The Practical Application of Research Advances and Emerging Data in the Management of Non-Small Cell Lung Cancer

CME INFORMATION

TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of non-small cell lung cancer (NSCLC).

OVERVIEW OF ACTIVITY

Lung cancer is a devastating disease with a broad-reaching impact on public health, accounting for 14% of all new cancer cases in the United States and the most cancer-related deaths among both men and women. Development of new therapeutic strategies beyond cytotoxic chemotherapy has been the focus of extensive recent research and has led to an explosion in lung cancer genetic and biologic knowledge. The advent of these next-generation targeted treatments presents new promise of both efficacy and enhanced safety for patients with lung cancer but also challenges practicing oncologists to appropriately select individuals who may benefit from these agents and to determine how to integrate such therapies, as they become available, into standard lung cancer treatment algorithms. Several consensus- and evidence-based treatment guidelines are available and aim to assist clinicians with making lung cancer management decisions in the face of this dynamic clinical environment, but despite the existence of these tools, many areas of controversy persist within academic and community settings. This program uses a review of recent relevant publications and other relevant presentations, ongoing clinical trials, actual patient case discussions and Q&A to assist medical oncologists, hematology-oncology fellows and other healthcare providers with the formulation of up-to-date clinical management strategies, including referral of appropriate patients to ongoing pivotal clinical trials.

LEARNING OBJECTIVES

- Develop an evidence-based strategy for systemic treatment of localized NSCLC.
- Apply the results of emerging clinical research to the multimodality management of Stage III NSCLC.
- Use biomarkers, clinical characteristics and tumor histology to select individualized front-line and subsequent treatment approaches for patients with metastatic NSCLC.
- Compare and contrast the benefits and risks of combination chemobiologic, doublet and single-agent chemotherapy regimens when developing treatment plans for patients with advanced NSCLC.
- Recognize the effect of NSCLC tumor-specific mutations on relative response or resistance to treatment with EGFR tyrosine kinase inhibitors, ALK inhibitors and other emerging molecular-targeted agents.
- Identify patients with metastatic NSCLC who may experience clinical benefit from the addition of continuation or switch maintenance biologic therapy and/or chemotherapy.
- Recall the design of ongoing clinical trials evaluating novel investigational agents in NSCLC, and counsel appropriately selected patients about availability and participation.

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Heather Wakelee, MD
Associate Professor of Medicine
Division of Oncology
Stanford University School of Medicine
Stanford Cancer Institute
Stanford, California

Consulting Agreement: Gilead Sciences Inc; **Contracted Research:** AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Clovis Oncology, Genentech BioOncology, Lilly USA LLC, Novartis Pharmaceuticals Corporation, Pfizer Inc.

Corey J Langer, MD
Director of Thoracic Oncology, Abramson Cancer Center
Professor of Medicine, University of Pennsylvania
Vice Chair, Radiation Therapy Oncology Group
Philadelphia, Pennsylvania

Advisory Committee: Abbott Laboratories, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Lilly USA LLC, Millennium: The Takeda Oncology Company, Morphotek Inc, Synta Pharmaceuticals Corp; **Consulting Agreements:** Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Lilly USA LLC; **Contracted Research:** AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech BioOncology, GlaxoSmithKline, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; **Data and Safety Monitoring Board:** Amgen Inc, Synta Pharmaceuticals Corp.

John Heymach, MD, PhD
Chief, Thoracic Medical Oncology
Associate Professor of Thoracic/Head
and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Advisory Committee: Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology, GlaxoSmithKline, Pfizer Inc; **Consulting Agreement:** OSI Oncology; **Contracted Research:** Bayer HealthCare Pharmaceuticals, GlaxoSmithKline, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Pfizer Inc.

D Ross Camidge, MD, PhD
Director, Thoracic Oncology Clinical Program
University of Colorado Cancer Center
Aurora, Colorado

Advisory Committee: Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology, Lilly USA LLC, Pfizer Inc.

Robert Pirker, MD
Professor of Medicine
Department of Medicine I
Medical University of Vienna
Vienna, Austria

Advisory Committee: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Merck Serono, Pfizer Inc, Roche Laboratories Inc; **Speakers Bureau:** AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Lilly USA LLC, Merck Serono, Pfizer Inc, Roche Laboratories Inc.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: August 2013

Expiration date: August 2014

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Friday, May 31, 2013
7:00 PM – 9:00 PM
Chicago, Illinois

Faculty

Heather Wakelee, MD
Corey J Langer, MD
John Heymach, MD, PhD
D Ross Camidge, MD, PhD
Robert Pirker, MD

Moderator

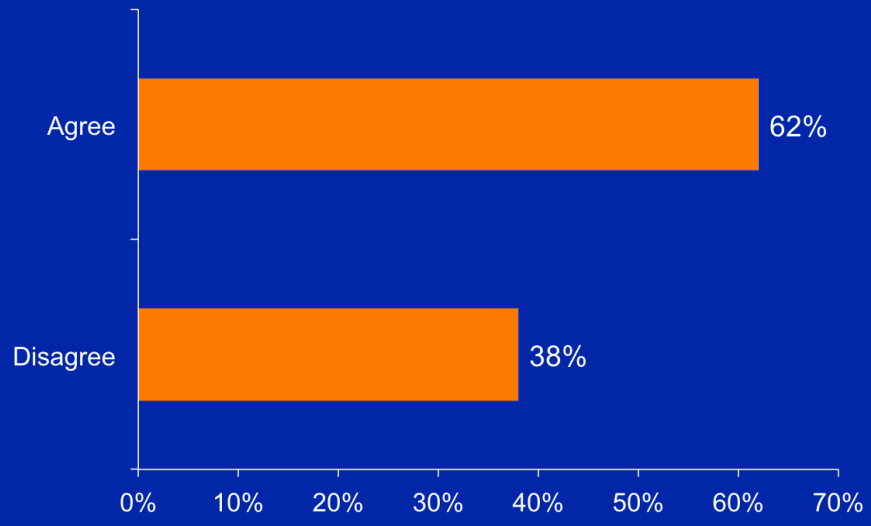
Neil Love, MD

Research To Practice®

Adjuvant Therapy for Localized NSCLC; Management of Locally Advanced Disease

Heather Wakelee, MD
Associate Professor of Medicine, Oncology
Stanford Cancer Institute
Stanford University

All patients with NSCLC for whom tissue has already been accessed, including those s/p surgical resection, should have their tumor specimens tested for EGFR and ALK.



Case: Dr Lowenthal (Dr Wakelee)
How old is too old for cisplatin and/or bevacizumab?

- 70 yo man, remote tobacco use (D/C 45 y ago)
- Routine pre-op (TURP) CXR abnormal
- CT and PET: 6-cm RLL mass (SUV 7), hilum 2.7 SUV
- VATS R lower lobectomy: 5.3-cm mod-poorly diff adeno, pan-WT, node-negative
- Patient is eligible for ECOG-E1505 (cis doublet with or without bevacizumab)

Question: Would you recommend participation, and if so, what doublet would you use?

A 70-year-old patient undergoes right lower lobectomy for a 5.3-cm pan-wild-type (PWT) adenocarcinoma (adeno) with negative nodes. What adjuvant systemic treatment would you recommend?

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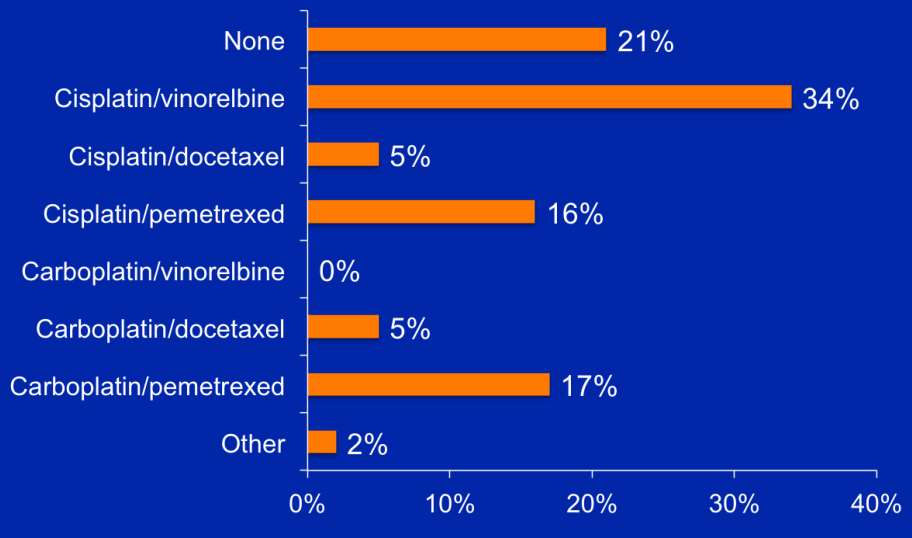

The same 70-year-old patient (5.3-cm PWT adeno, negative nodes) is eligible for the ECOG-E1505 study evaluating the addition of bevacizumab to cisplatin-based adjuvant chemotherapy. Would you recommend participation for this patient?

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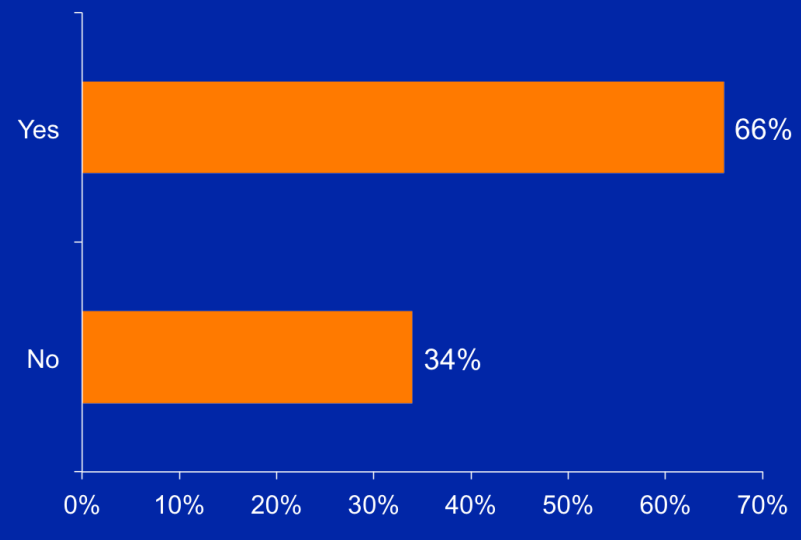

A 67-year-old remote smoker s/p surgery for stage IIIA adenocarcinoma with positive surgical margin and 7 out of 8 positive nodes. EGFR testing reveals an exon 19 deletion. In addition to other treatment, would you use an EGFR TKI?

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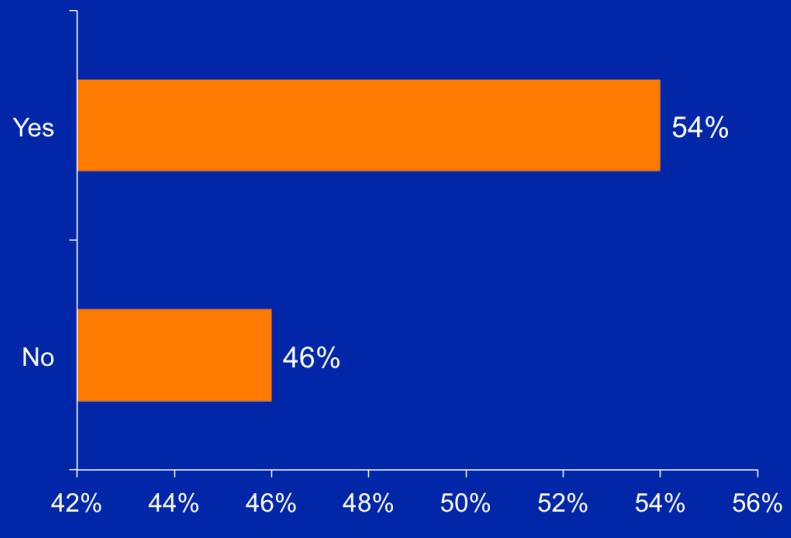


The Questions

- What is your preferred non-protocol adjuvant chemotherapy doublet for younger patients with adenocarcinoma?
- What key clinical trial evidence has helped you shape your decision?

Which Chemotherapy in the Adjuvant Setting?

- All 3 positive adjuvant trials used cisplatin (2 with vinorelbine) for 4 cycles
- Cisplatin is THE standard (unless not tolerated)
  - but high use of carboplatin in NA in the elderly
- For the 2nd drug, can we extrapolate from the metastatic setting?

Which Chemotherapy in the Adjuvant Setting?

- Metastatic disease:
- Carboplatin/paclitaxel = cisplatin/paclitaxel = cisplatin/docetaxel = cisplatin/gemcitabine
- Cisplatin/docetaxel > cisplatin/vinorelbine
- Cisplatin/pemetrexed > cisplatin/gemcitabine for non-squamous histology

Schiller NEJM 346:92, 2002; Fossela JCO 21:3016, 2003; Scagliotti JCO 26:3543, 2008

A simple proof in adjuvant chemotherapy

- So IF in metastatic disease:
- Cis/Vin < Cis/Doce
- Cis/Doce = Cis/Gem
- Cis/Gem < Cis/Pem (non-squam)

- Then: either cis/doce, cis/gem or cis/pem (non-squam) > cis/vin for adjuvant therapy
- But this is BIOLOGY, not simple math

However, NCCN Guidelines

- Adjuvant Chemotherapy, NSCLC-D
- Includes 5 published cisplatin regimens
  - Cis 50 d 1,8 + vin 25 d 1, 8, 15, 22 q 28
  - Cis 100 d 1 + vin 30 d 1,8,15, 22 q 28
  - Cis 75-80 d 1 + vin 25-30 day 1,8 q 21
  - Cis 100 d 1 + etop 100 day 1-3, q 28
  - Cis 80 d 1 + vinblastine 4 q wk - q 2 wk q 21
- Includes 3 other regimens – all cis 75 q 21
  - Gem 1250 d 1,8: Doce 75 d 1, Pem 500 d 1

Wakelee ASCO 2011

Phase II TREAT Trial

- 132 pts resected NSCLC
- 38% IB, 57% II : 43% Squamous
- Randomized to cis (50 D1,8)/vin (25 q wk) vs cis(75)/Pem (500) q 3 wk

- Delivery of total mean doses
  - 90% CP vs 66% CV

Kreuter Ann Oncol 24:986, 2013

TREAT Trial Summary

- Study met the predefined primary endpoint of "feasibility"
- Mean cisplatin dose higher for the cisplatin/pemetrexed vs cisplatin/vinorelbine
- No survival data to date BUT
  - 45% squamous cell histology, 38% stage IB
- So unclear what survival data with adjuvant pemetrexed will mean in this setting

Kreuter Ann Onc 24:986, 2013

Which Adjuvant Chemotherapy?

- Strongest evidence for adjuvant chemotherapy in NSCLC is with cisplatin/vinorelbine
- TREAT trial gives some evidence to support common practice of substituting other cisplatin doublets

Chemotherapy on E1505

Chemotherapy	Total	Arm A	Arm B (BEV)
Cisplatin +	670	341	329
Vinorelbine	179(27%)	88(26%)	91(28%)
Docetaxel	213(32%)	110(32%)	103(31%)
Gemcitabine	164(25%)	85(25%)	79(24%)
Pemetrexed* (non-sq only)	112(17%)	57(17%)	55(17%)

* Squamous (~30%) not eligible, option added 2009

Wakelee IASLC WCLC 2011: Abstract O42.03

The Questions

- Are any promising investigational agents or strategies in clinical testing for Stage IIIA/B disease, including the use of targeted therapy before chemoradiation?

Unresectable Stage III NSCLC: Truths we know
1: Chemotherapy adds to Radiation
2: Concurrent Chemo/Radiation Trumps Sequential

1: CALGB 8433	Median Survival
Radiation Alone	9.7 mo
Sequential Chemotherapy - Radiation	13.8 mo

2: RTOG 9410	Median Survival
Sequential Chemotherapy - Radiation	14.6 mo
Concurrent Chemotherapy/Radiation	17.1 mo

Dillman NEJM 1990
Curran JNCI 2011

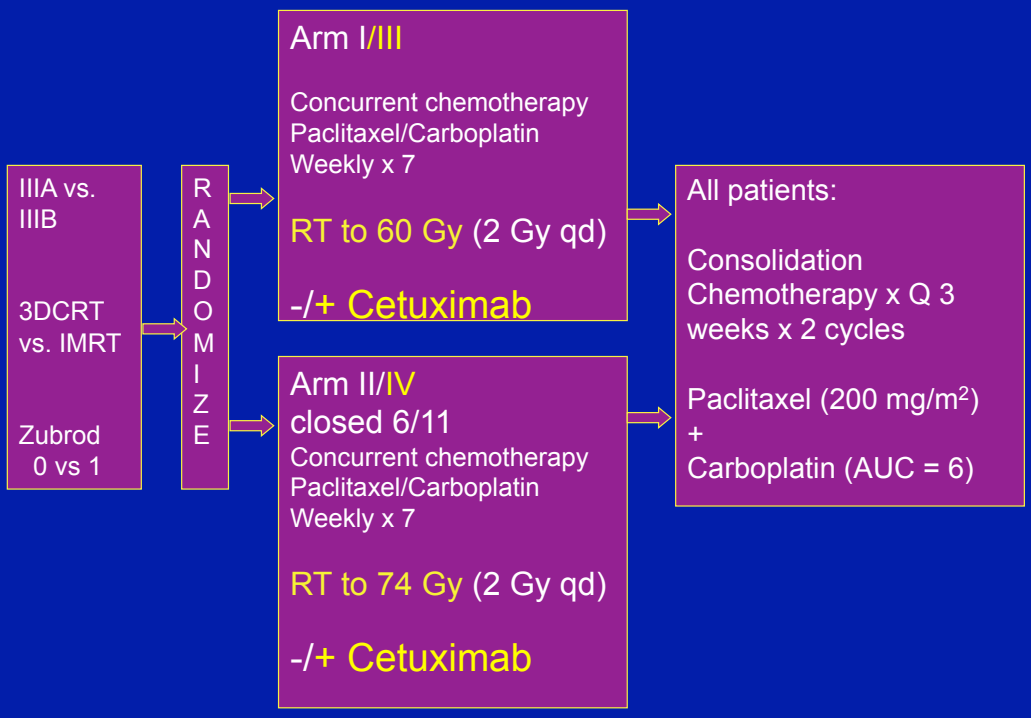
Wakelee ASCO 2012

Unresectable Stage III NSCLC:
What We Don't Know:
Benefit of Induction or Consolidation Chemotherapy

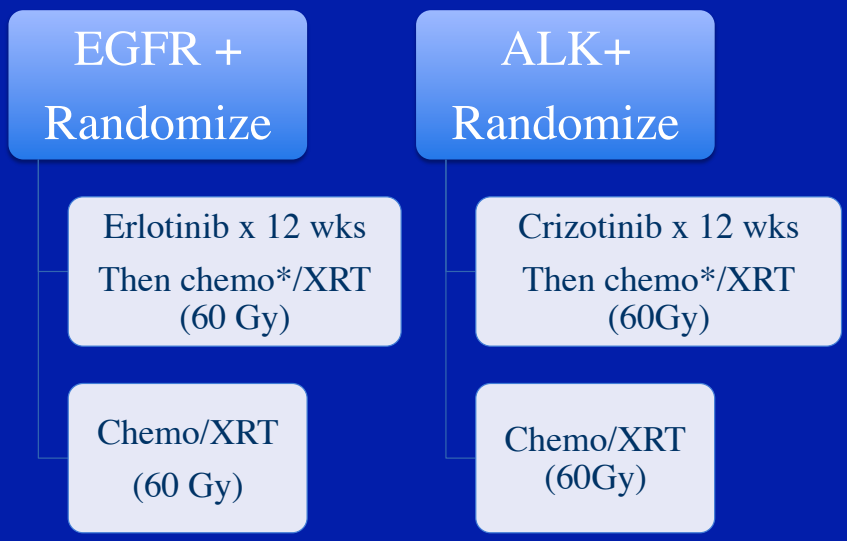
- Induction chemotherapy –
  - CALGB 39801* negative
    - Weekly carboplatin/paclitaxel/XRT
      - +/- 2 cycles carboplatin AUC 6/Paclitaxel 200 mg/m2
- Consolidation chemotherapy –
  - Routinely included
  - Limited data from randomized trials…
- Benefit of additional agents not shown to date

*Vokes EE, et al. *J Clin Oncol.* 2007

Ongoing Phase III Trial: HD XRT +/- Cetuximab



Phase II RTOG 1306 NeoAdj Targeted Therapy Intergroup Stage III Proposal



*Chemo is cis/etop OR weekly carbo/paclitaxel

Histologic Distinctions in the Management of Non-small Cell Lung Cancer in 2013

Corey J Langer, MD, FACP
Director Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
University of Pennsylvania
Philadelphia, PA 19104

Case: Dr Rupard (Dr Langer)

50 yo woman

- Auto accident → imaging: Large peripheral right lower lobe lung mass, bilateral hilar and mediastinal lymphadenopathy and diffuse left-sided lesions, likely from metastases
- PET scan: Bilateral hilar and lung lesions, no disease outside of the chest
- Percutaneous biopsy: Poorly differentiated pan-WT adenocarcinoma
- Patient is on multiple medications for difficult-to-control psychiatric disease (hypomania)

Question: What induction treatment would you use?

Which first-line chemotherapy and/or biologic therapy would you generally administer to an otherwise healthy 50-year-old patient with metastatic PWT adenocarcinoma of the lung?

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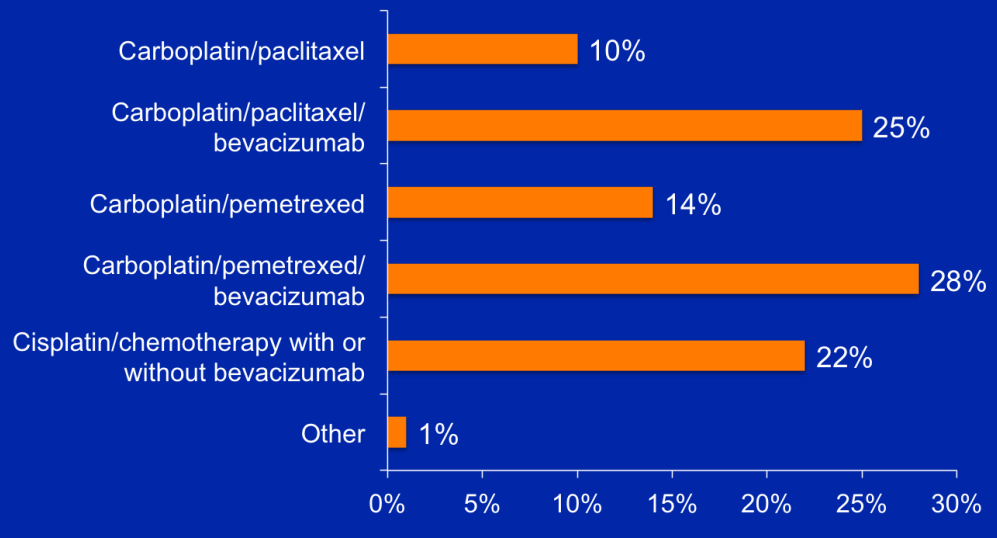

Case: Dr Rupard (Dr Langer)

83 yo woman

- Several months of increasing cough and chest pain
- CT scan of chest: Large left pleural effusion and a 2.5-cm soft tissue mass in the left upper lobe of the lung abutting the mediastinum, with a satellite left lower lobe nodule
- Thoracentesis: Adenocarcinoma, pan-WT
- Talc pleurodesis: Initial good result but patient is PS 1-2

What is your usual first-line therapy for an older symptomatic patient (~80) with metastatic PWT adeno and PS 1-2 secondary to aging and the tumor?

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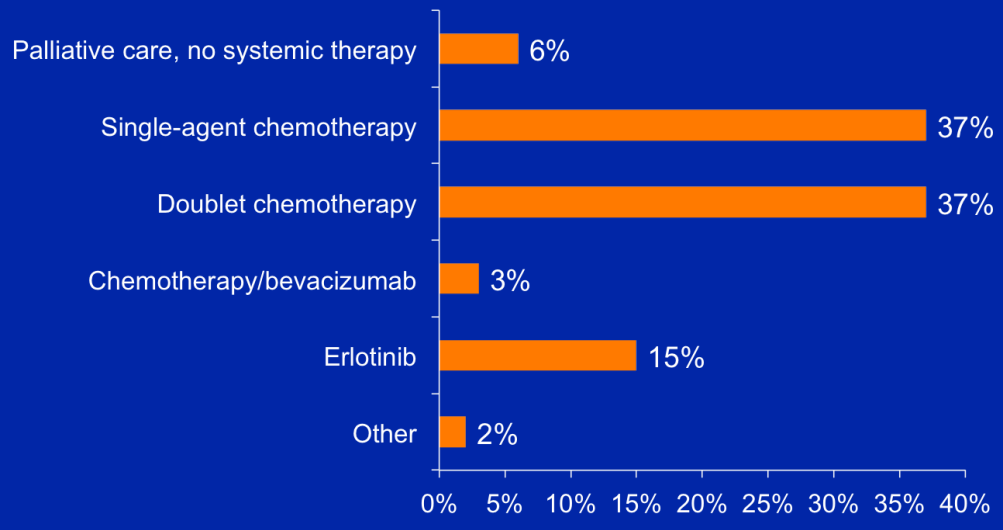

A 62-year-old patient receives cisplatin/pemetrexed as adjuvant therapy for PWT adeno and tolerates it well but experiences systemic disease relapse 2 years later. What is your next likely treatment?

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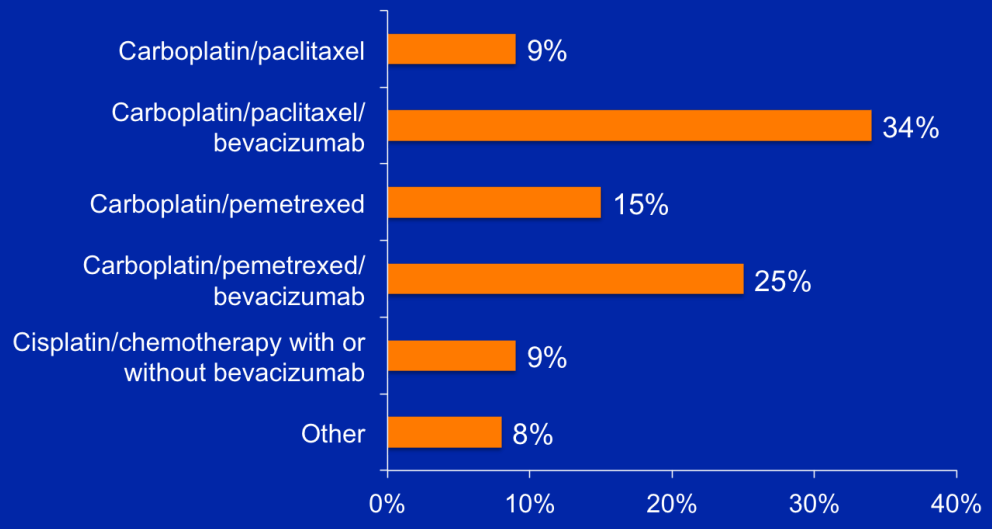

A 50-year-old patient underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy. He now has histologically documented metastatic disease to bone and liver. What is your usual first-line systemic therapy?

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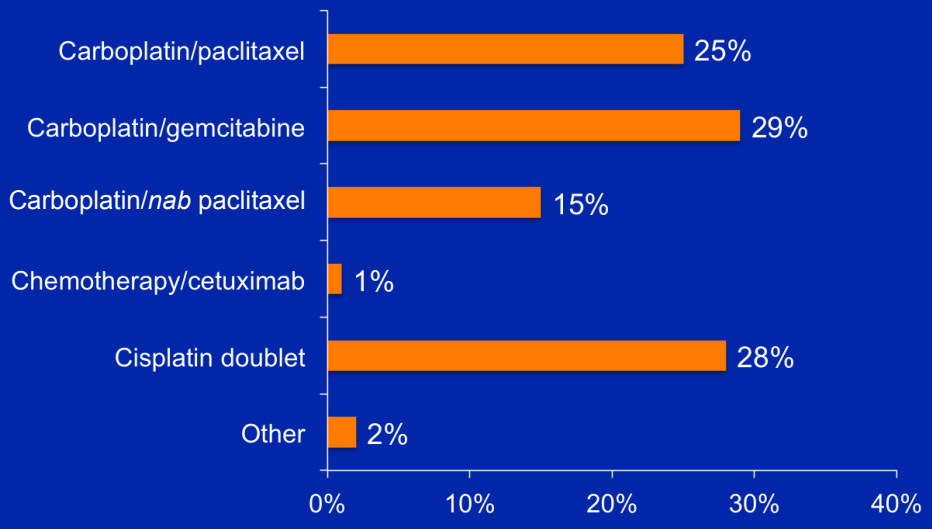

For the same 50-year-old patient who underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy and now has histologically documented metastatic disease to bone and liver. Would you likely use bevacizumab in addition to chemotherapy?

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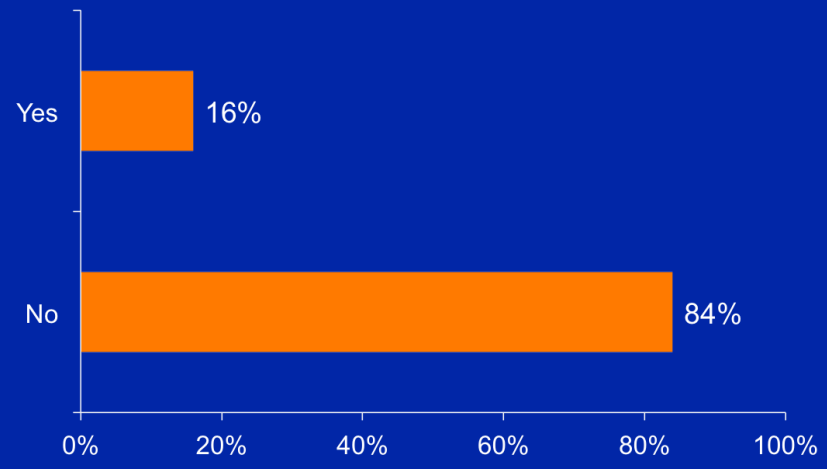
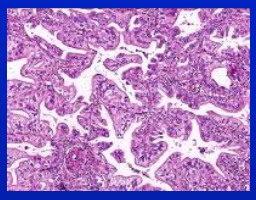


Nonsmall Cell Lung cancer

- **Adenocarcinoma**
  - −Glandular pattern
  - −Mucin positivity (50%)

  WHO
  - −CK7+/CK20-
  - −TTF-1+ (75%)

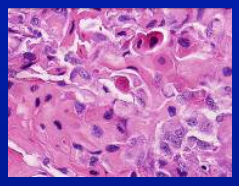
  Common, but not 100%

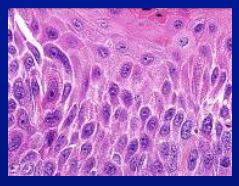


- **Squamous cell carcinoma**
  - −Cellular keratinization
  - −Intercellular bridges
  - −Keratin “pearl” formation

  WHO
  - −CK7-/CK20-
  - −TTF-1 neg
  - −P63+ or p40+ CK5/6+

  Common, but not 100%





Emergence of Histology as Determinant of Therapy

Sandler: Paclitaxel-Carboplatin +/- Bevacizumab

Scagliotti: Gem-DDP vs. Pem-DDP

Socinski: nab-paclitaxel –Carbo vs Pac-Carbo

ECOG 4599: Phase III Trial of Bevacizumab in Non-Squamous NSCLC

Eligibility
- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

PC
Paclitaxel 200 mg/m^2
Carboplatin AUC 6 mg/m^2 q3wk

PCB
Paclitaxel/carboplatin x 6 cycles
+
bevacizumab
(15 mg/kg q3wk) to PD

No crossover to bevacizumab permitted

Stratification variables
- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs ≥5%
- Measurable vs nonmeasurable

Parameter	PC	PCB	*P* value
RR (%)	15	35	<0.001
PFS (mo)	4.5	6.2	<0.001
Median survival (months)	10.3	12.3	*P* = 0.003
1-year survival (%)	44	51	
2-year survival (%)	15	23	

RT = radiotherapy; PD = progressive disease.
Sandler A et al. N Engl J Med. 2006;355:2542-2550.

Study Design

- Stage IIIB/IV NSCLC
- PS 0 - 1
- No prior chemo
- Randomization: gender, PS, stage, histo vs cyto dx, brain mets

R

Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 day 1

Primary objective: Overall Survival

15% Non-inferiority margin (HR 1.17)

N = 1700 Patients , Power 80%

Gemcitabine 1250 mg/m^2 days 1 + 8 Cisplatin 75 mg/m^2 day 1;

B12, folate, and dexamethasone given in both arms

Scagliotti GV et al. JCO 2008; 26:3543

Overall Survival - All Patients: Cisplatin + Gemcitabine vs Cisplatin + Pemetrexed

Endpoint	CP (n = 862)	CG (n = 863)	Adjusted HR (95% CI)
Median overall survival	10.3 mo	10.3 mo	0.94 (0.84-1.05)

Scagliotti. *JCO.* 2008;26(21):3543-3551.

1.176 was non-inferiority margin

Overall Survival in Patients with Nonsquamous Histology (N = 1,000)

Endpoint	CP (n = 512)	CG (n = 488)	Adjusted HR (95% CI)
Median overall survival	11.8 mo	10.4 mo	0.81 (0.70-0.94)

Scagliotti. *JCO.* 2008;2:3543-3551.

Pemetrexed Plus Cisplatin in 1st-line: Survival with Gemcitabine/Cisplatin for Patients with Squamous Cell Carcinoma (n = 473)

Endpoint	CP (n = 244)	CG (n = 229)	Adjusted HR (95% CI)
Squamous cell (n = 473)	9.4 mo	10.8 mo	1.23 (1.00-1.51)

Scagliotti GV et al: J Clin Oncol. 26 (21), 2008: 3543-3551.

Phase III Trial of *nab*-paclitaxel-carbo vs carbo-paclitaxel

Chemo-naïve NSCLC

IIIB/IV

ECOG PS 0-1

Baseline peripheral neuropathy ≥ grade 2

N=1050

RANDOMIZED

Nab-paclitaxel 100 mg/m² d1, 8, 15
Carbo AUC 6 d1
No premeds

Paclitaxel 200 mg/m² d1
Carbo AUC 6 d1
Premeds: dex, antihistamines

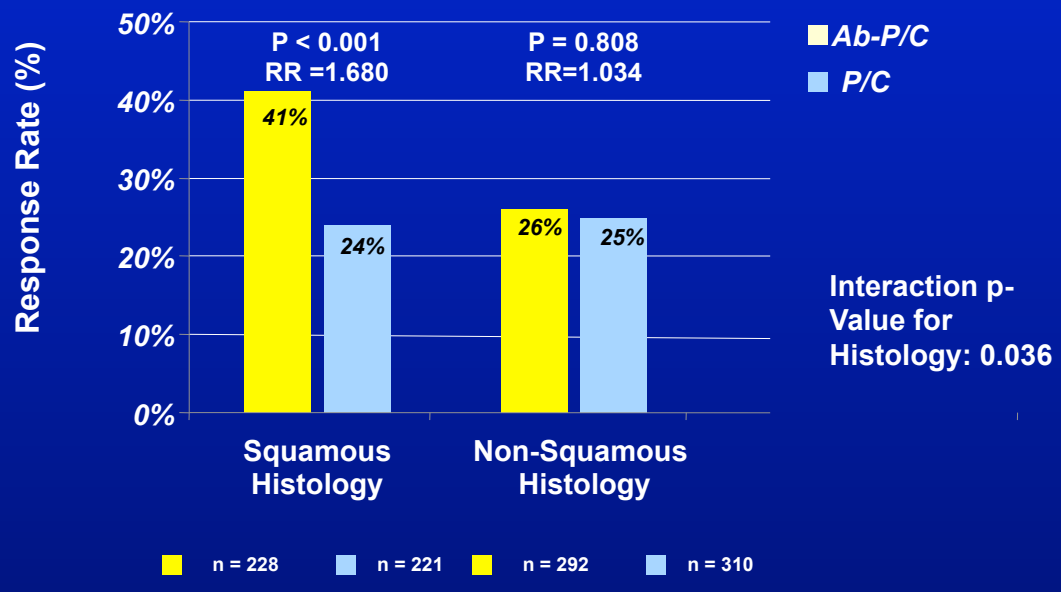
Stratification factors: stage IIIb vs IV, age <70 or ≥ 70, gender, histology (SCC vs non-SCC), geography

Primary endpoint: ORR

Secondary endpoint: PFS, OS, DCR, safety (NCI CTCAE v3)

Socinski MA et al. ASCO 2010;Abstract LBA7511

Objective Responses by Histology*



Interaction p-Value for Histology: 0.036

* Not a pre-specified subgroup analysis

PFS – ITT Population

	Ab-P/Carbo (n = 521)	Paclitaxel/ Carbo (n = 531)	HR	P-Value
N/Events	521/297	531/312		
Median PFS (mo)*	6.3	5.8	0.902	0.214
95% CI	5.6-7.0	5.6-6.7	0.767-1.060	

*** PFS based on Independent assessment**

Secondary Endpoint: OS

			Median OS (mo)	
	Events / N	HR	*nab*-P/C	P/C
All patients	744 / 1052	0.922	12.1	11.2
Japan	86 / 149	0.950	16.7	17.2
Russia/Ukraine	521 / 724	1.019	11.0	11.1
North America	127 / 165	0.622	12.7	9.8
Male	589 / 789	0.894	11.4	10.0
Female	155 / 263	0.995	16.8	16.0
<70 yrs	639 / 896	0.999	11.4	11.3
≥70 yrs	105 / 156	0.583	19.9	10.4
Squamous	343 / 450	0.890	10.7	9.5
Nonsquamous	401 / 602	0.950	13.1	13.0
Stage IIIB	142 / 218	0.896	12.4	13.6
Stage IV	602 / 834	0.917	12.0	11.0

Socinski MA et al, J Clin Oncol 2012;30(17):2055-2062.

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Socinski MA et al, J Clin Oncol 2012;30(17):2055-2062.

Paclitaxel + Carboplatin Show Significant Benefits in Patients ≥70 yo with Advanced NSCLC

- Methods: Phase 3 study in 451 patients 70-89 yo
  - **Arm A:** Carboplatin AUC 6 every 4 weeks + paclitaxel 90 mg/m² (d1,8,15) Q 4wk vs
  - **Arm B:** Single-agent gemcitabine 1150 mg/m² or vinorelbine 30 mg/m², d1, d8
- Results

Parameter	Arm A	Arm B
Median OS, mon	10.4	6.2
Median PFS, mon	6.3	3.2
Grade 3-4 hematologic tox	54.1%	17.9%

- Conclusions: Paclitaxel + carboplatin provides a significantly longer survival in elderly patients with advanced NSCLC than current standard single-agent therapy, with acceptable toxicity

Quoix et al, *J Clin Oncol*. 2010;28(suppl);abstr 7606. – ASCO; Lancet 2011

Overall survival (ITT)

Endpoint	Monotherapy (n = 226)	Doublet chemotherapy (n = 225)
Overall survival	6.2 mo (95% CI 5.3-7.4)	10.3 mo (95% CI 8.3-13.3)
1-year survival	26.9% (95% CI 21-33.1)	45.1% (95% CI 38.2-51.8)

p = 0.00004

Exploratory Sub-group analysis

	N	HR	95% LCL	95% UCL	p
All (B:A)	451	**0.639**	0.515	0.792	0.000046
PS 0/1	329	**0.622**	0.479	0.806	0.0003
PS 2	122	**0.646**	0.439	0.951	0.0268
Age ≤ 80 yr	337	**0.668**	0.519	0.859	0.0016
Age > 80 yr	114	**0.559**	0.368	0.851	0.0067
Adenocarcinoma	229	**0.712**	0.518	0.979	0.0365
Other histology	222	**0.539**	0.399	0.727	0.000053
Smokers	356	**0.631**	0.498	0.800	0.0001
Never smokers	94	**0.625**	0.368	1.060	0.0810
Weight loss < 5 %	198	**0.610**	0.431	0.864	0.0053
Weight loss ≥ 5 %	246	**0.732**	0.553	0.968	0.0287
ADL = 6	351	**0.593**	0.462	0.761	0.000042
ADL < 6	87	**0.655**	0.417	1.029	0.0665
MMS ≥ 24	372	**0.601**	0.473	0.764	0.000032
MMS < 24	70	**0.909**	0.540	1.530	0.7188

OS – The univariate hazard ratio was derived from a Cox model with a single treatment covariate

Phase III Trial Design: Tx-naïve PS 2 NSCLC

Eligibility:
- Stage IIIB/IV NSCLC (malignant effusion)
- ECOG PS 2
- No prior chemotherapy
- Stable CNS disease
- Measurable disease
- Adequate organ function (including GFR≥ 45 ml/min)
- Signed informed consent

1:1 RANDOMIZATION

Stratification factors:
- Stage: IIIB vs IV
- Age: ≥70 vs <70
- Wt loss: ≥5% vs <5%

Arm A
Pemetrexed
500 mg/m2 IV Q3W

X 4 cycles

Arm B
Pemetrexed
500 mg/m2 IV Q3W
+
Carboplatin
AUC 5 IV Q3W

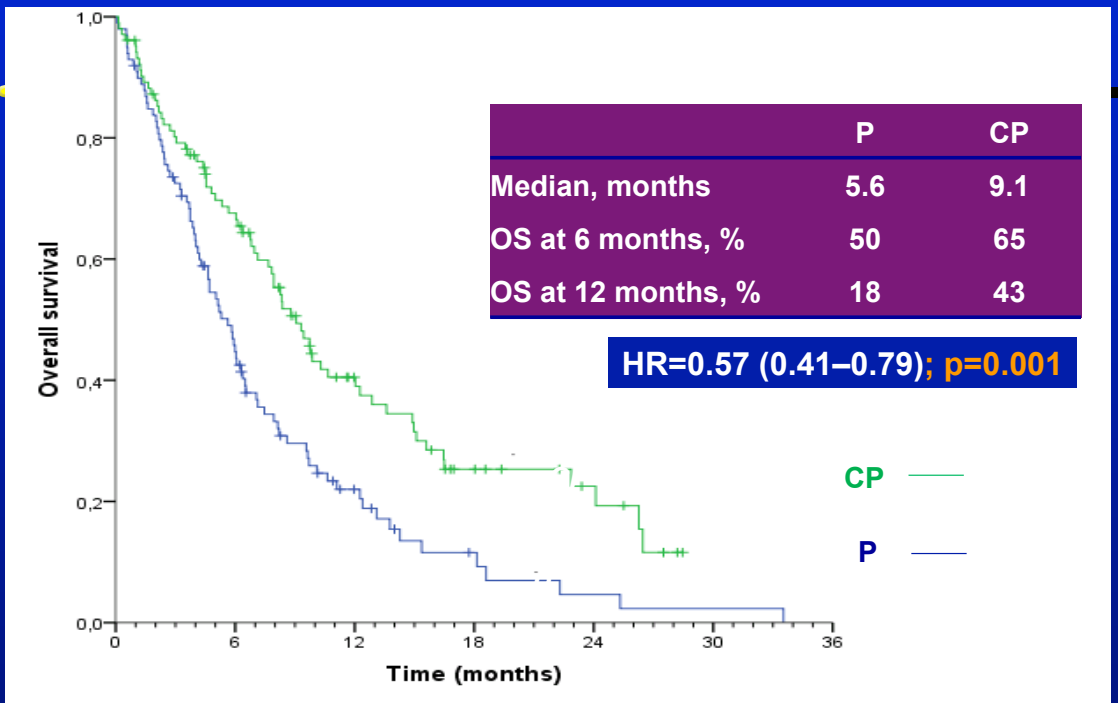
Primary endpoint:
- Overall Survival

Secondary endpoints:
- Progression-free survival
- Overall response rate
- Safety

Pre-medications:
- Vitamin B12: 1mg IM Injection
- Folic Acid: 350-1,000mcg po daily
- Dexamethasone 4mg po BID the day before, the day of, and the day after

Lilenbaum R et al. ASCO 2012;Abstract 7506

OVERALL SURVIVAL



	P	CP
Median, months	5.6	9.1
OS at 6 months, %	50	65
OS at 12 months, %	18	43

HR=0.57 (0.41–0.79); p=0.001

With permission from Lilenbaum et al. ASCO 2012;Abstract 7506

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Maintenance Therapy in the Management of NSCLC

John Heymach, M.D., Ph.D
Chair, Department of Thoracic/Head & Neck Medical Oncology
MD Anderson Cancer Center

Research To Practice Meeting

May 31, 2013

Case: Dr Morganstein (Dr Heymach)

57 yo woman, heavy smoker

- Presented with cough unresponsive to antibiotics
- Lung mass found, further workup revealed multiple masses in liver
- Biopsy confirmed pan-WT adenocarcinoma
- Carbo/pem/bev for 4 cycles resulting in a PR
- Treatment was tolerated with some difficulty (fatigue, GI symptoms), and patient required 3 antihypertensives (hydrochlorothiazide, amlodipine, lisinopril)

A 57-year-old patient is diagnosed with PWT adenocarcinoma in the lung and corresponding liver mets. The patient is treated with 4 cycles of carboplatin/pemetrexed/bevacizumab and achieves a PR. What type of maintenance treatment, if any, would you recommend?

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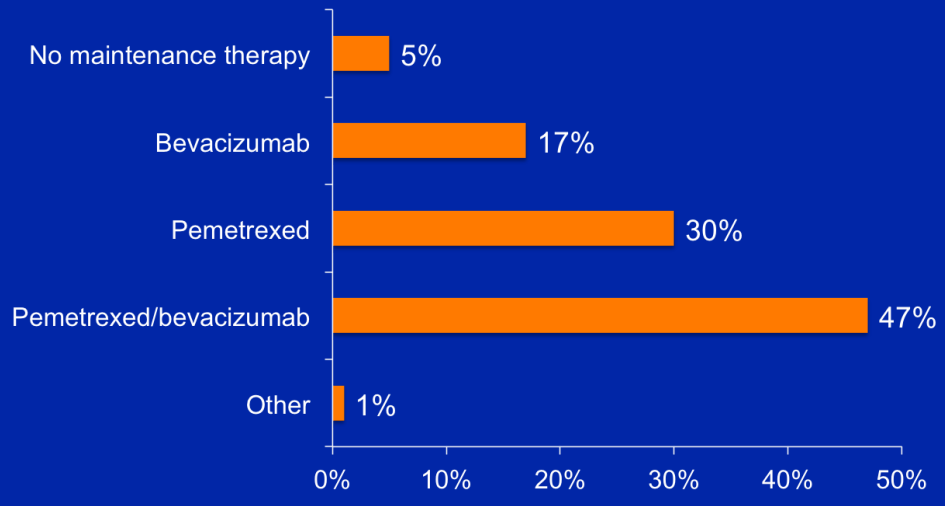

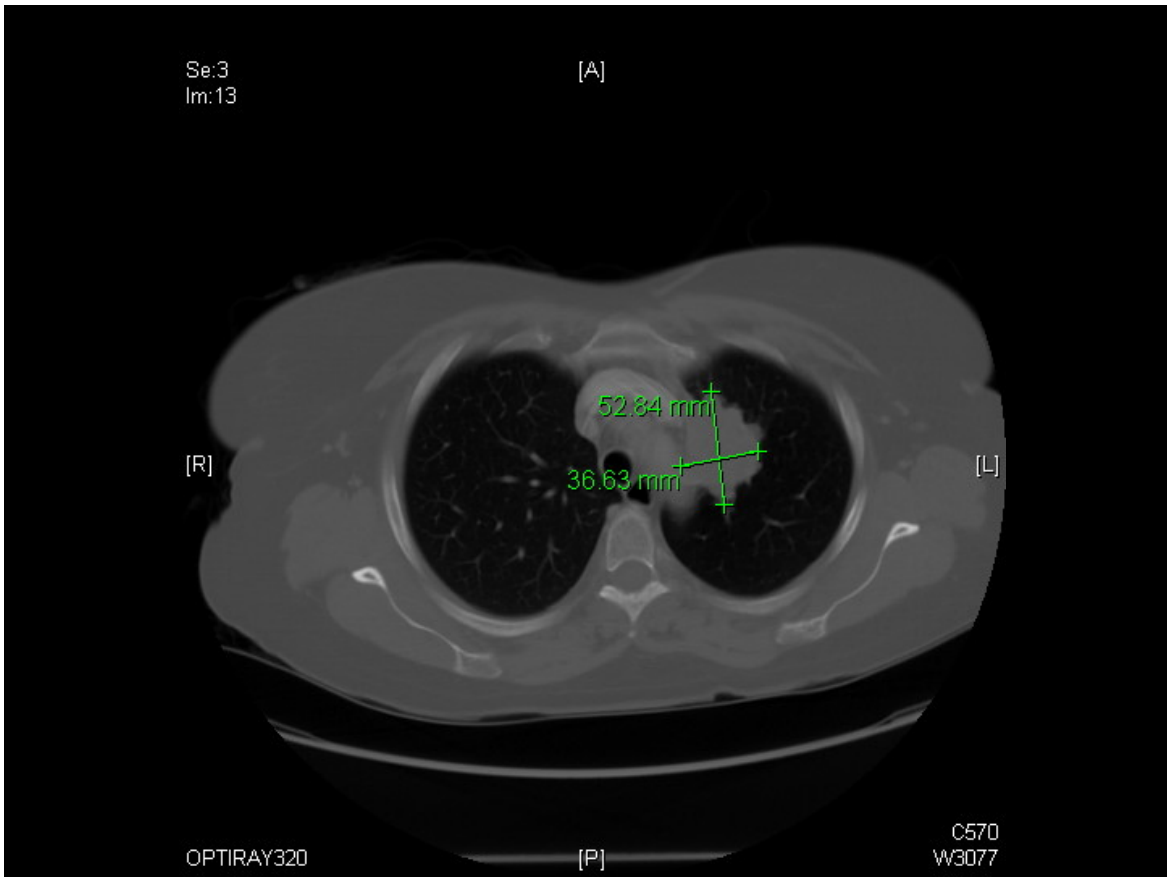
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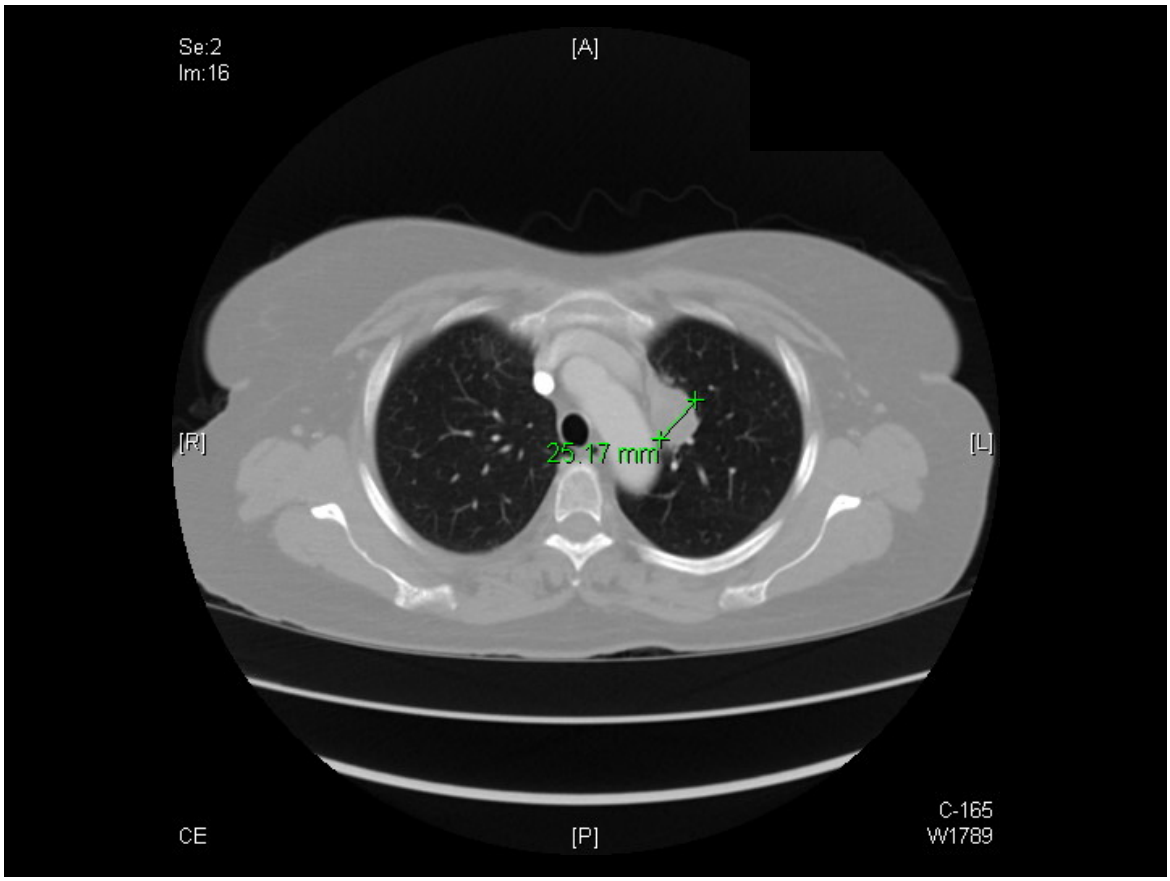
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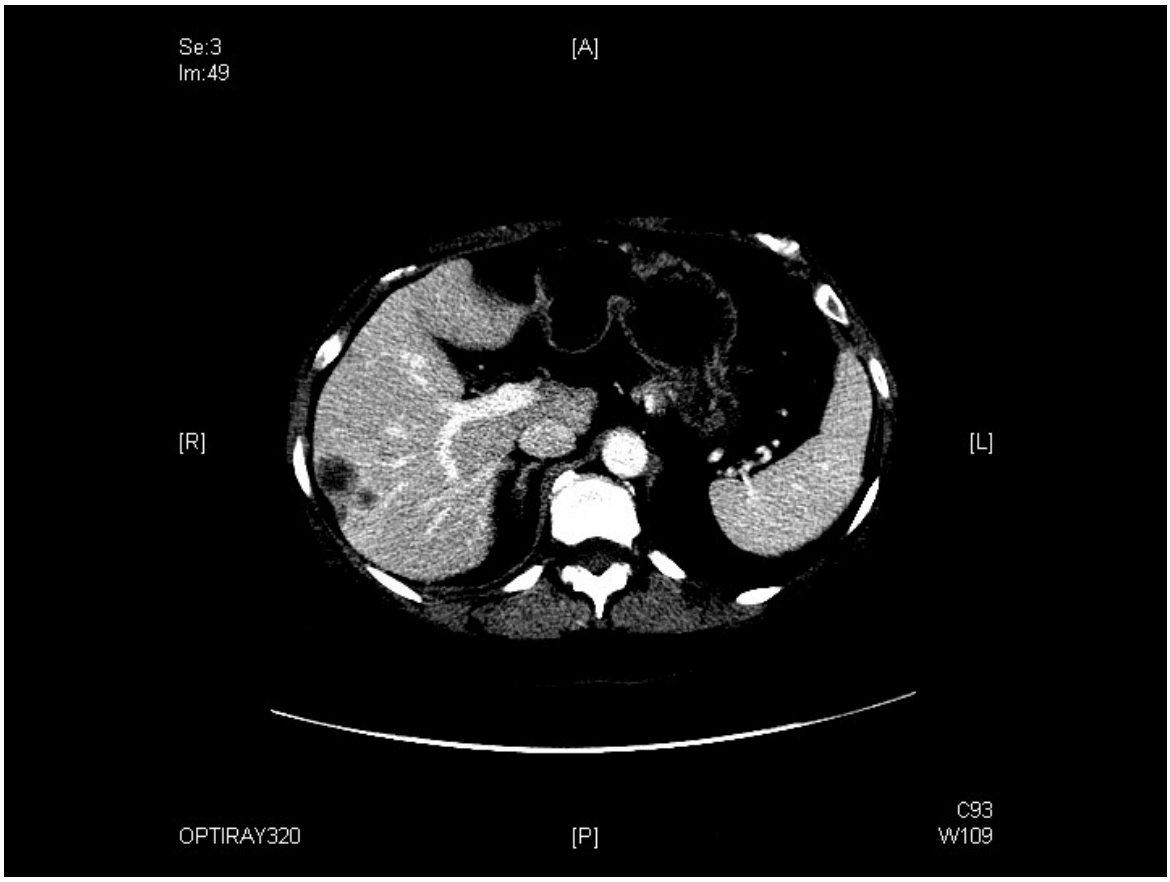
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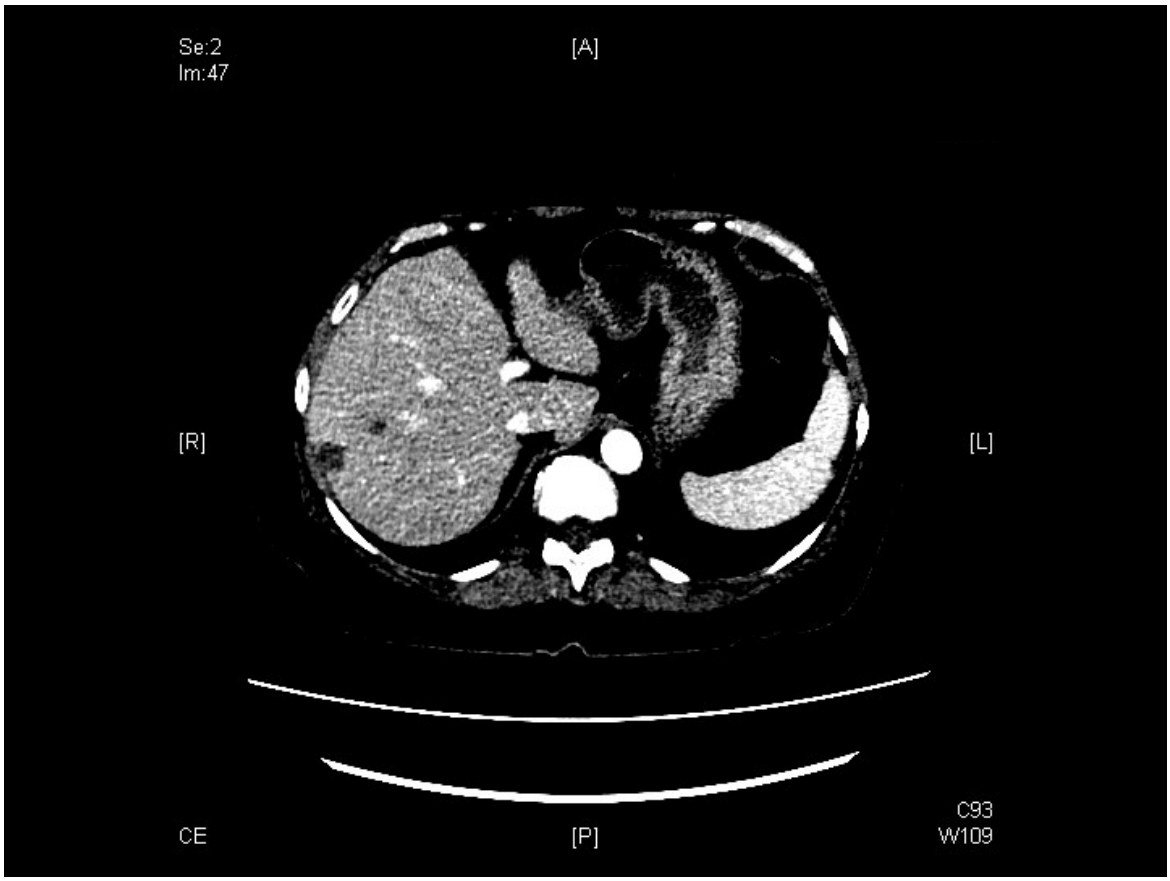
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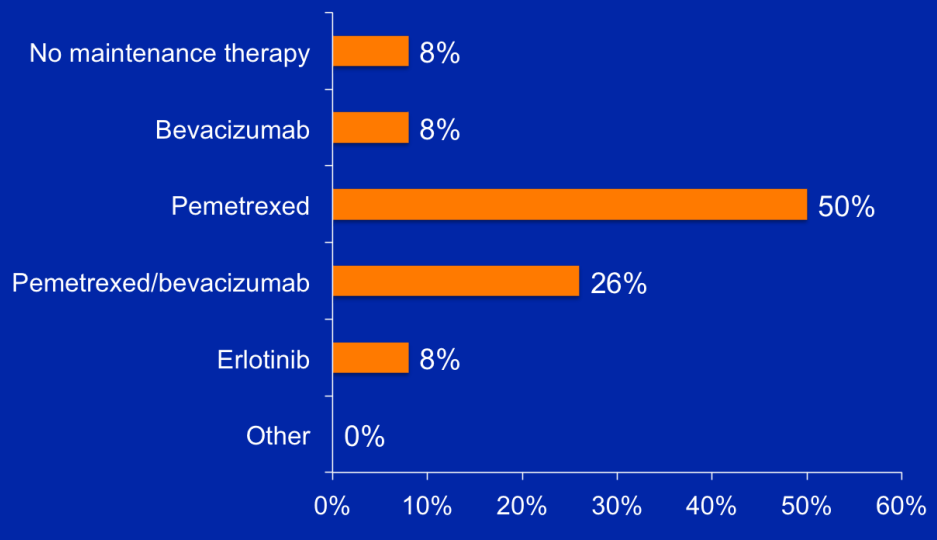
W109

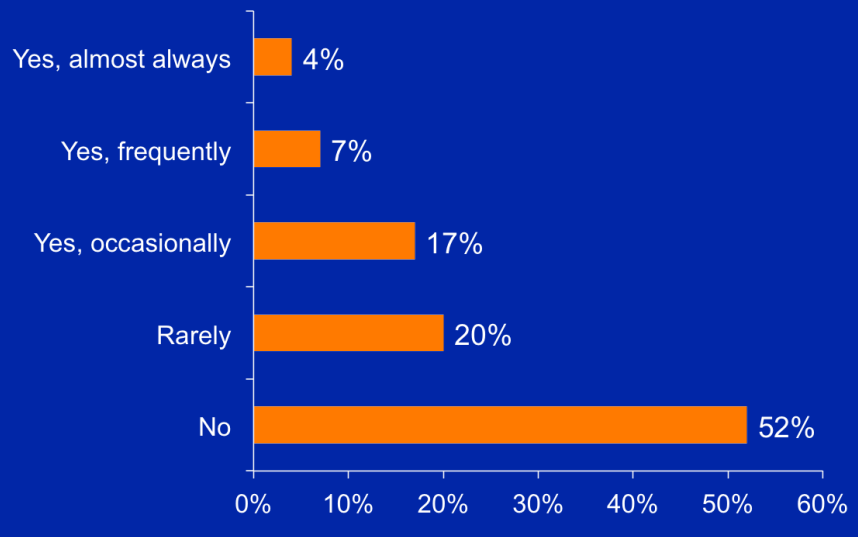
An otherwise healthy 50-yo with PWT adeno experiences a partial response to your recommended first-line treatment. Which maintenance therapy, if any, would you likely use?

An otherwise healthy 50-yo with PWT adeno experiences a partial response to your recommended first-line treatment. Which maintenance therapy, if any, would you likely use?

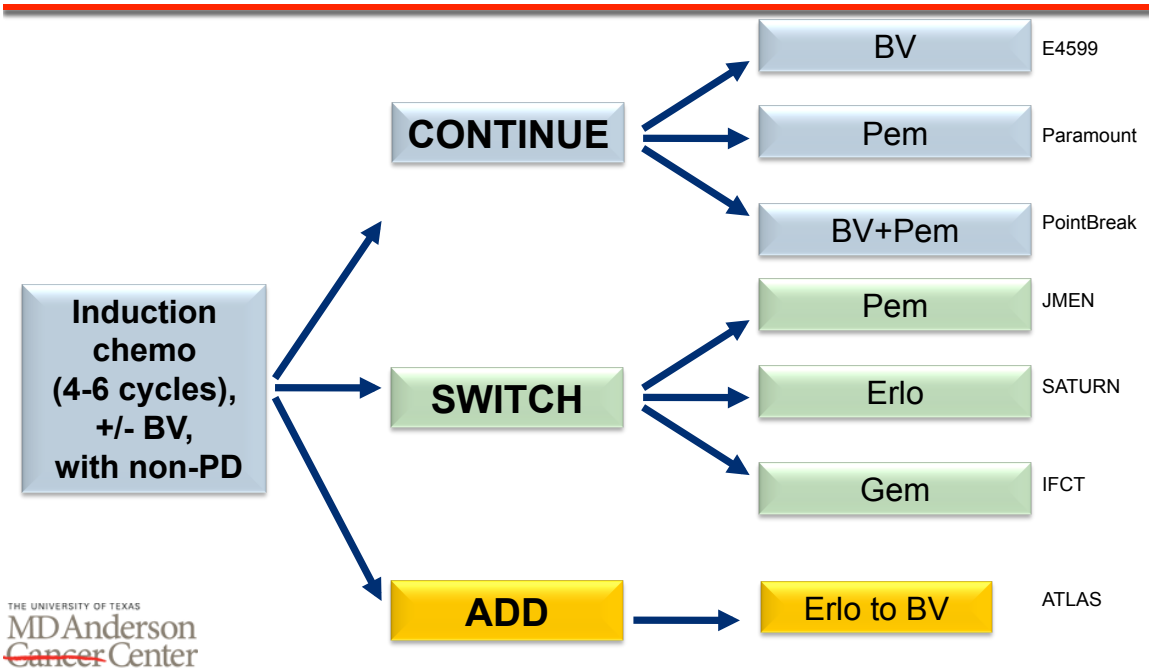


Do you use maintenance therapy for your patients with metastatic squamous cell lung cancer?

Do you use maintenance therapy for your patients with metastatic squamous cell carcinoma?



Decisions, decisions: choices for maintenance therapy in lung adenocarcinoma



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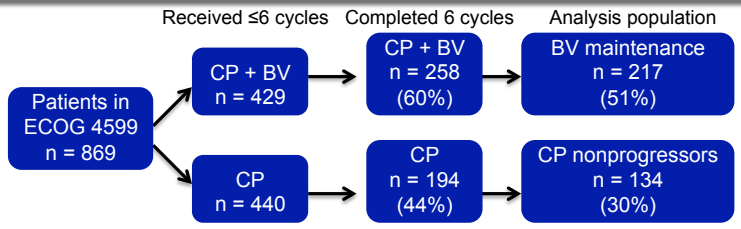
Exploratory analysis of BV maintenance from E4599



Survival	CP + bev induction followed by bev maintenance (n = 217)	CP induction + no maintenance (n = 134)
Median overall survival	4.4 mo	2.8 mo
	HR = 0.75, $p = 0.03$	
Median progression-free survival	12.4 mo	11.2 mo
	HR = 0.64, $p < 0.001$	

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Lopez-Chavez, JTO, 2012

PARAMOUNT: Phase III study of maintenance pem vs BSC after Pem/Cis induction

Survival	Pemetrexed + BSC	Placebo + BSC	Log-rank p	HR (95% CI)
Median PFS (95% CI)	4.1 mo (3.2-4.6)	2.8 mo (2.6-3.1)	<0.0001	0.62 (0.49-0.79)

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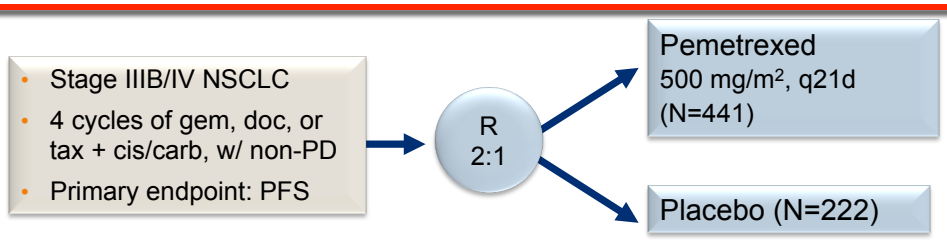
Paz-Ares et al, Lancet Oncology, 2012

JMEN Phase III trial of "switch" maintenance for NSCLC (non-squamous subset)



Efficacy parameter	Pemetrexed (n = 326)	Placebo (n = 156)	Hazard ratio	p-value
PFS Nonsquamous	4.5 mo	2.6 mo	0.44	<0.0001
OS Nonsquamous	15.5 mo	10.3 mo	0.70	0.002

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Ciuleanu et al, Lancet, 2009

Phase III IFCT-GFPC 0502 results: gem maintenance prolongs PFS

- Maintenance therapy with gemcitabine significantly delayed disease progression compared with the observation arm

PFS by independent review: gemcitabine versus observation

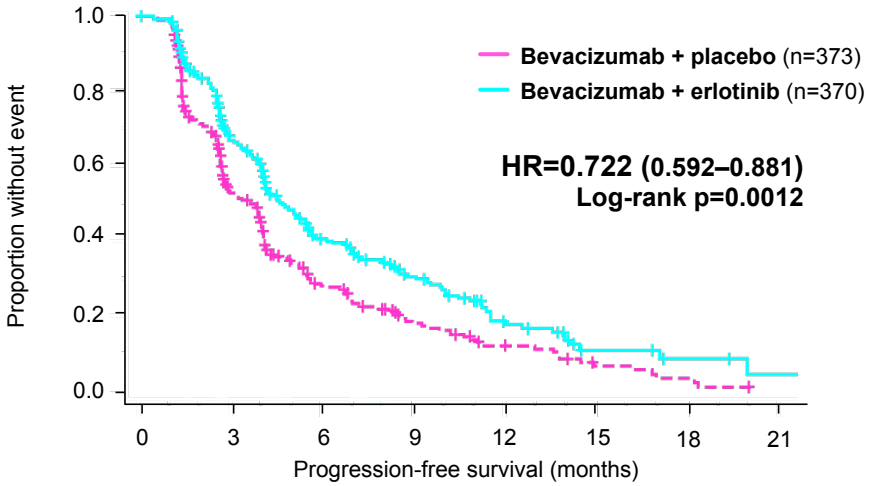
	Observation n=152	Gemcitabine n=149
Median PFS, months	1.9	3.8
PFS at 3 months, %	30.3	55.0
PFS at 6 months, %	8.6	22.1

HR=0.55 (0.43–0.70)
Log-rank test, p<0.0001

Perol M. *J Clin Oncol* 2010;28:15s (suppl; abstr 7507)

PFS is measured from time of randomization into the maintenance phase

ATLAS – maintenance erlotinib prolongs PFS in combination with BV

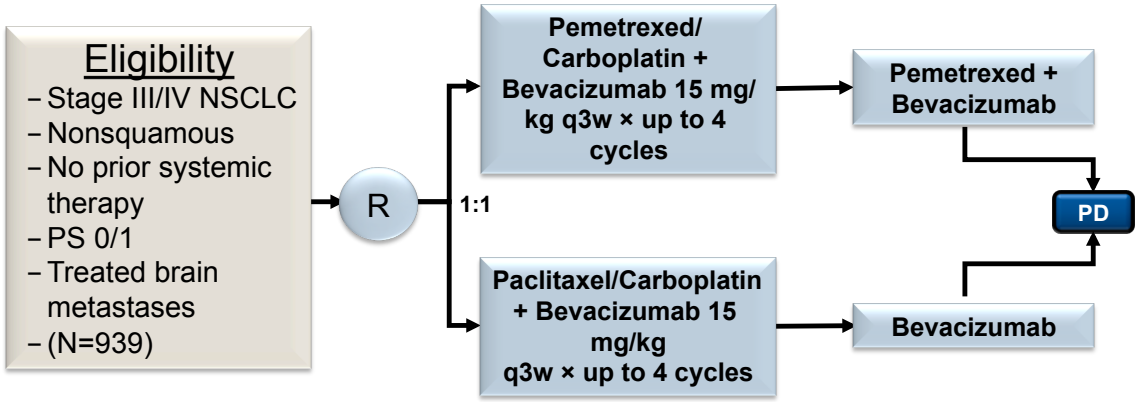


No. of patients at risk:

Bev + placebo	373	142	58	27	15	6	3	0
Bev + erlotinib	370	178	81	43	20	6	3	1

With permission from Miller VA, *et al. J Clin Oncol* 2009;27(Suppl 1):Abstract LBA8002

PointBreak (JMHD): Phase III Study Design



Stratified for:
- PS (0 vs 1)
- Sex (M vs F)
- Disease stage (IIIB vs IV)
- Measurable vs nonmeasurable disease

Superiority Trial
Primary endpoint: OS
Secondary endpoint: PFS

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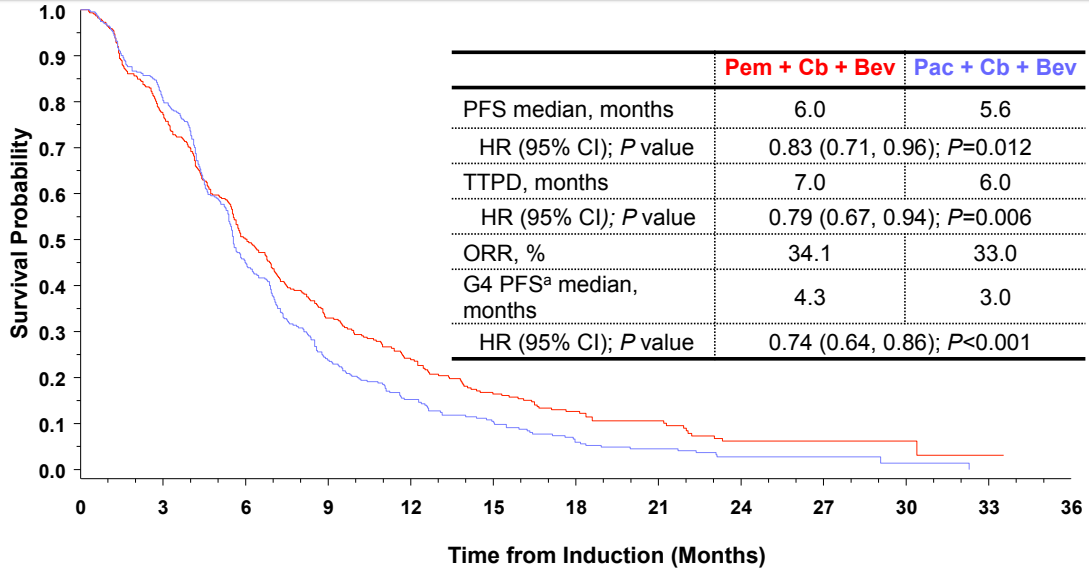
Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

PointBreak: PFS from Randomization (ITT)



	Pem + Cb + Bev	Pac + Cb + Bev
PFS median, months	6.0	5.6
HR (95% CI); *P* value	0.83 (0.71, 0.96); *P*=0.012	
TTPD, months	7.0	6.0
HR (95% CI); *P* value	0.79 (0.67, 0.94); *P*=0.006	
ORR, %	34.1	33.0
G4 PFS[a] median, months	4.3	3.0
HR (95% CI); *P* value	0.74 (0.64, 0.86); *P*<0.001	

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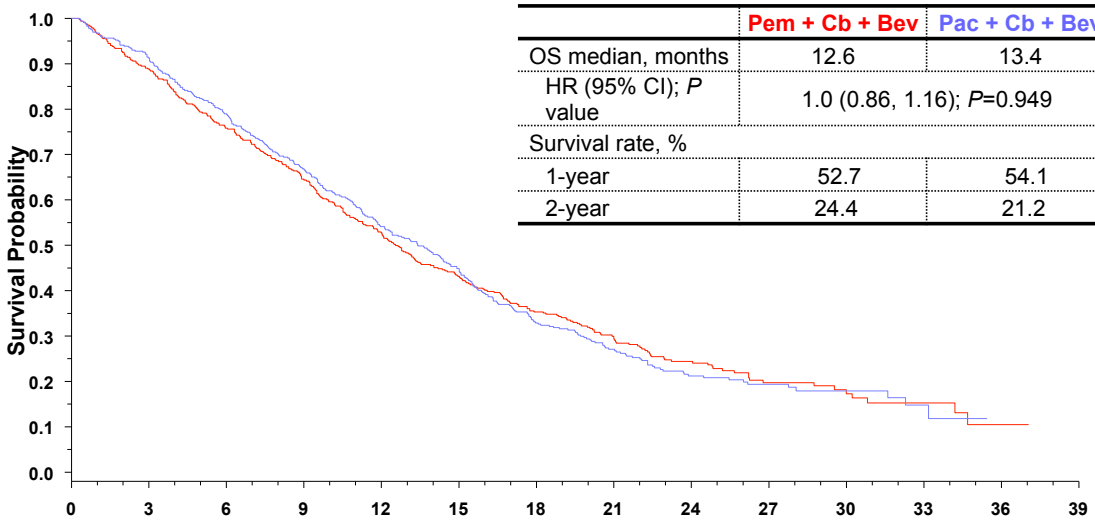
[a]Exploratory analysis
Censoring rate for Pem + Cb + Bev was 26.9; for Pac + Cb + Bev was 23.3.
TTPD=time to progressive disease.
With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

PointBreak: OS From Randomization (ITT)



	Pem + Cb + Bev	Pac + Cb + Bev
OS median, months	12.6	13.4
HR (95% CI); *P* value	1.0 (0.86, 1.16); *P*=0.949	
Survival rate, %		
1-year	52.7	54.1
2-year	24.4	21.2

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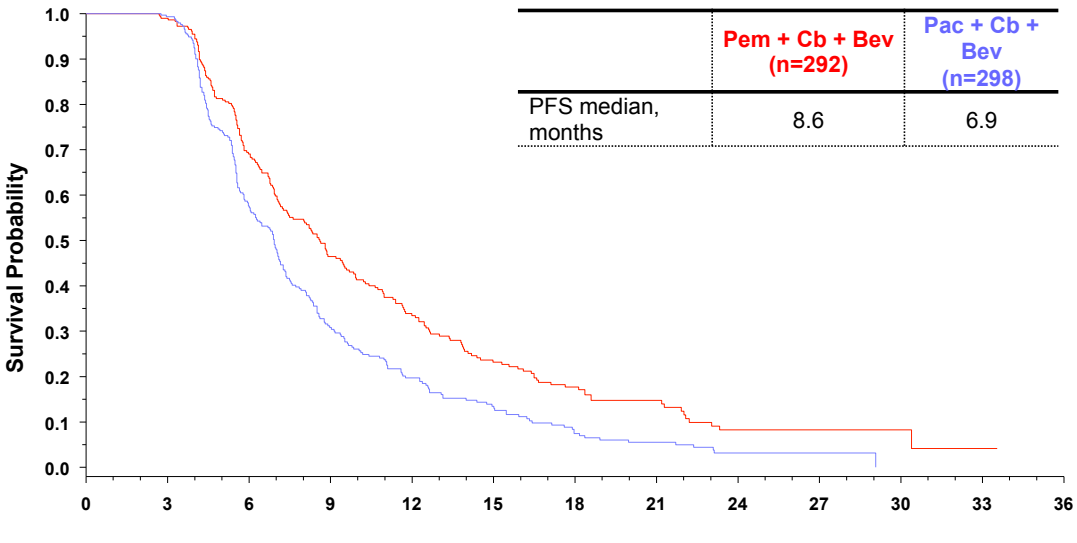
Censoring rate for Pem + Cb + Bev was 27.8; for Pac + Cb + Bev was 27.2
With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

PointBreak Prespecified Analysis: PFS From Randomization (Maintenance Group)



	Pem + Cb + Bev (n=292)	Pac + Cb + Bev (n=298)
PFS median, months	8.6	6.9

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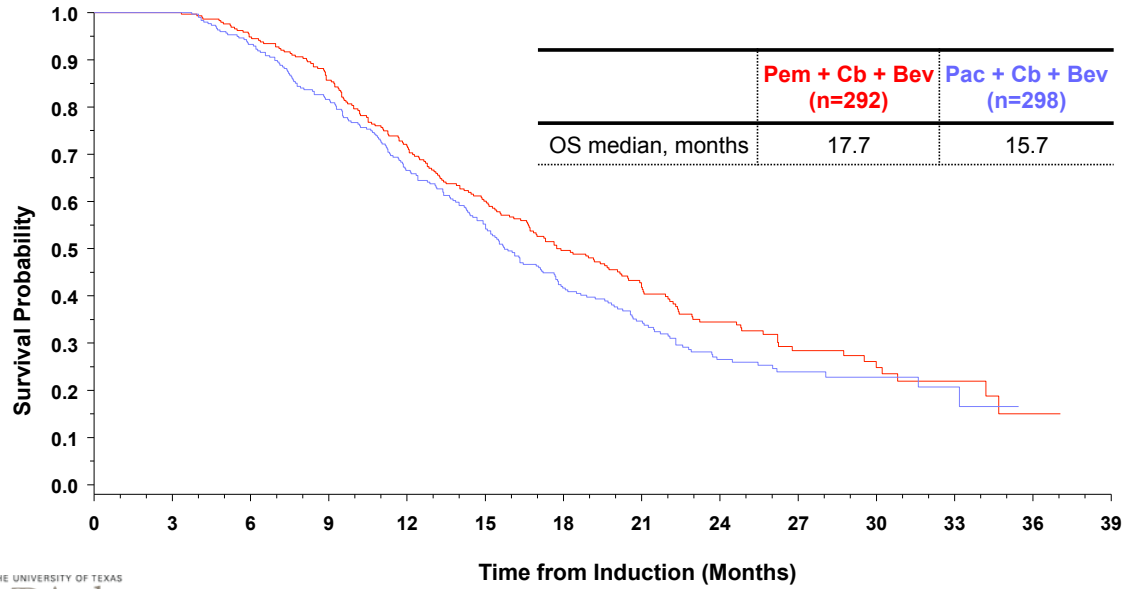
Prespecified exploratory noncomparative subgroup analyses.
Censoring rate for Pem + Cb + Bev was 24.7; for Pac + Cb + Bev was 14.1
With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

PointBreak Prespecified Analysis: OS From Randomization (Maintenance Group)



	Pem + Cb + Bev (n=292)	Pac + Cb + Bev (n=298)
OS median, months	17.7	15.7

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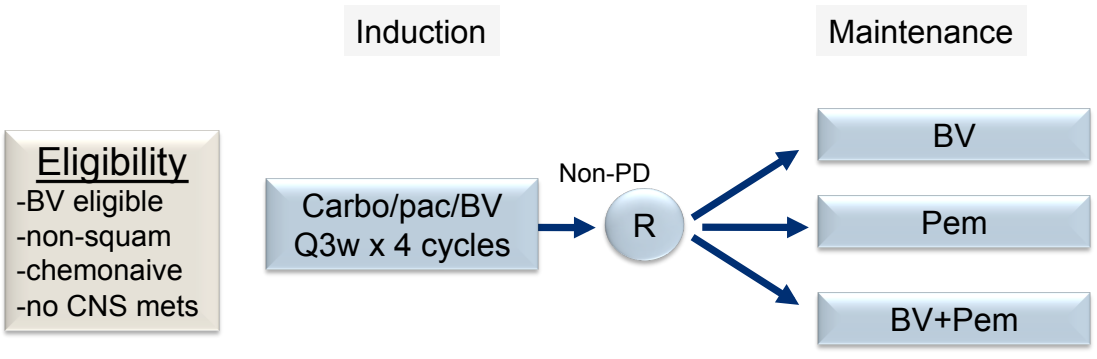
Prespecified exploratory noncomparative subgroup analyses.
Censoring rate for Pem + Cb + Bev was 36.0; for Pac+ Cb + Bev was 30.2
With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

ECOG-E5508: Phase III trial of BV, Pem, or BV+Pem as maintenance therapy in advanced NSCLC



Primary endpoint: OS
Secondary: PFS

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PI: S. Ramilingam; clinicaltrials.gov; trial NCT01107626

Maintenance therapy for adenocarcinoma: my approach

- If using BV with induction without pem:
  - Continue BV
  - if EGFR M+ or suspicion high use BV/erlotinib
- If Pem/platinum/BV induction
  - Continue BV (consider adding pem if progression)
  - Consider Pem/BV in good PS pts tolerating rx well
  - if EGFR M+ or suspicion use BV/erlotinib
- If not using BV with induction:
  - Pem (cont. or switch) in good PS pts tolerating rx well
  - if EGFR M+ or suspicion use erlotinib

Module IV: Management of ALK and ROS1-positive NSCLC

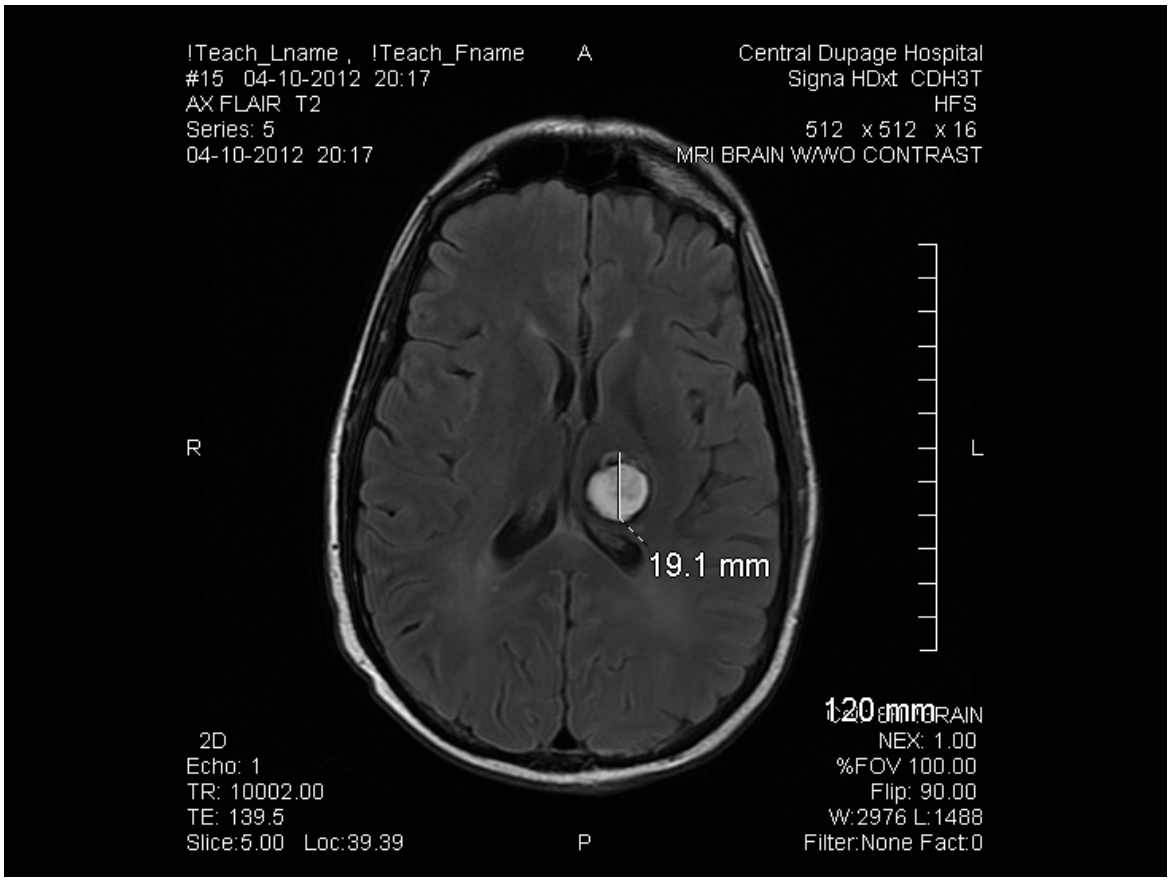
D. Ross Camidge, MD PhD
Director, Thoracic Oncology Clinical Program
Associate Director for Clinical Research
University of Colorado Comprehensive Cancer Center

Neil Love, May 31st 2013

University of Colorado
Cancer Center

Case: Dr Ferris (Dr Camidge)

- 43 yo man, never smoker
- 2/2012:
  - Mental status change, right-sided weakness, visual changes, seizure
  - Brain MRI: Multiple lesions, some with hemorrhage
  - CT: RLL mass, extensive bone and thoracic mets
  - Bronchoscopy: Adenoca, EGFR mutant-negative
  - Whole-brain RT, ZDA, carbo/pem/bev → GI toxicity
- 4/2012:
  - ALK mutation assay returns as positive
  - Crizotinib 250 mg BID → neutropenia, dental infection → 200 mg BID
  - Excellent PR, PS 0, doing well
  - Still on treatment (14 mo)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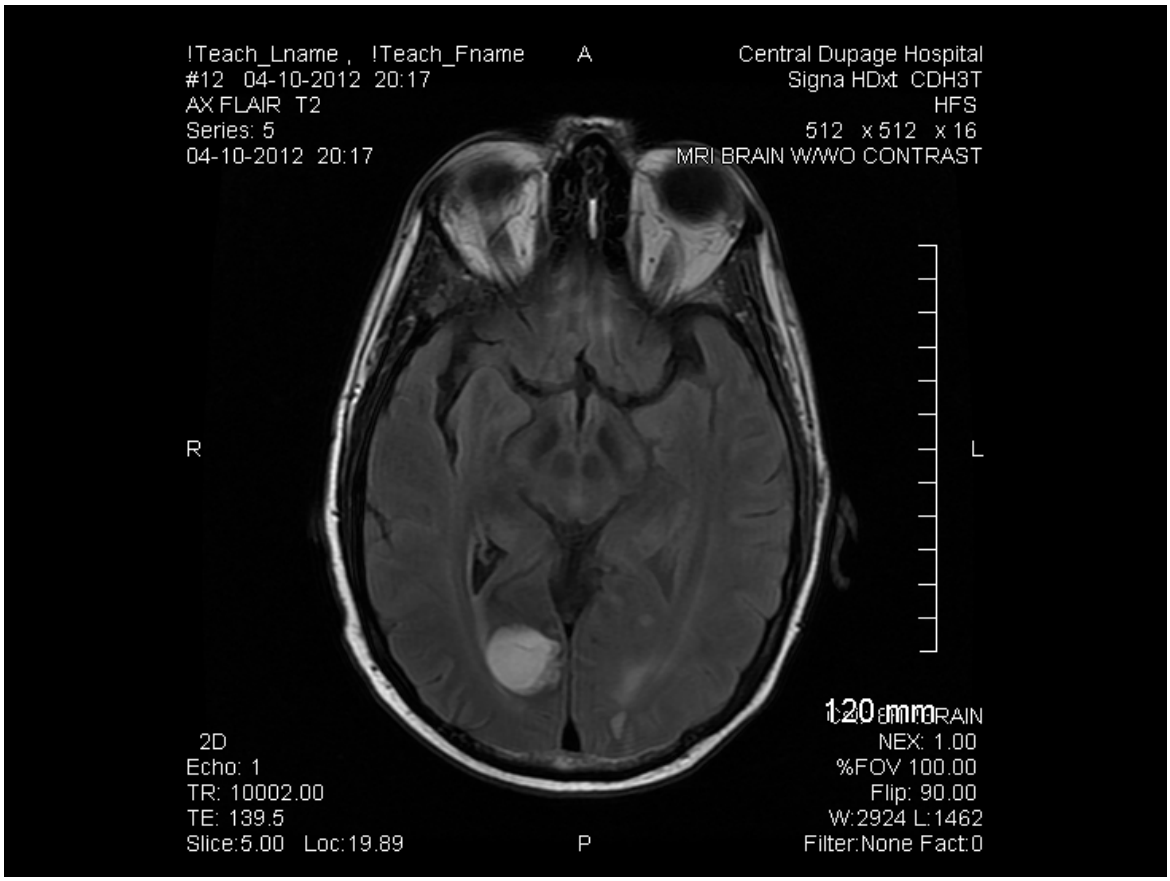
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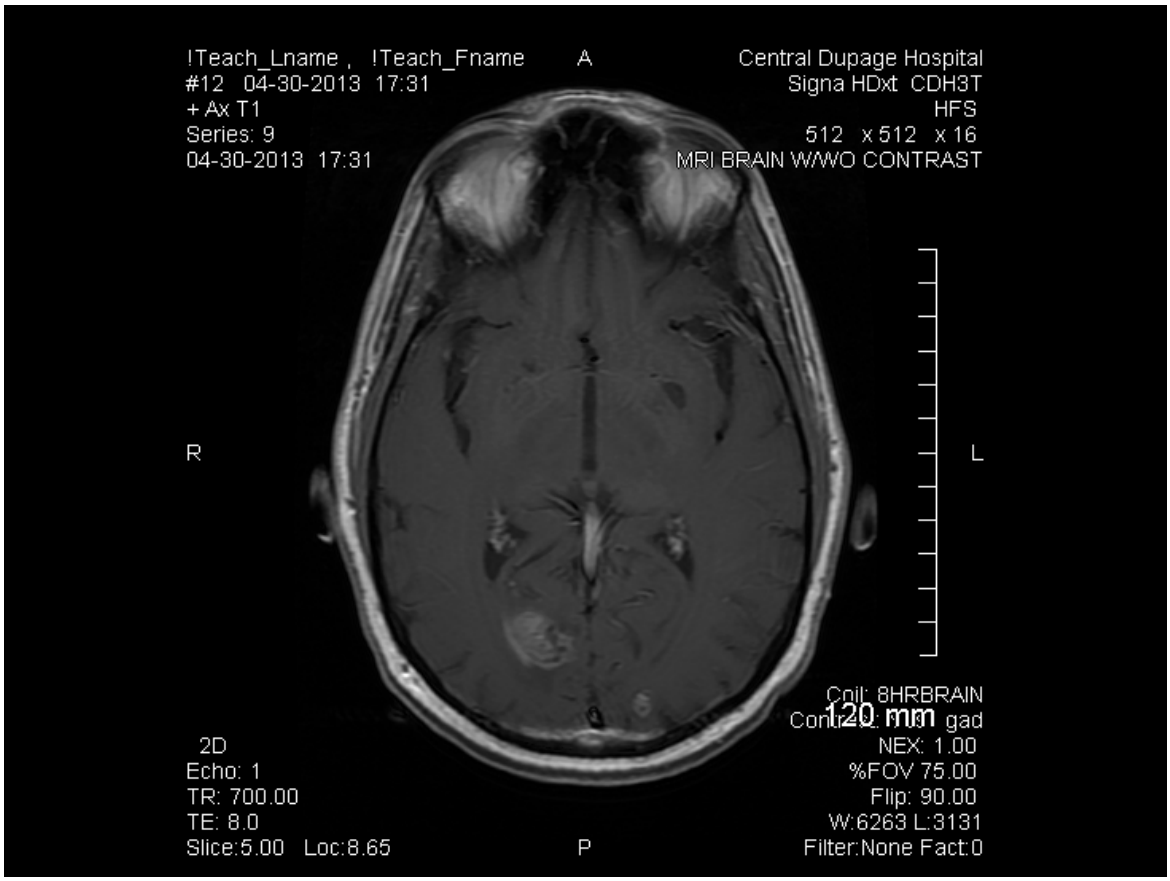
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120 mm
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Contrast: gad
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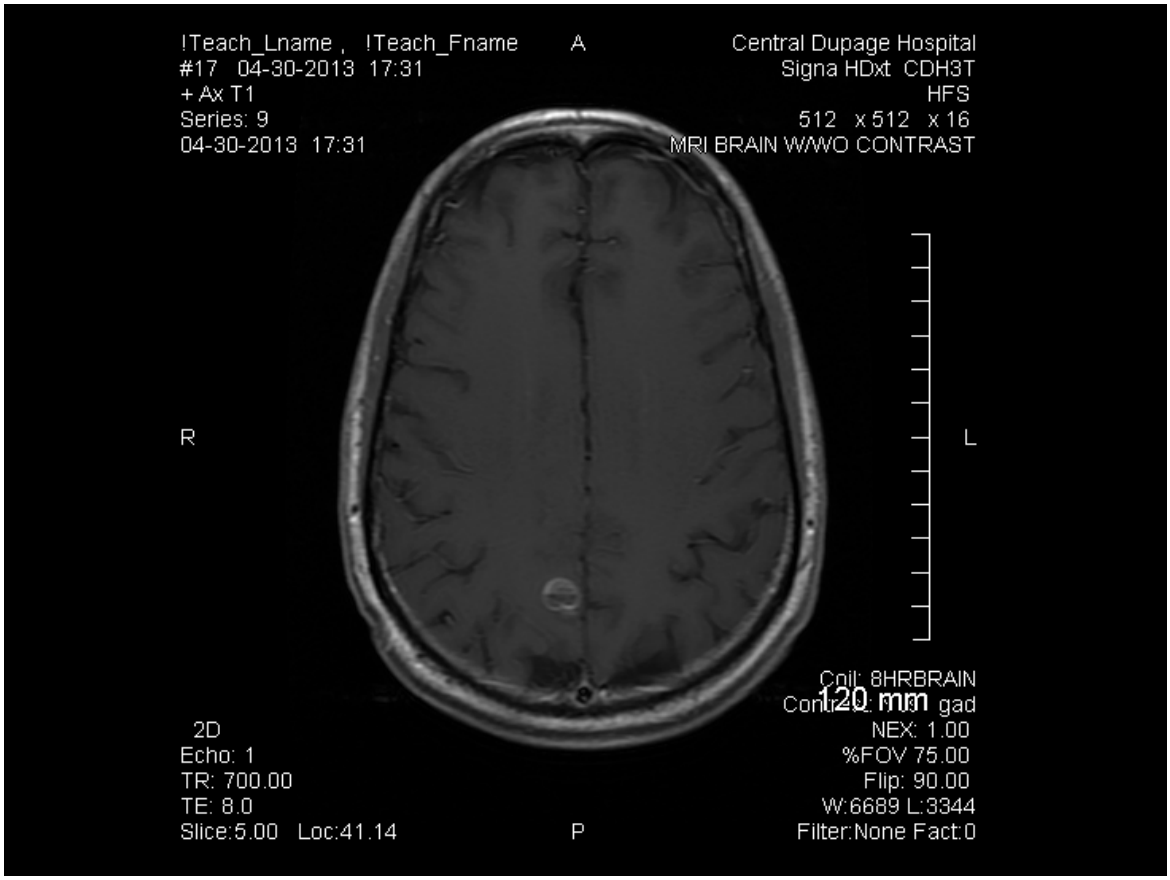
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Signa HDxt CDH3T
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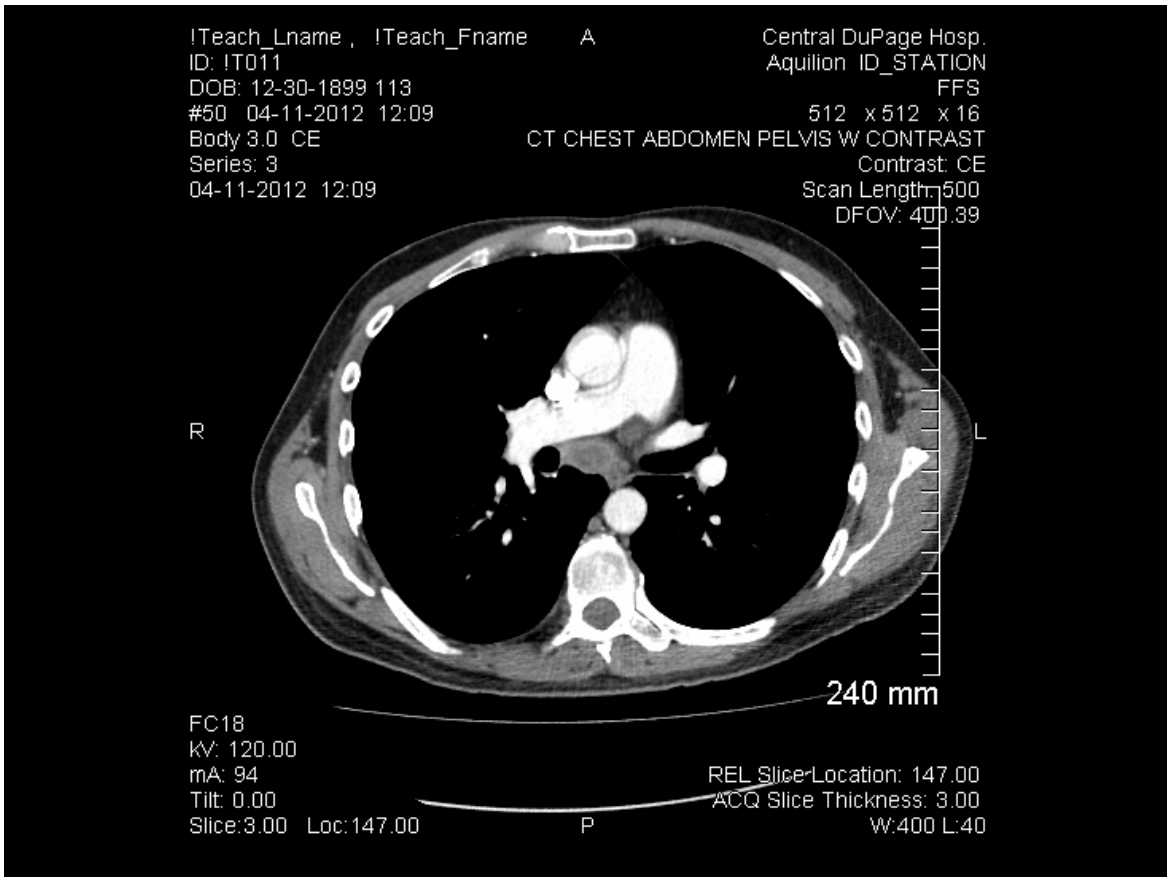
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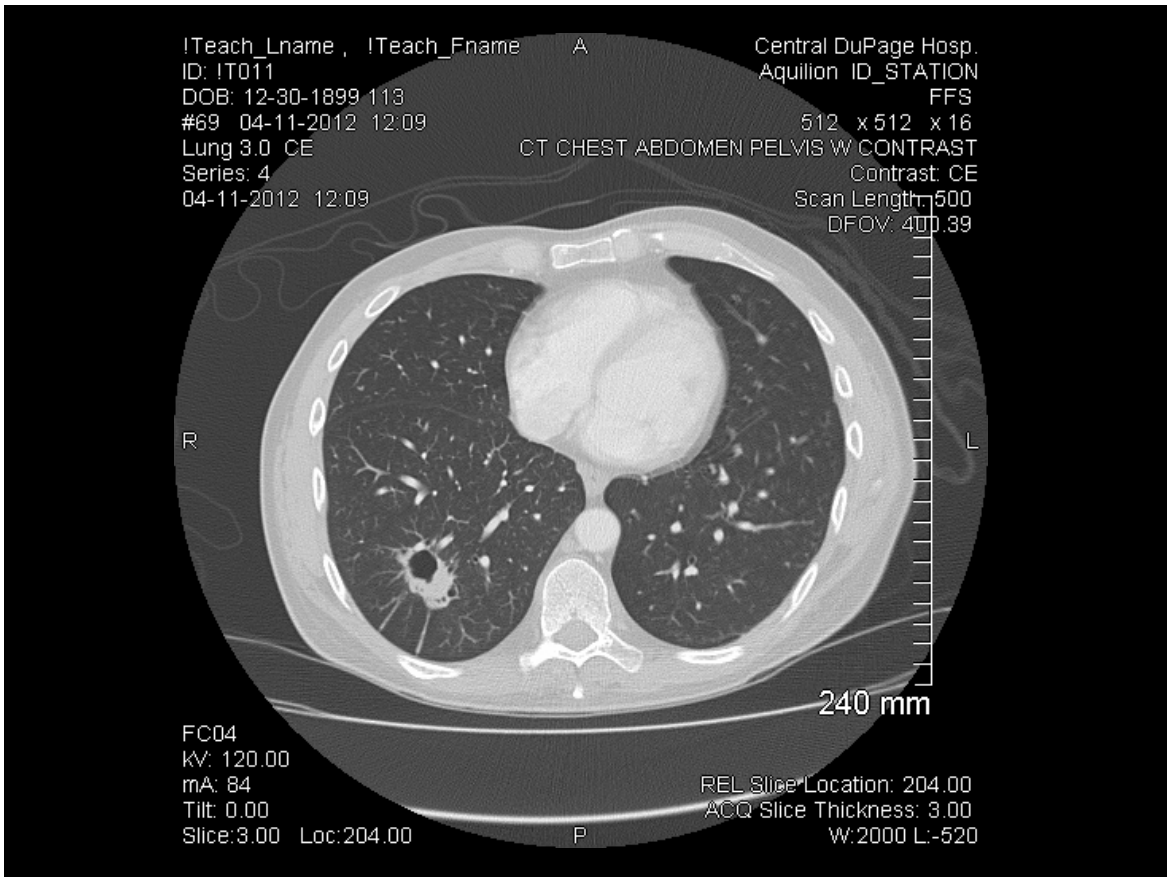
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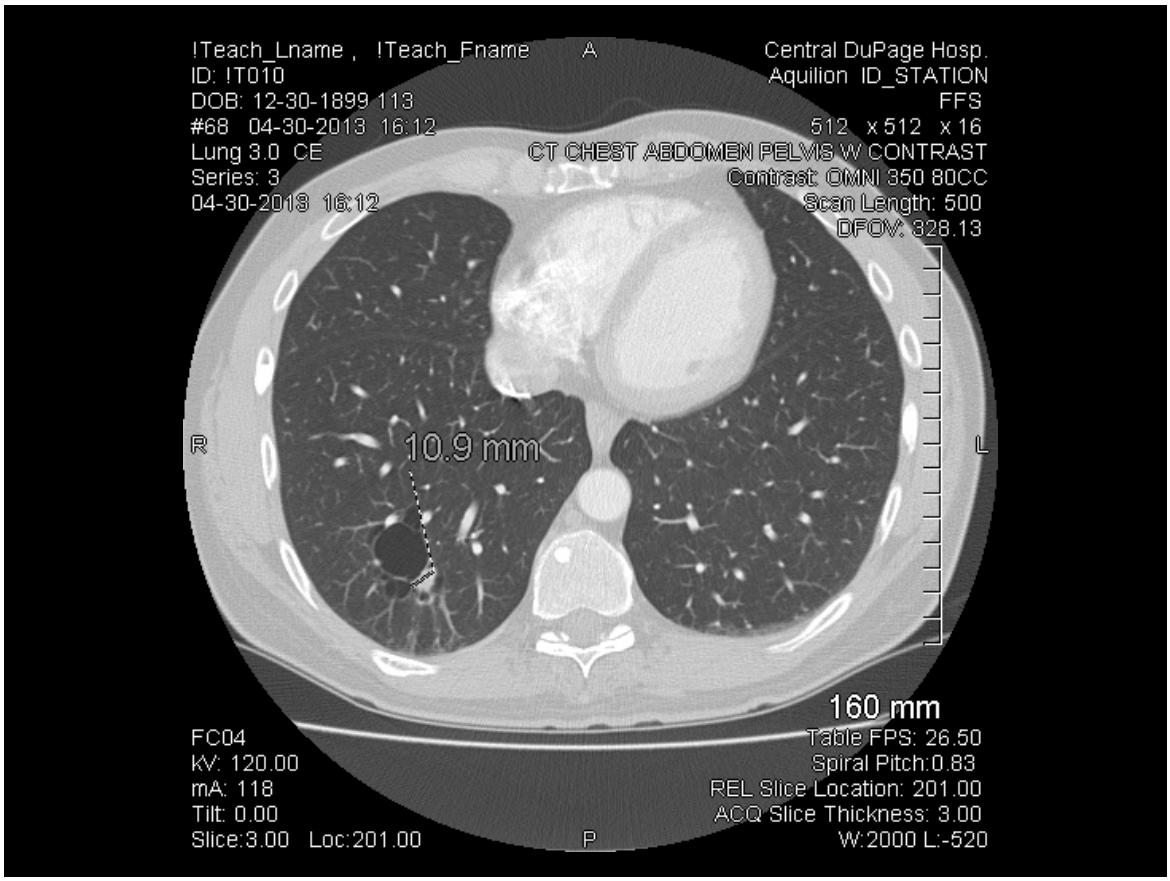


Case: Dr Ferris (Dr Camidge), continued

- 5/30/13
  - Asymptomatic with controlled systemic disease
  - Surveillance brain MRI every 3 months noted all brain lesions stable except 1:
    - Right parietal lesion increased in size with associated hemorrhage and surrounding edema
    - Stereotactic radiosurgery and dex (crizotinib held during radiosurgery, then resumed)

Case: Dr Ferris (Dr Camidge)
Discussion points

- Nausea with crizotinib: ? taking with food
- Neutropenia and dose reduction: Patient is 130 pounds
- Continuing ZDA in the face of response → dental infection
- Assessment for androgen deprivation syndrome:
  - Free testosterone = 19.8 (normal 35-150)
  - Total testosterone = 65 (normal 250-1,100)
  - Asymptomatic for hypogonadism (true deficit or lab aberration?)
- What to do if the disease progresses systemically?

Should all patients with ALK or ROS1-positive disease be started on crizotinib, or should select patients receive first-line chemotherapy/ biologic therapy?

1st line Facts

- Crizotinib and ALK
  - PROFILE 1001 – phase I any line (24/149 (16%)*)
  - PROFILE 1005 – phase II ≥2nd line (3/901**)
  - PROFILE 1007 – phase III 2nd line
  - [PROFILE 1014] – 1st line – ongoing
- Crizotinib and ROS1
  - PROFILE 1001 – phase I any line (2/15 (13%)***)

*Camidge et al, TLO 2012
**protocol deviations, Kim et al, ASCO 2012
***Shaw et al, ASCO 2012

	n/N	Proportion with objective response (95% CI)*
Age		
<65 years	74/123	60·2% (50·9–68·9)
≥65 years	13/20	65·0% (40·8–84·6)
Sex		
Men	46/71	64·8% (52·5–75·8)
Women	41/72	56·9% (44·7–68·6)
ECOG PS score		
0	29/53	54·7% (40·4–68·4)
1	46/72	63·9% (51·7–74·9)
2	12/17	66·7% (44·0–89·7)
3	0/1	0·0% (0·0–97·5)
Number of previous advanced or metastatic systemic treatments		
0	14/22	63·6% (40·7–82·8)
1	26/44	59·1% (43·2–73·7)
2	20/31	64·5% (45·4–80·8)
≥3	27/46	58·7% (43·2–73·0)
Ethnic origin		
Asian	30/39	76·9% (60·7–88·9)
Non-Asian	57/104	54·8% (44·7–64·6)

143 patients were evaluable for response. ECOG PS=Eastern Cooperative Oncology Group performance status. *Using the exact method based on the F distribution.

Table 2: **Objective response rate according to patient characteristics**

Camidge et al, TLO 2012

ORR: Appears independent of line of therapy

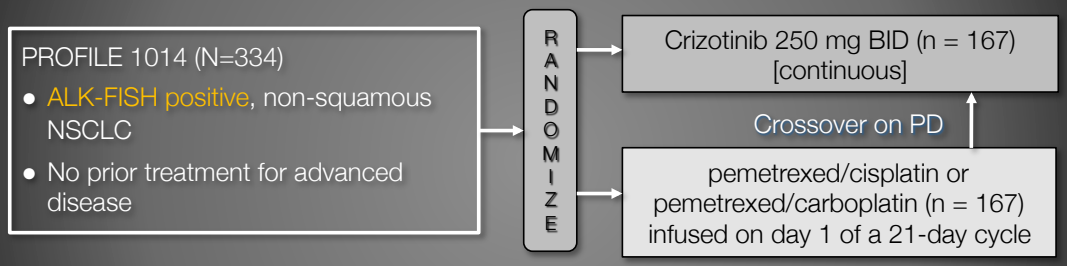
Median PFS:
1st line (n=24)
18.3m (95% CI:8.3-NR)

≥2nd line (n=125) 9.2m (95% CI: 7.3-12.7)

Main approaches

- Theoretical
  - *'Best drug' given first*
- Legal
  - *FDA ALK license is not line of therapy restricted*
  - *EMEA ALK license is line of therapy restricted*
  - *ROS1 not a licensed indication anywhere (yet)*
- Pragmatic
  - *Molecular test result back in time for 1st line therapy?*

Randomized trials of crizotinib in *ALK*+ NSCLC: 1014



Are specific chemotherapeutic agents/regimens more effective than others in patients with known ALK rearrangements?

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Cancer Center

'EGFR TKI'
Median TTP
5 mo ALK+
13 mo EGFR+

10 ALK+, no PRs to erlotinib

'1st line platinum-based combination regimen'
Median TTP
8-10 mo all groups

13 ALK+, 3 PRs (25%) to platinum-based chemo
(all non-pemetrexed containing*)

Shaw et al, JCO 2009

* Alice Shaw, Personal communication

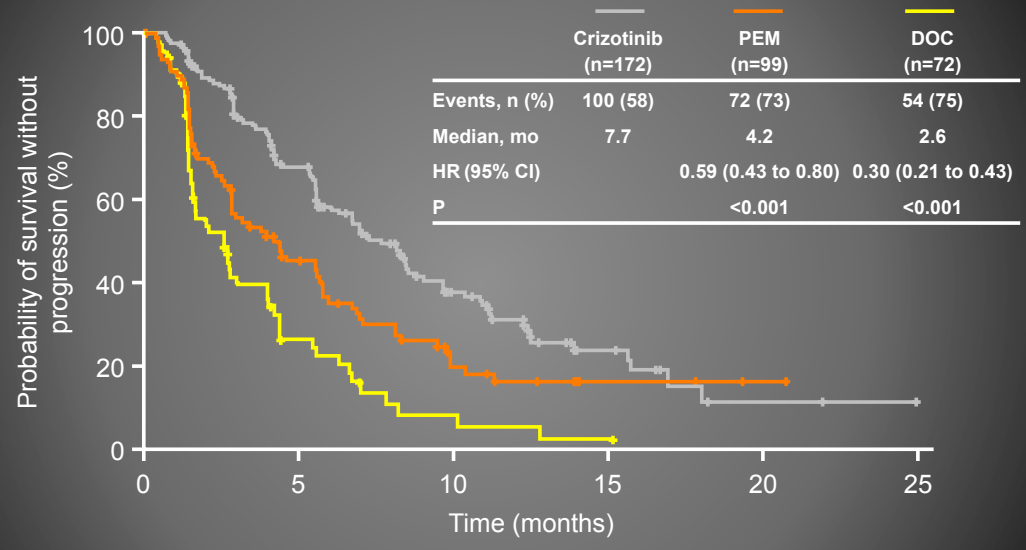
PFS by molecular status on pemetrexed-based therapy

Parameter	HR	95% CI	P value (Chi squared)
Molecular status (vs triple negative)			
ALK+	0.36	0.17-0.73	0.0051*
EGFR mutant	1.0	0.49-2.04	0.9983
KRAS mutant	0.55	0.28-1.1	0.0952

* P values <0.05

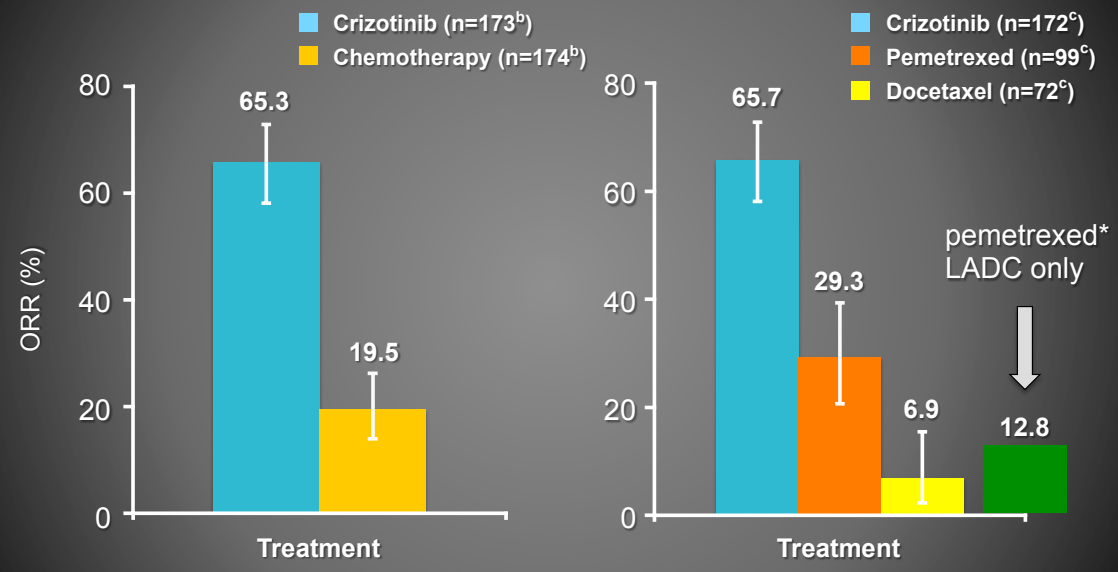
Camidge et al., *J Thoracic Oncol.* (2011)

PROFILE 1007: PFS of Crizotinib vs Pemetrexed or Docetaxel



With permission from Shaw et al, ESMO 2012

PROFILE 1007:
ORR[a] by Independent Radiologic Review



[a]RECIST v1.1; [b]ITT population; [c]as-treated population

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.0001

With permission from Shaw et al., ESMO 2012 abstr LBA1
*Hanna et al., JCO 2004
*Scagliotti et al., Oncologist 2009

Are other ALK inhibitors either available or under investigation?

University of Colorado Cancer Center

Many new ALK inhibitors in development –

Table 4. Anaplastic lymphoma kinase inhibitors currently in development.

Drug	Company	Phase of testing	Status	Clinicaltrials.gov ID
Crizotinib (PF-023341066)	Pfizer	Phase II/III	Open	NCT00585195, NCT00932893, NCT01154140 and NCT00932451
ASP-3026	Astellas	Phase I	Open	NCT01284192
XL228	Elexis	Phase I	Completed	NCT00526838
LDK378	Novartis	Phase I with data in criz failures		NCT01283516
AP-26113	Ariad	Phase I with data in criz failures		
CH5424802	Chugai	Phase I with data in criz naive		
CEP-37440	Cephalon	Preclinical		

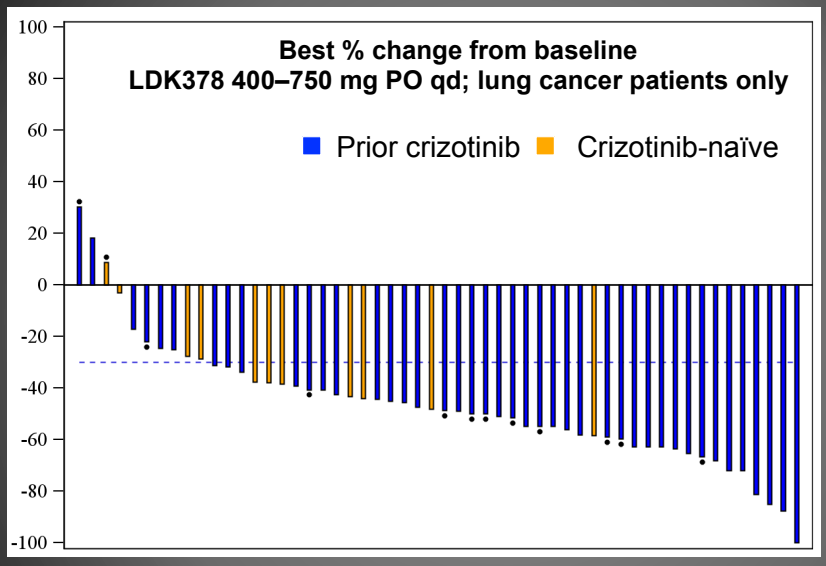
Data taken from [101].

+HSP90 inhibitors e.g. from Astex, Infinity, Novartis, Synta
+ pemetrexed studies (SWOG1300)
+ immune stimulant studies (PD-1/PDL-1)

University of Colorado Cancer Center

Modified from:
Weickhardt and Camidge, *Clin Invest* 2011

LDK378 in advanced ALK+ NSCLC



With permission from Shaw et al, ESMO 2012

	N	CR	CR + PR (RECIST 1.0)	CR + PR + uPR
NSCLC with prior crizotinib, ≥400 mg/d	45	1 (2%)	21 (47%)	36 (80%)

Therapeutic Decision-Making for Patients with EGFR Mutations

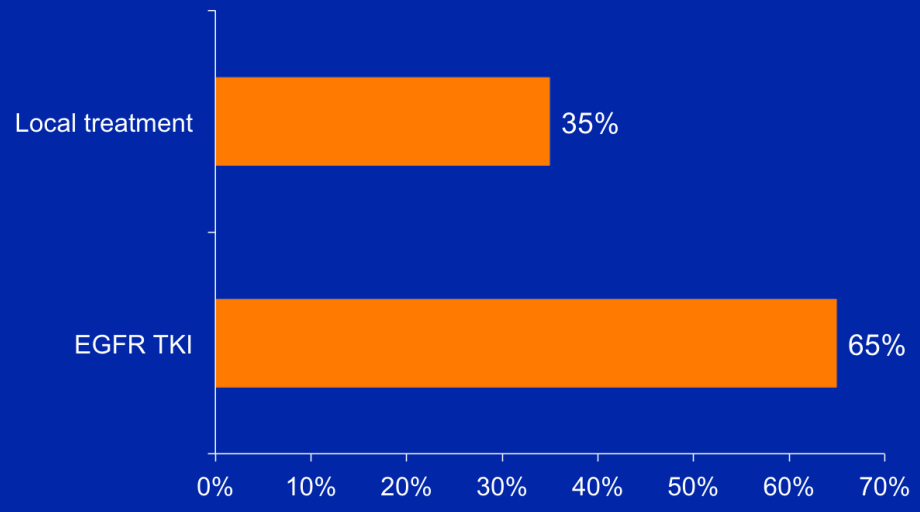
Robert Pirker
Medical University of Vienna

The Practical Application of Research Advances and Emerging Data in the Management of Non-Small Cell Lung Cancer
Chicago, 31 May 2013

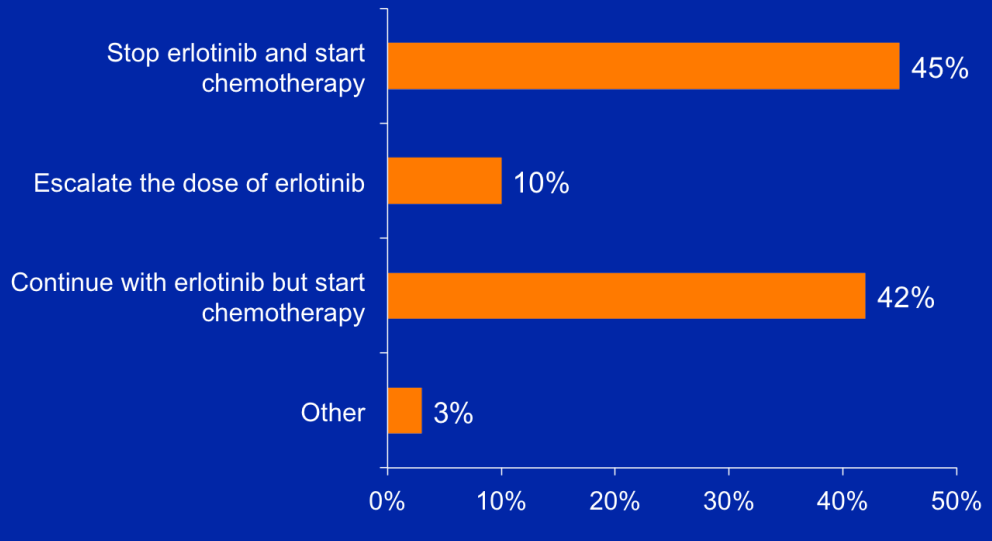
Case: Dr Hager (Dr Pirker)

- 56 yo woman, nonsmoker
- S/p RLL lobectomy for asymptomatic adenoca
- 27 mm, 1 node + → cis/vinorelbine (GI toxicity)
- Routine restaging: Mets to mediastinum, lung, liver, bone and brain (4 lesions)
- EGFR del(19) mutation
- Erlotinib 150 mg qd → near complete response
- No radiation therapy yet

A 56-year-old patient with adenocarcinoma of the lung and an EGFR exon 19 deletion presents with extensive systemic metastases and 4 small brain lesions. The patient is asymptomatic. Would you use local treatment to the brain (radiation therapy) or start an EGFR TKI?



A patient with an EGFR mutation receives erlotinib 150 mg PO daily and after responding for 1 year starts to show asymptomatic but definitive disease progression. What would you likely do outside of a trial setting?



EGFR-directed tyrosine kinase inhibitors (TKIs)

- Gefitinib
- Erlotinib
- Icotinib (EGFR)
- Afatinib (ErbB Family Blocker)
- Dacomitinib (pan-HER)
- AZD8931 (EGFR, HER2, HER3)
- Lapatinib (EGFR, HER2)
- Canertinib (EGFR, HER2)
- Neratinib (EGFR, HER2)
- Vandetanib (EGFR, VEGFR, RET)

Gefitinib & erlotinib in advanced NSCLC

- No improvement of 1st line chemotherapy

INTACT-1, INTACT-2; TALENT, TRIBUTE

- Gefitinib in patients pre-treated with chemotherapy

IDEAL-1, IDEAL-2

ISEL: Gefitinib vs BSC *Thatcher N et al. Lancet 2005,366,1527*

INTEREST: Gefitinib vs docetaxel *Kim ES et al. Lancet 2008,372,1809*

- Erlotinib established in patients pretreated with chemotherapy

BR.21 *Shepherd FA et al. NEJM 2005,353,133*

- Erlotinib established as maintenance therapy in patients with stable disease after 1st line chemotherapy (European Union)

SATURN *Cappuzzo F et al. Lancet Oncol 2010,11,521*

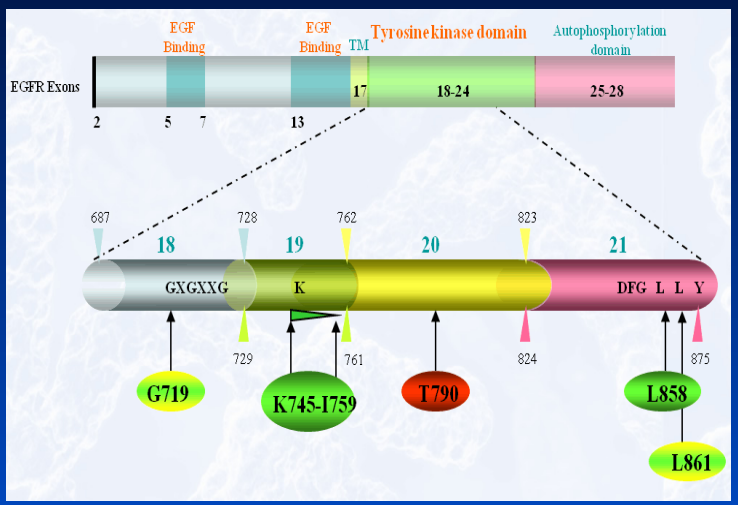
Gefitinib & erlotinib in advanced NSCLC

- Initially studied in unselected patients (IDEAL, ISEL, BR.21)
- Preferential efficacy in selected patients

Response rate	*Survival*
Adenocarcinoma	Never-smokers
Females	South-East Asians
Never-smokers	
South-East Asians	

- Efficacy in patients with EGFR-activating mutations
  - Exon 19 deletions, exon 21 point mutations (L858R)
- Studies in selected patients
  - Clinical selection
  - EGFR-activating mutations

EGFR mutations and response to TKIs



Green = responsive
Red = non-responsive
Yellow-green = mixed response outcomes

http://www.somaticmutations-egfr.info

Randomized studies of first-line EGFR TKIs in patients with EGFR mutation

Author	Study	N (EGFR mut+)	RR (%)	Median PFS (Months)
Mok *et al.*	IPASS	261	71.2 *vs.* 47.3	9.8 *vs.* 6.4
Han *et al.*	First-SIGNAL	27	84.6 *vs.* 37.5	8.4 *vs.* 6.7
Mitsudomi *et al.*	WJTOG 3405	86	62.1 *vs.* 32.2	9.2 *vs.* 6.3
Maemondo *et al.*	NEJGSG002	114	73.7 *vs.* 30.7	10.8 *vs.* 5.4
Zhou *et al.*	OPTIMAL	154	83 *vs.* 36	13.1 *vs.* 4.6
Rosell *et al.*	EURTAC	174	58 *vs.* 15	9.7 *vs.* 5.2
Yang *et al.*	LUX LUNG-3	345	56 *vs.* 23	11.1 *vs.* 6.9

Mok et al. NEJM 2009, 361, 947; Han et al. JCO 2012, 30, 1122; Mitsudomi et al. Lancet Oncology 2010, 11, 121; Maemondo et al. NEJM 2010, 11, 121; Zhou et al. Lancet Oncology 2011, 12, 735; Rosell et al. Lancet Oncol 2012, 13, 239; Yang et al. ASCO 2012, abstr LBA7500.

IPASS: PFS by Mutation Status within Treatment Arm

	Gefitinib	Carboplatin/ paclitaxel	Hazard ratio	*p*-value
PFS events (intent-to-treat population, N = 609; 608)	74.4%	81.7%	0.74	<0.001
PFS events (EGFR mutation-positive population, N = 132; 129)	73.5%	86.0%	0.48	<0.001

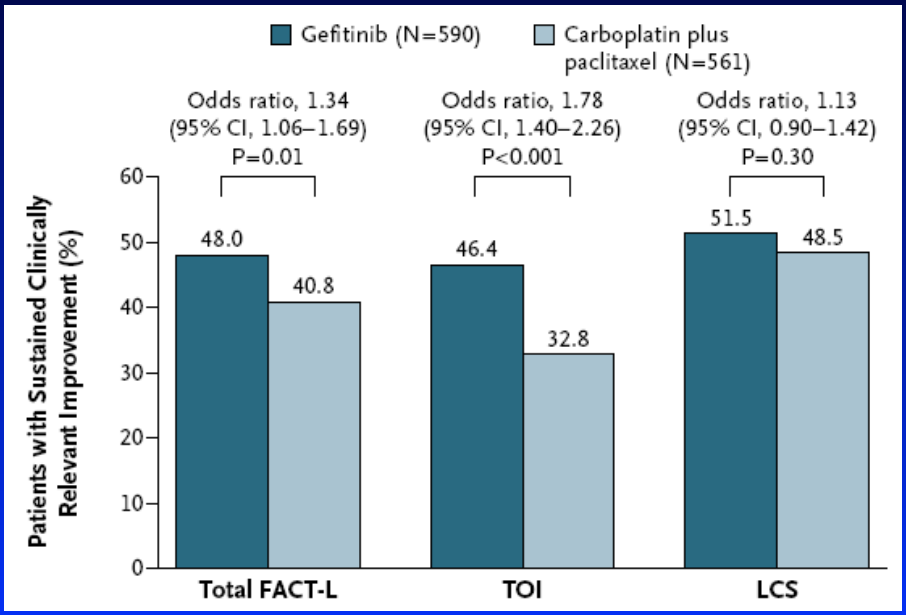
Gefitinib, HR=0.19, 95%CI (0.13, 0.26), p<0.001
No. events M+ = 97 (73.5%), No. events M- = 88 (96.7%)

Carboplatin/paclitaxel, HR=0.78, 95%CI (0.57, 1.06), p=.1103
No. events M+ = 111 (86.0%), No. events M- = 70 (82.4)

Mok T, et al. ESMO 2008.
Mok T et al. N Engl J Med 2009;361:1
0.1056/NEJMoa0810699

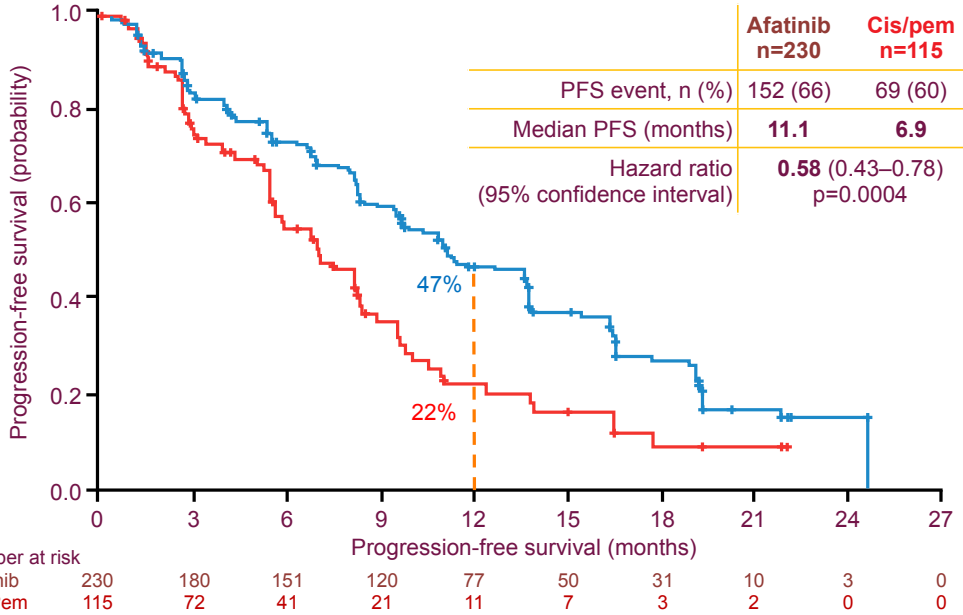
IPASS

Mok T et al. NEJM 2009, 361, 947



Primary endpoint: PFS

Independent review – all randomized patients



	Afatinib n=230	Cis/pem n=115
PFS event, n (%)	152 (66)	69 (60)
Median PFS (months)	**11.1**	**6.9**
Hazard ratio (95% confidence interval)	**0.58** (0.43–0.78) p=0.0004	

With permission from Yang JC, et al.

EGFR-directed TKIs
Progress

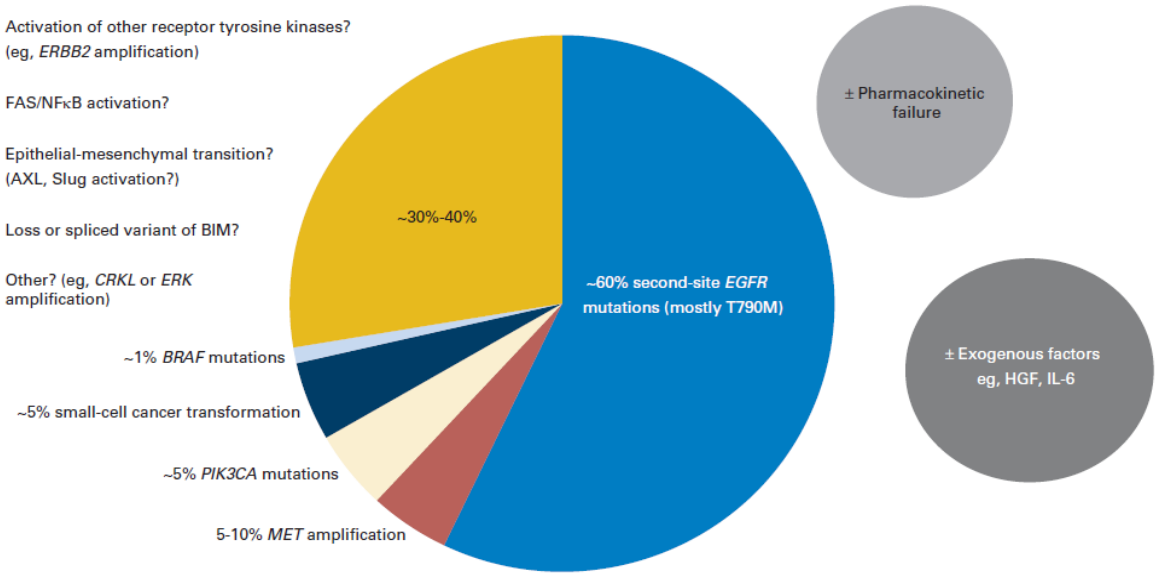
- EGFR TKIs show preferential efficacy in tumors with EGFR-activating mutations.
- Gefitinib, erlotinib & afatinib administered until disease progression improve progression-free survival & quality of life compared to first-line chemotherapy in patients who harbor EGFR-activating mutations in their tumors.
- Mutation testing at the time of diagnosis has been established as a standard for patients with advanced NSCLC.
- Assessment as adjuvant therapy in patients with resected NSCLC
  - RADIANT
- Major impact on molecular research

EGFR-directed TKIs
Hurdles

- A survival benefit has not been proven.
  - Crossover ?
  - Acquired resistance to subsequent chemotherapy ?
  - Detrimental effect on survival in earlier stages ?
- TKIs versus 1st line chemo plus maintenance therapy ?
- Patients develop resistance against TKIs.
  - Primary versus acquired resistance
- Re-biopsy at time of resistance ?
- Reversal studies are ongoing.
- Response assessment
  - Are RECIST appropriate for these patients ?
  - Treatment beyond progression ?

EGFR TKI-resistant NSCLC

Ohashi K et al. JCO 2013, 31, 1070



Reversal of TKI resistance

- MET inhibitors
  - Phase III trial with erlotinib ± onartuzumab (MetMAb) is ongoing in patients with MET high tumors.
  - Tivantinib failed in a Phase III trial in unselected patients.
- Second & third generation TKIs
  - Afatinib did not improve survival but prolonged PFS (LUX-Lung 1).
    Miller VA et al. Lancet Oncol 2012,13,528
- Afatinib plus cetuximab: 30% response rate
  Janjigian YYet al. J Clin Oncol. 2011;29 (suppl; abstr 7525). & Ann Oncol. 2012;23 (suppl9; abstr12270).
- Other approaches

TKIs in advanced NSCLC
Treatment at time of progression

- Switch to chemotherapy (e.g. platinum-based doublet) and consider re-treatment with TKI after chemotherapy
- Experimental strategies
  - Continue with TKI
  - Add chemotherapy to TKI
  - Second or third generation TKIs
  - Afatinib plus cetuximab
  - Other approaches

SELECT PUBLICATIONS

Camidge DR et al. **Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed.** *J Thorac Oncol* 2011;6(4):774-80. **Abstract**

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Fidias PM et al. **Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer.** *J Clin Oncol* 2009;27(4):591-8. **Abstract**

Han JY et al. **First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung.** *J Clin Oncol* 2012;30(10):1122-8. **Abstract**

Kabbinavar FF et al. **Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 7526**.

Kim ES et al. **Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial.** *Lancet* 2008;372(9652):1809-18. **Abstract**

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Maemondo M et al. **Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.** *N Engl J Med* 2010;362(25):2380-8. **Abstract**

Miller VA et al. **A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract LBA8002**.

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Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57. **Abstract**

Patel J et al. **A randomized, open-label, Phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients (pts) with Stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC).** *Proc IASLC* 2012;**Abstract LBPL1**.

Patel JD et al. **Treatment rationale and study design for the pointbreak study: A randomized, open-label phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *Clin Lung Cancer* 2009;10(4):252-6. **Abstract**

Paz-Ares L et al. **Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): A double-blind, phase 3, randomised controlled trial.** *Lancet Oncol* 2012;13(3):247-55. **Abstract**

Perol M et al. **Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study.** *Proc ASCO* 2010;**Abstract 7507**.

Quoix E et al. **Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial.** *Lancet* 2011;378(9796):1079-88. **Abstract**

Quoix E et al. **Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 2**.

Randomized Phase III study of maintenance therapy with bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed following carboplatin, paclitaxel and bevacizumab for advanced non-squamous NSCLC. NCT01107626

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