclitaxel* + Veliparib 120 mg BID† (n = 105)

2:1 randomization

→ Carboplatin/Paclitaxel* + Placebo BID† (n = 53)

*Carboplatin AUC 6 mg/mL/min and paclitaxel 200 mg/m^2 on Day 3 of 21.
†Veliparib/placebo on Days 1-7 of 21-day cycle.

Veliparib: A poly(ADP-ribose) polymerase inhibitor that interferes with DNA damage repair and sensitizes tumors to radiation and chemotherapy treatments

Ramalingam S, et al. 2014.

Carbo and Pacl ± Veliparib: PFS, OS, ORR

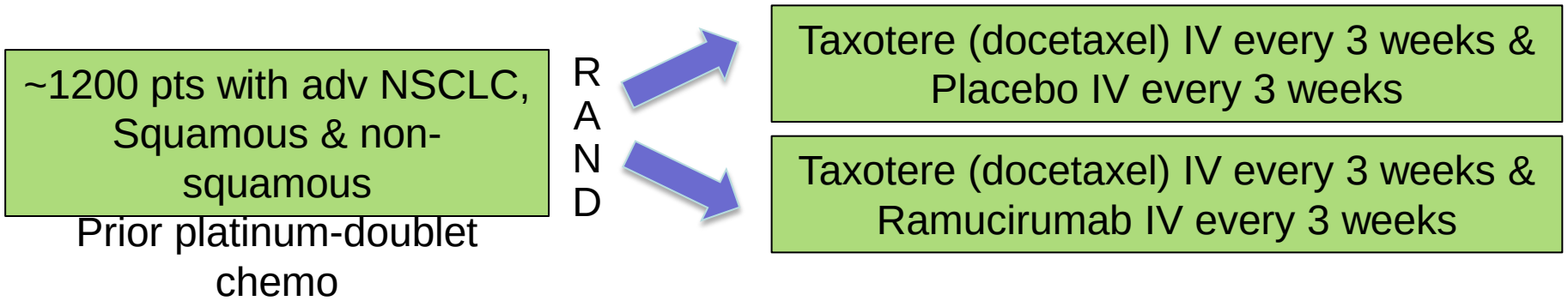
Ramalingam S, et al. 2014.

Outcome	Placebo and Carbo + Pacl (n = 53)	Veliparib and Carbo + Pacl (n = 105)	[illegible] HR*	[illegible] HR*
PFS, median mos (95% CI)				
Squamous				[illegible] (0.14-0.73)
Non[illegible]			[illegible]-1.71)	0.76 (0.41-1.42)
OS		[illegible]	0.77 (0.52-1.15)	0.71 (0.48-1.07)
Squ[illegible]		10.3 (8.3-13.2)	0.71 (0.41-1.23)	0.70 (0.39-1.24)
Nonsq[illegible]	[illegible].1 (4.8-14.6)	12.8 (8.0-17.5)	0.85 (0.48-1.51)	0.72 (0.40-1.29)
ORR, % (9[illegible]	28 (17-42)	31 (22-40)	--	--
DOR, median mos (95% CI)	3.3 (2.7-4.3)	6.9 (4.4-7.0)	0.11 (0.03-0.50)	--

- **improvements in PFS and OS**
- Particularly in the **squamous** histology subgroup
- **well tolerated**
- **Phase III trial** has been initiated (*M11-089; Clinical Trial NCT02106546*)

REVEL Trial: Ramucirumab for 2nd L NSCLC

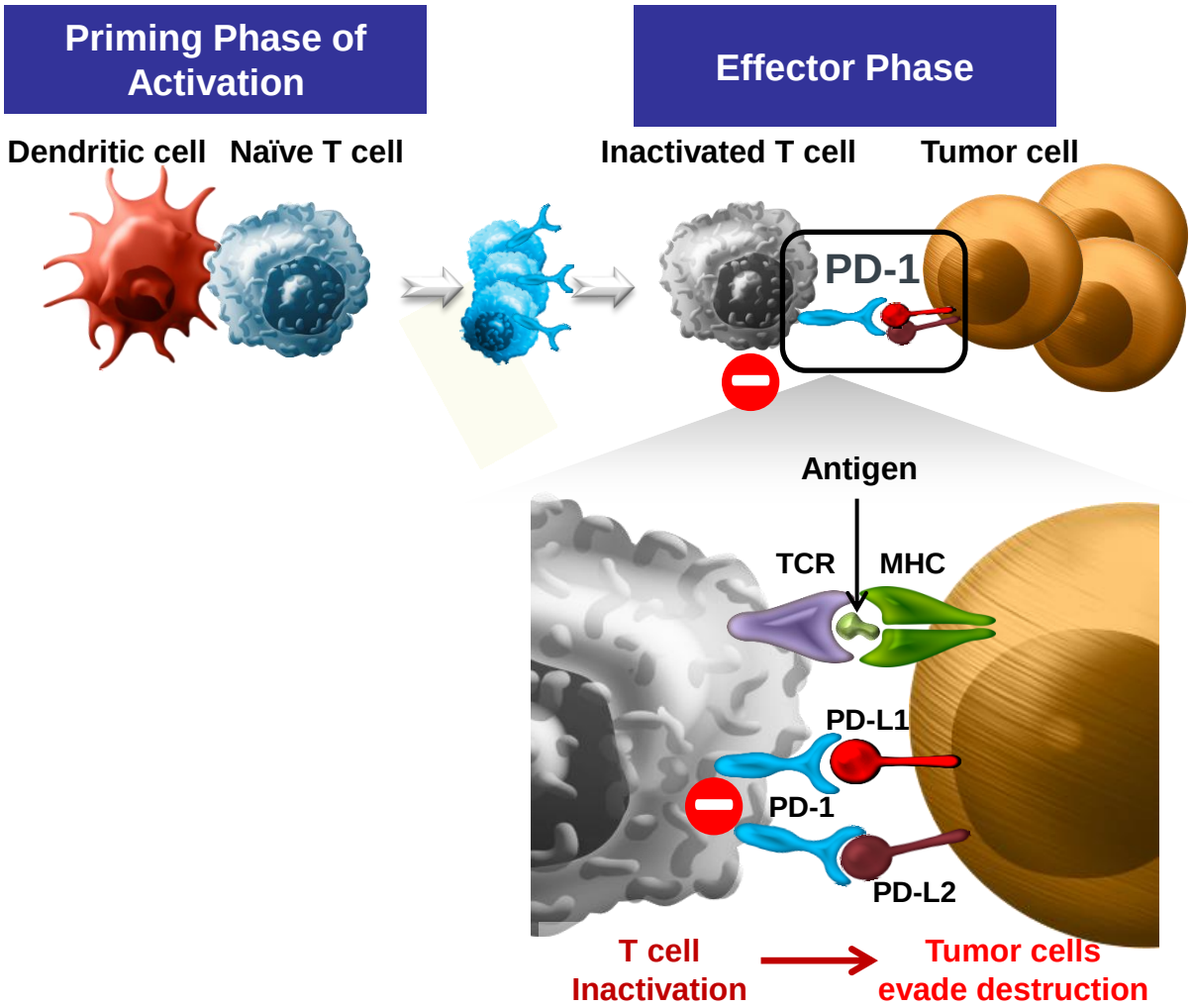
- An anti-angiogenic monoclonal antibody inhibitor of VEGF-R2



- Improves PFS & OS in all histologies

	RAM + DOC (N = 628)	PL + DOC (N = 625)	P
ORR (CR + PR)	22.9%	13.6%	<0.001
DCR (CR + PR +SD)	64.0%	52.6%	<0.001

Exploiting the PD-1 Immune Checkpoint Pathway



- PD-L1 and PD-L2 are the ligands of PD-1.
- Tumor cells express them to engage the PD-1 receptor on T cells and downregulate T-cell activity in the effector phase

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PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

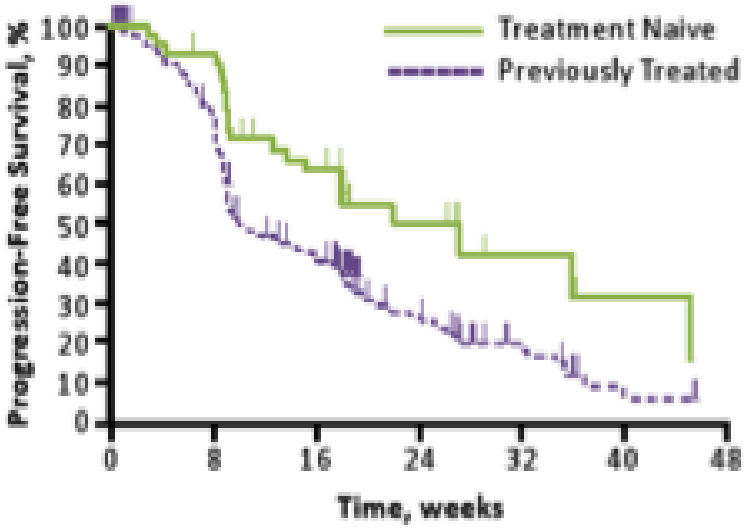
Survival outcomes in 1st line NSCLC patients treated with nivolumab plus platinum-based chemotherapy

	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis (n = 12)	Pem/Cis (n = 15)	Pac/Carb (n = 15)	Pac/Carb (n = 14)
ORR, %	33	47	47	43
SD, %	58	47	27	43
18-mo OS rate, %	33	60	40	86
Median OS, wks	51	83	65	NR

Antonia SJ, et al. Chicago Multidisciplinary Symposium in Thoracic Oncology 2014. Abstract 3.

Pembrolizumab monotherapy in 1st line NSCLC

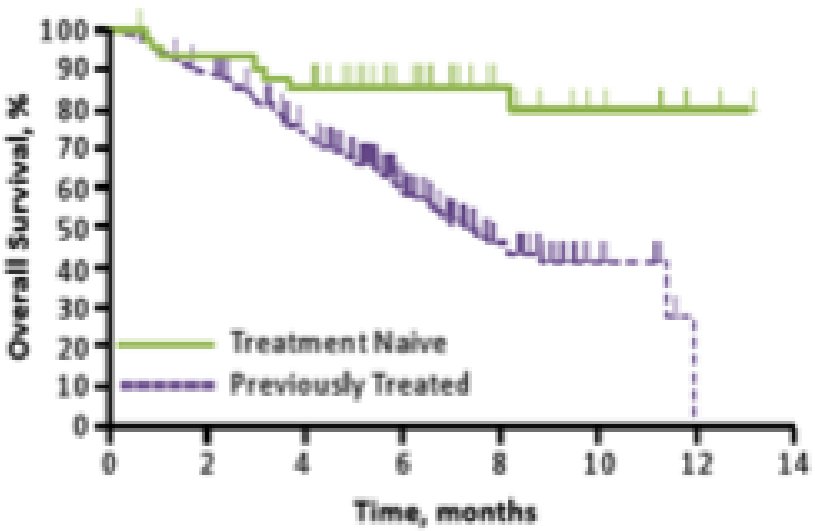
PFS (RECIST v1.1, Central Review)



n at risk							
Treatment Naive	45	39	25	11	4	2	0
Previously Treated	217	159	81	33	13	2	0

- Treatment naive
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%

OS

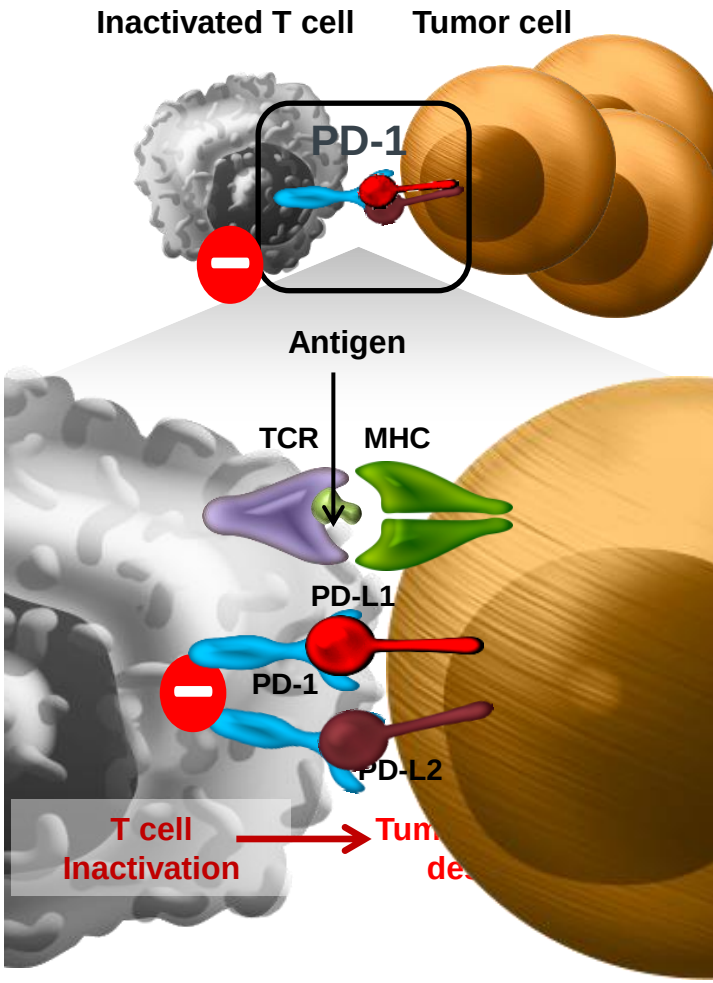


	45	41	38	24	13	7	2	0
	217	192	146	77	33	8	0	0

- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%

Immunotherapy in 1st L. NSCLC

- ✓ Anti PD-1 or anti PDL-1?
- ✓ Which molecule?
- ✓ Which surrogate marker?
- ✓ Which is the optimal combination?
- ✓ For how long?
- ✓ Short and long term toxicities
- ✓ Cost ??



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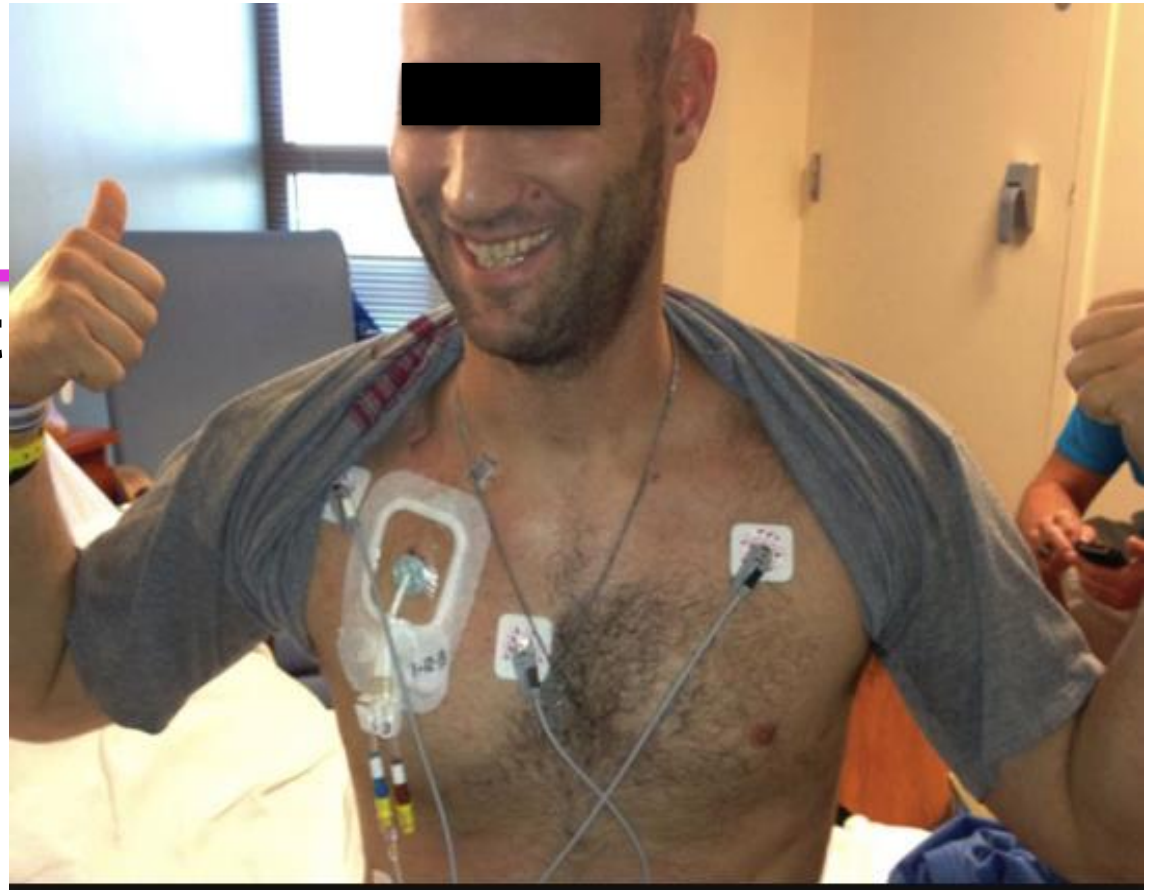
- ✓ Patient Selection
- ✓ Regimen Selection
- ✓ Toxicities Management
- ✓ Maintenance Issues



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