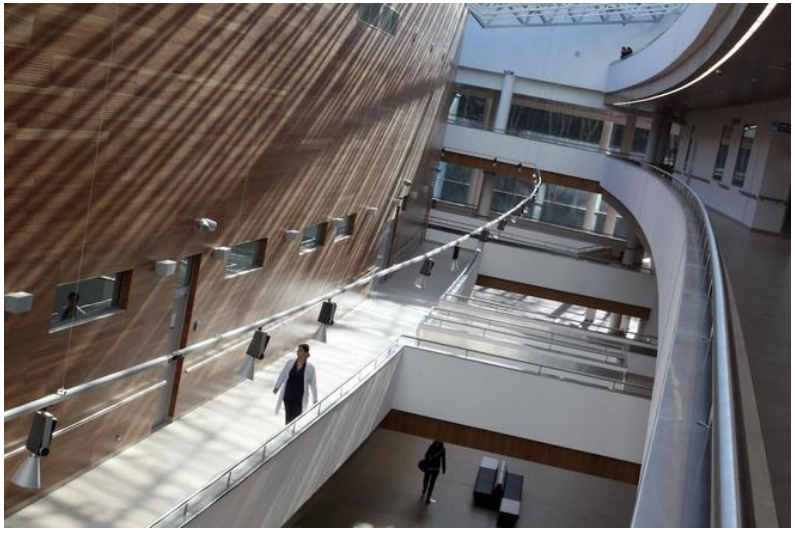


Interaction between radio(chemo)therapy and targeted agents: Toxicity issues

Rafal Dziadziuszko

Medical University of Gdańsk, Poland

15-18 April 2015, Geneva, Switzerland

Organisers

Partners

Disclosures

Clovis, AstraZeneca,
Boehringer Ingelheim, Lilly, Pfizer, Roche

Current use of targeted agents in lung cancer

Oncogene addicted tumors („Total dependence”):

- EGFR mutation
- HER2 mutation
- ALK translocation
- ROS1 translocation
- TRKA, B, C translocation
- RET translocation
- KRAS mutation
- BRAF mutation
- MET amplification

Partial dependence:

- EGFR amplification (?)
- High EGFR IHC score (?)
- Angiogenesis

Five reasons to combine drugs and RT

Rationale	Basic idea	Primary endpoint	Example
Spatial cooperation	RT → LR disease CT → DM	LRC & distant progression, PFS	Adjuvant CT + RT for breast cancer
Cytotoxic enhancement	Enhancing radiation cell killing	LRC	Low dose cDDP + RT in NSCLC
Biological cooperation	Different biological targets	LRC	Tirapazamine + RT
Temporal modulation	Modulating the 4Rs of radiotherapy	LRC	Cetuximab + RT
Normal tissue protection	Reduce toxicity	Toxicity	KGF, amifostine

Bentzen, Harari, Bernier *Nat Clin Pract Oncol* 2007;4:172-80

RT and targeted agents in stage III NSCLC

15-18 April 2015, Geneva, Switzerland

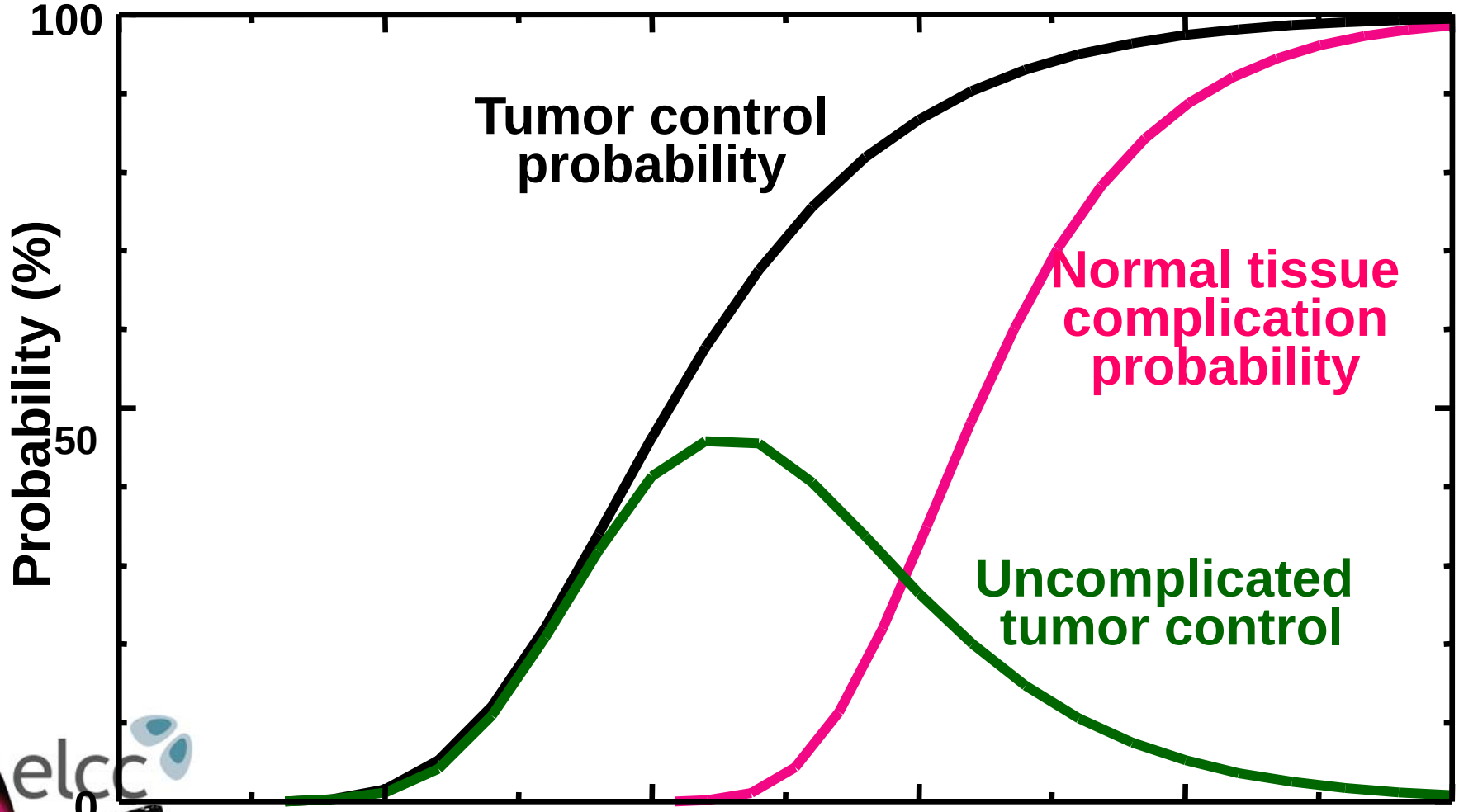
Organisers

Partners

Background

- One-third of NSCLC patients are diagnosed at stage III (T4 and/or N2/N3) disease
- Limited activity of sequential or concurrent chemoradiotherapy (75% local + distant relapse rate)
- No benefit from escalating doses beyond 60 Gy when combined with concurrent chemotherapy
- Therapeutic plateau reached with conventional chemoradiation
- Targeted agents create new opportunity for their potential interaction with radiotherapy

Therapeutic ratio may only be increased if the drug enhances the cytotoxic effect of radiotherapy in cancer cells more strongly than in normal cells



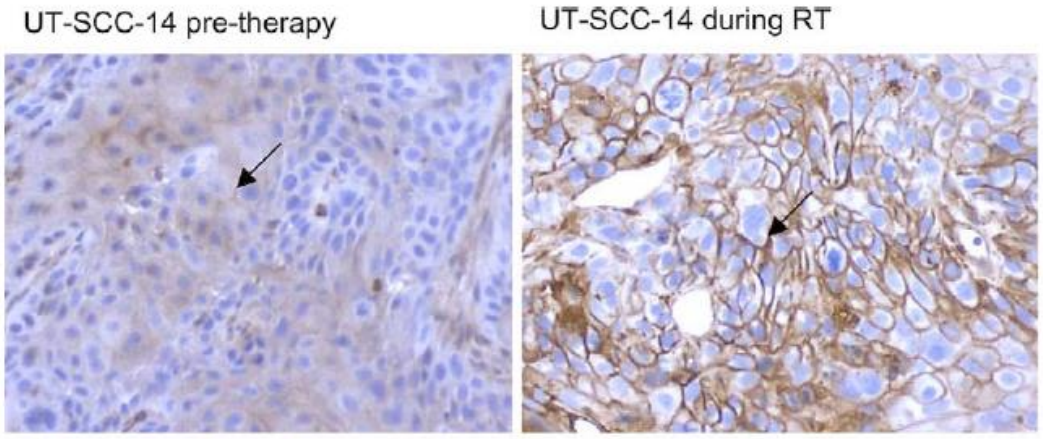
Currently available targeted agents for potential radiotherapy combinations in NSCLC

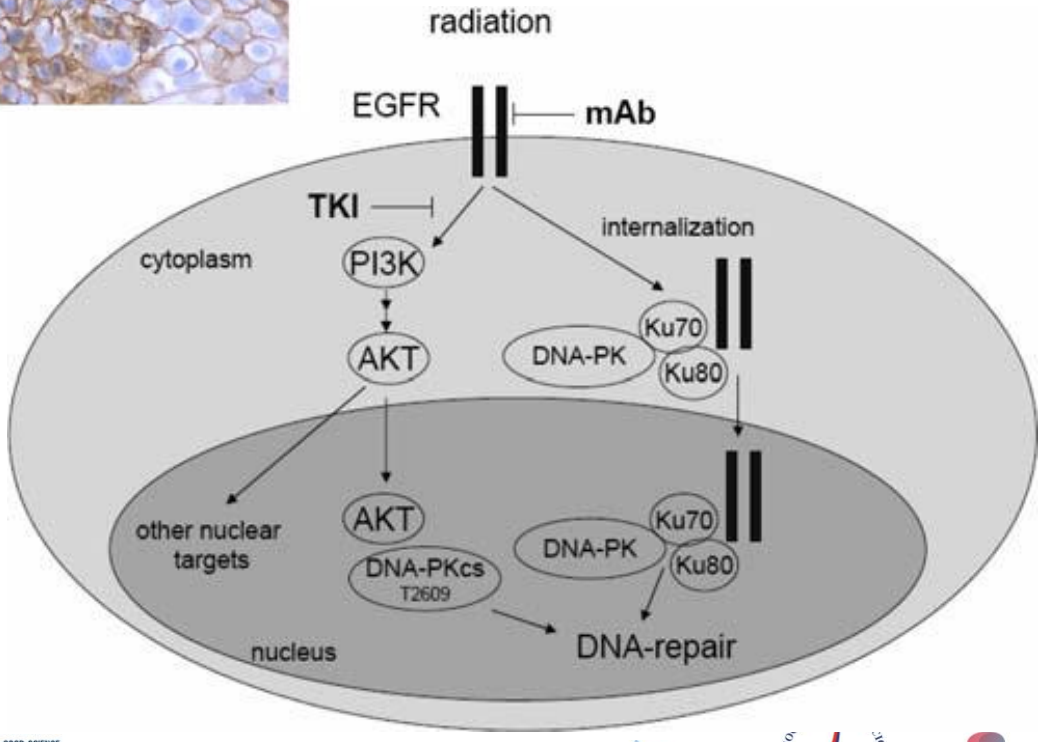
- Anti-EGFR agents
  - TKI inhibitors (gefitinib, erlotinib, afatinib)
  - monoclonal antibodies (cetuximab, panitumumab)

- Antiangiogenic and vascular disrupting agents
  - bevacizumab
  - multi-targeted TKI (vandetanib)
  - endostatin
  - thalidomide
  - AE-941 (a shark cartilage extract)

Anti-EGFR agents

Radiotherapy and EGFR inhibitors





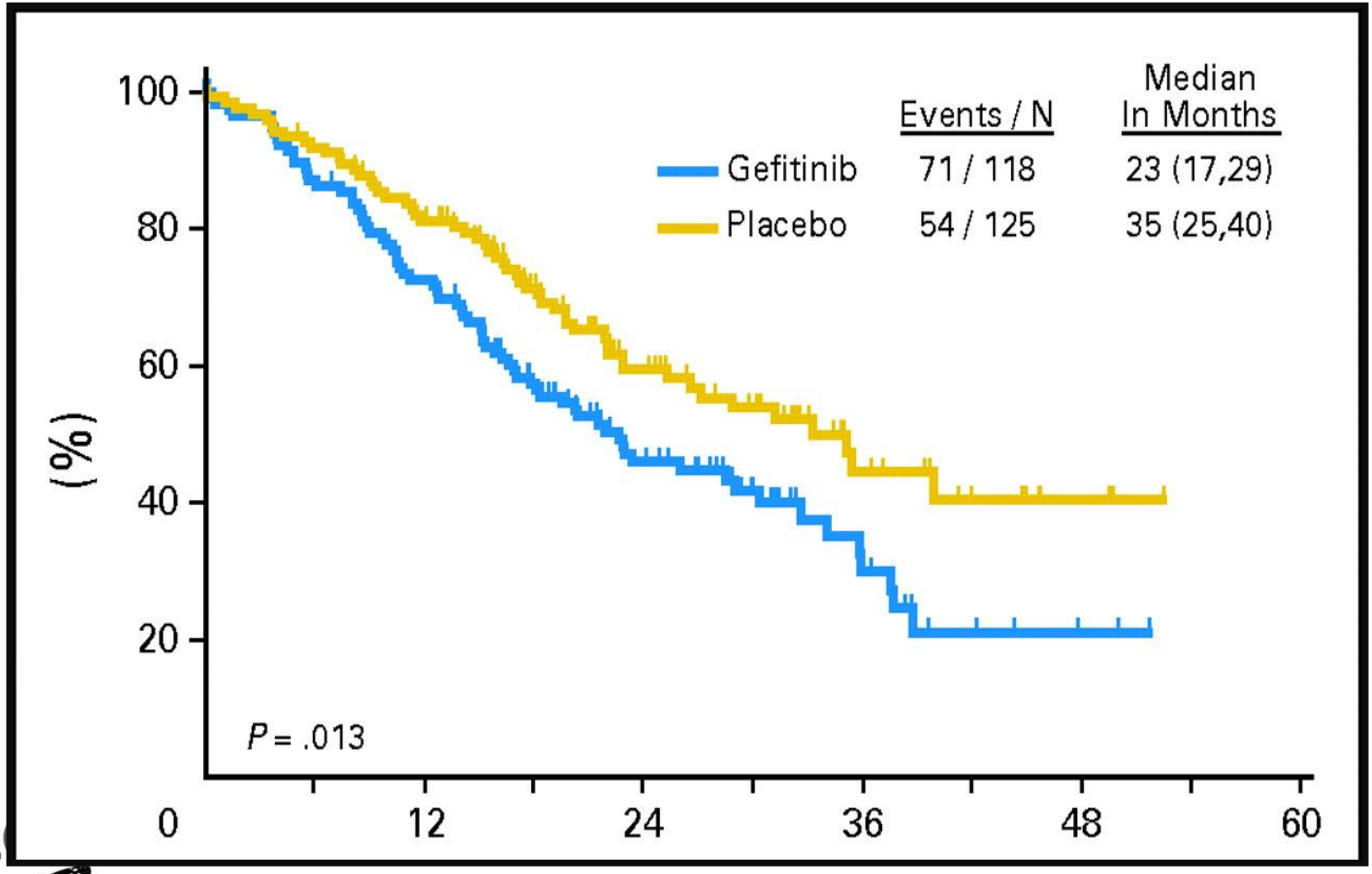
Eicheler, Radiother Oncol 2005;
Baumann, Radiother Oncol 2007

Selected phase I/II studies of concurrent EGFR-TKIs and chemoradiotherapy for NSCLC

Study	No. of Patients	Concurrent	*EGFR* Inhibition	Adverse Events (%)		Response Rate (%)	OS			
				Esophagitis Grades 3-4	Neutropenia Grades 3-4		Median (months)	1-Year (%)	2-Year (%)	3-Year (%)
University of Chicago[44]	16	Cisplatin, etopside	Erlotinib MTD: 150 mg/d	19	50	65	11			20
	15	Carboplatin, paclitaxel	Erlotinib MTD: 150 mg/d	40	20	59	15			16
CALGB 30106 (good risk)[43]	39	Carboplatin, paclitaxel	Gefitinib 250 mg/d	31	38	81	13	53		
Zurich[45]	14	Cisplatin (optional)	Gefitinib 250 mg/d	22	11	21	12.5		NS	
MD Anderson Cancer Center[46]	48	Carboplatin, paclitaxel	Erlotinib 150 mg/d	NS	NS	80	26	84		
University of North Carolina[47]	23	Carboplatin, paclitaxel	Gefitinib 250 mg/d	19.5	19	NS	16		20	

Salama, J Clin Oncol 2013; 31:1029-1038

Gefitinib as consolidation after chemoradiation

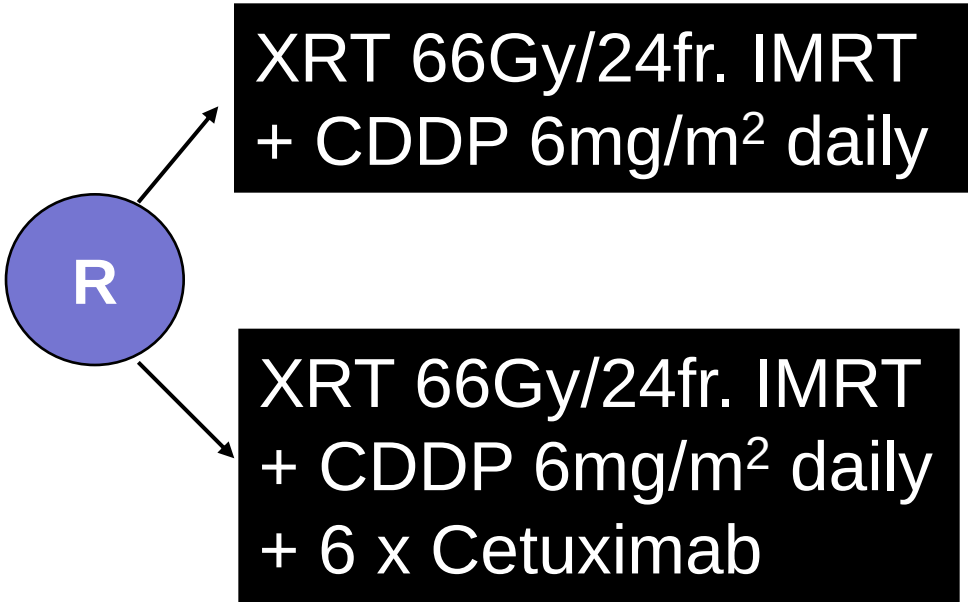


Kelly, J Clin Oncol. 2008;26:2450-2456

Definitive Radio(chemo)therapy + cetuximab: phase II data in lung cancer

Reference	Chemotherapy	N	Median OS months (toxicity)
Jensen 2011 NEAR study	None (pts unfit for chemo)	30	19.5 (36.7% G3 tox)
Jatoi 2010	None (pts >65 y.o. or PS=2)	57	15.1 (54% G3 tox)
Blumenschein 2011 RTOG 0324	Carbo-Paclitaxel weekly + cetuximab weekly – Carbo-Paclitaxel q 3weeks x 2 + weekly cetuximab x 6	87	22.7 (44% G3, 5% G5)
Govindan 2011 CALGB 30407	Carbo-PEM x 4 – PEM x 4 Carbo-PEM-Cetuximab x 4 - PEM x 4	48 53	21.2 (42% G3 tox) 25.2 (38% G3 tox)
Beldebos/van den Heuvel RADITUX ESTRO/ASCO2012	DDP daily DDP daily + Cetuximab x 6	Total = 102	1-yr OS 72% (45% G3 tox) 1-yr OS 76% (69% G3 tox)

Raditux Phase II NKI Trial



RADITUX: Acute Toxicity Grade ≥ 3 (CTCAE v 3.0)

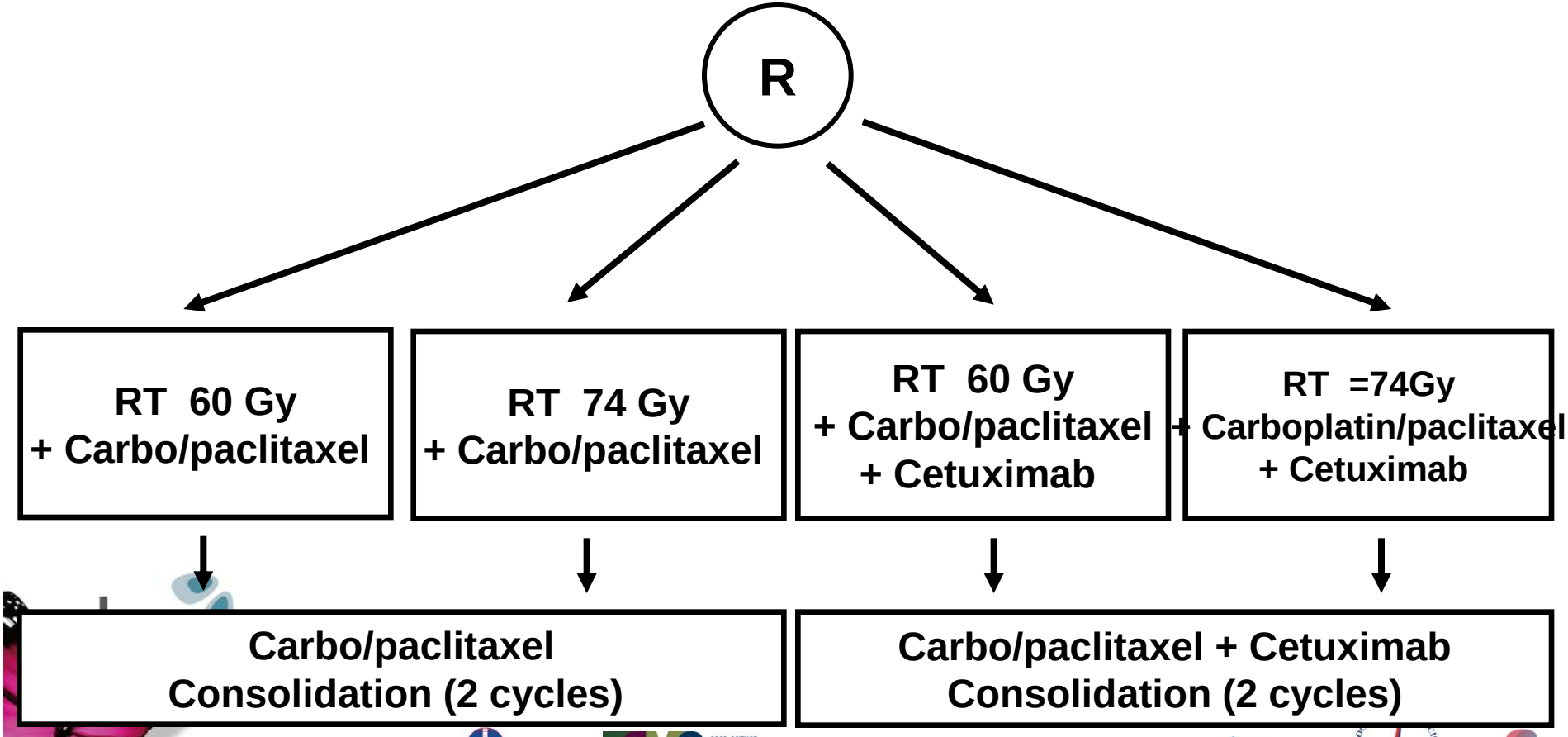
		CCRT (%)	CCRT+Cet (%)	
Non-hematological	Acne like rash	-	8	
	Anorexia	6	22	(p=0.04)
	Dysphagia	14	22	
	Fatigue	16	18	
	Nausea	6	4	
	Vomiting	-	2	
	Pain	2	10	
	Cough	-	2	
	Pneumonia	-	10	(p=0.06)
	Anemia	-	2	
Hematological	Leukopenia	10	8	
	Neutropenia	6	8	
		45%	69%	(p=0.03)

Data presented at ESTRO 2012 Conference by Dr. J. Belderbos

Chemoradiation + cetuximab: Phase III RTOG 0617/ US Intergroup Trial

2 x 2 factorial design

Bradley et al. 2015; Lancet Oncol 16:187-199



Chemoradiation + cetuximab: Phase III RTOG 0617/ US Intergroup Trial

Toxicity according to cetuximab

Bradley et al. 2015; Lancet Oncol 16:187-199

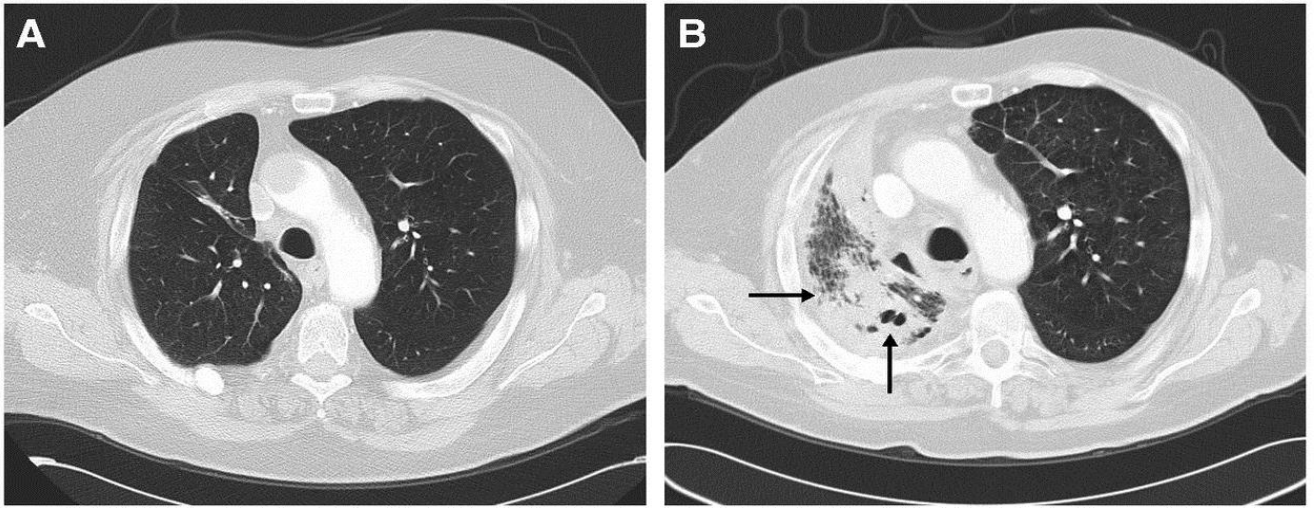
Toxicity	Cetuximab arms	Control arms
Any; G3 – G5	86%	70%
Toxic deaths	10	5
Acute pulmonary; G3 – G5	18%	13%
Acute GI; G3 – G5	30%	22%
Worst haematological; G3 – G5	71%	51%

Anti-angiogenic agents

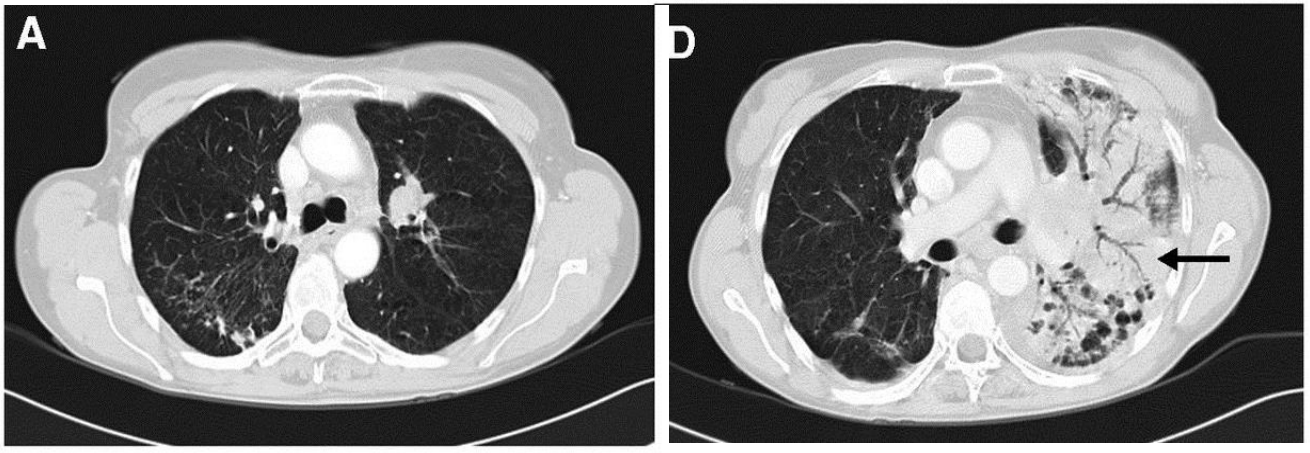
Chemoradiotherapy and bevacizumab: phase I/II trial outcomes

- High-grade toxicities
  - tracheoesophageal fistula
  - pulmonary hemorrhage, particularly in squamous histology
- No improvement in OS and PFS over chemoradiotherapy alone
- Change in the bevacizumab package labeling
- Further studies abandoned

Severe pulmonary toxicity after chemoradiotherapy combined with bevacizumab

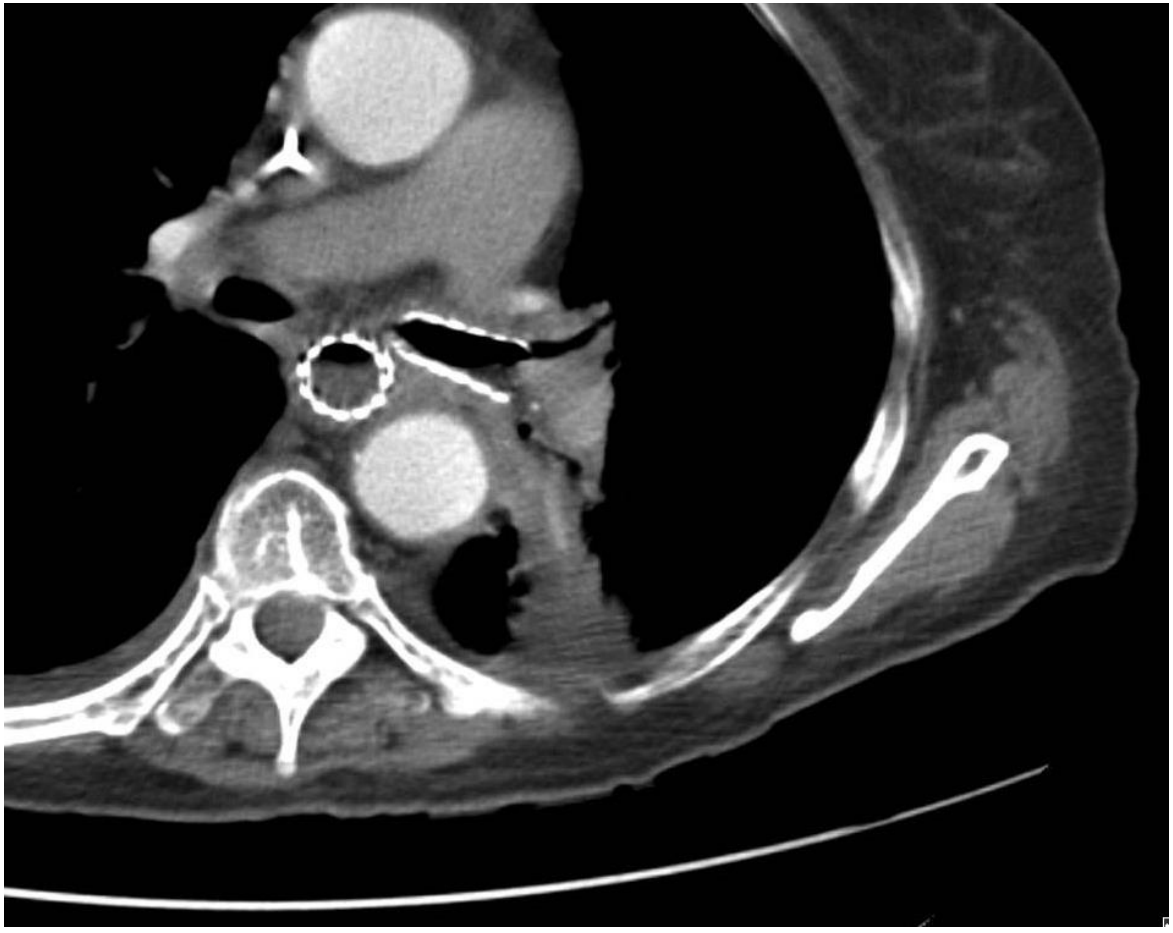


Lind J S et al. J Clin Oncol 2012;30:e104-e108

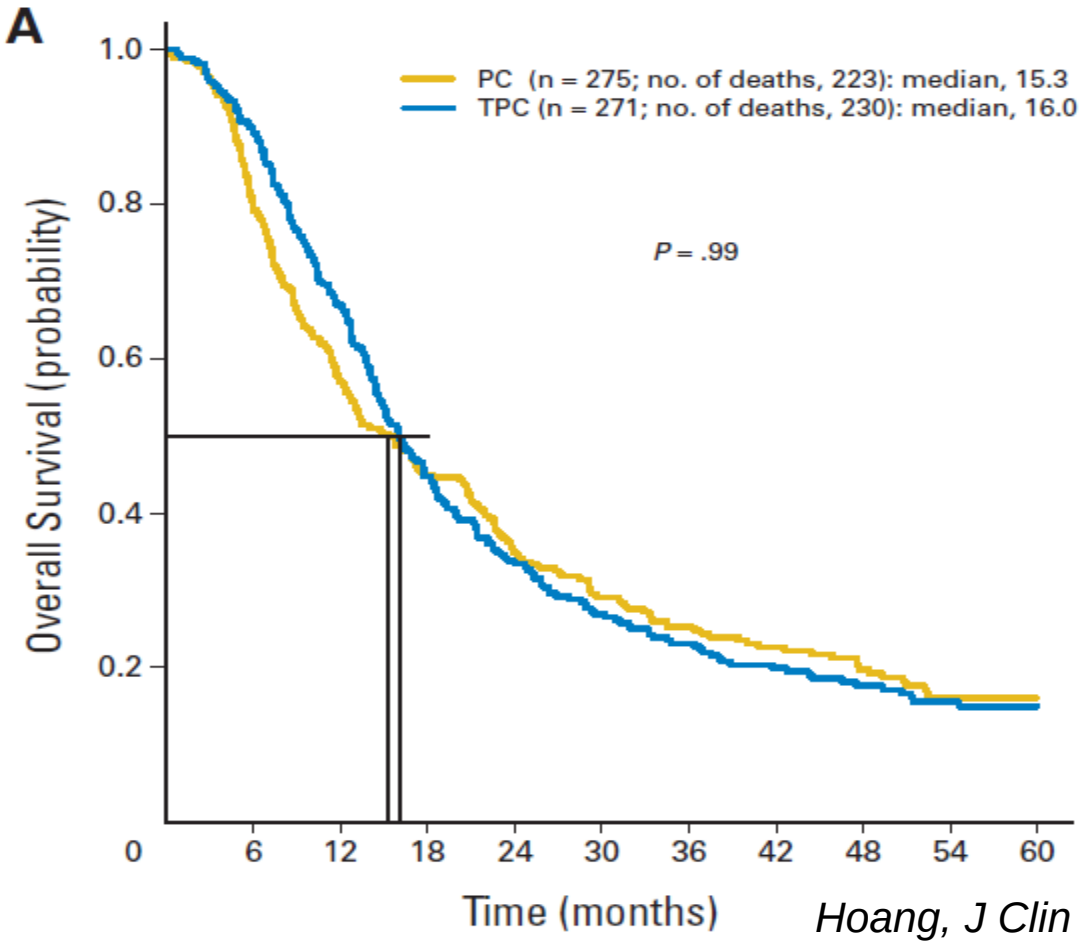


Tracheoesophageal fistula after chemoradiotherapy combined with bevacizumab

Lind J S et al. J Clin Oncol 2012;30:e104-e108



Radiochemotherapy and thalidomide: a phase III study



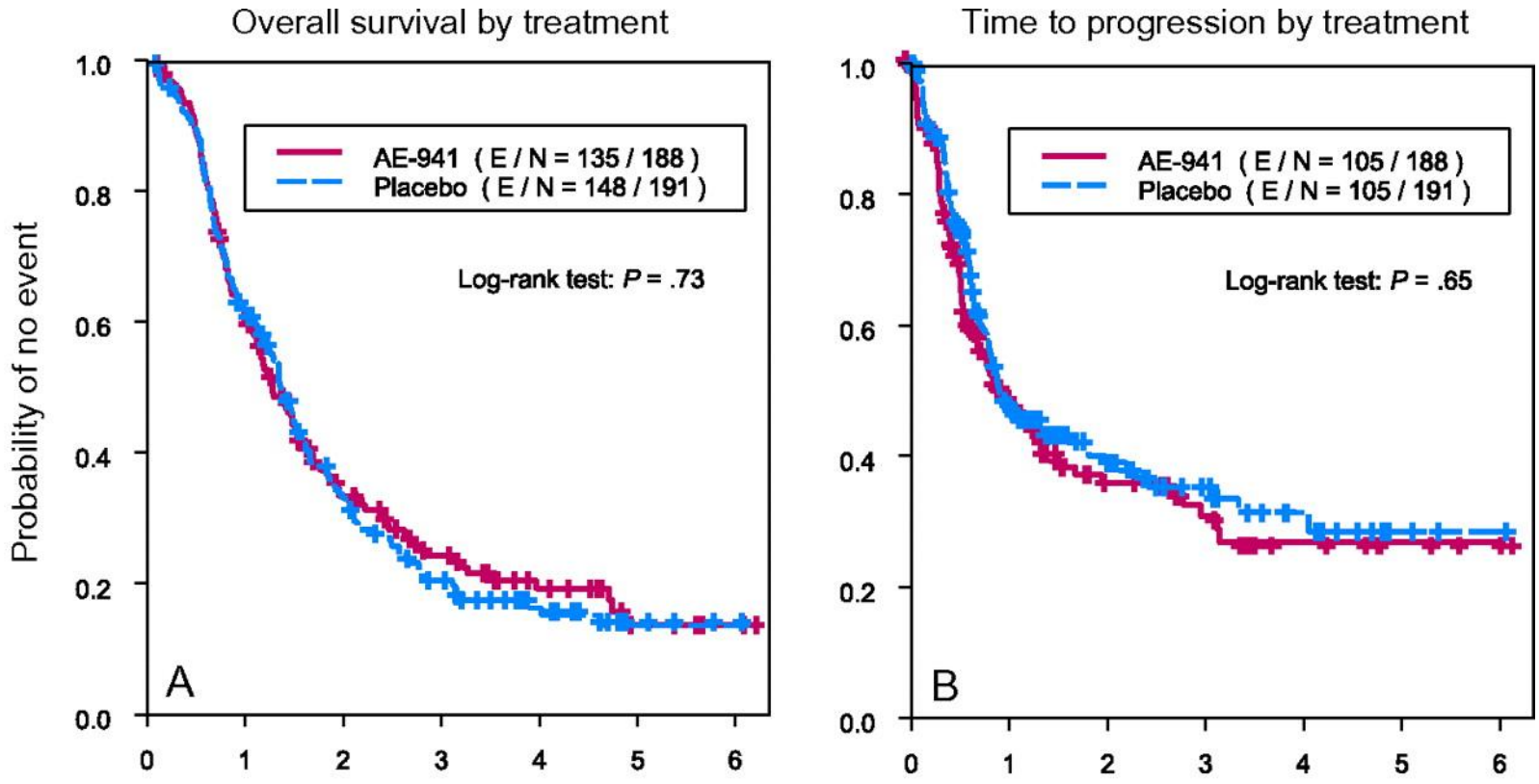
Hoang, J Clin Oncol 2012;30:616-622

Radiochemotherapy and thalidomide: a phase III study

Toxicity/G3-G5	TPC	PC
Thrombosis/embolism	11%	2%
Febrile neutropenia	3%	3%
Fatigue	15%	6%
Dyspnea	13%	7%
Pneumonitis	5%	3%
Esophagitis	1%	1%

Hoang, J Clin Oncol 2012;30:616-622

Chemoradiotherapy and AE-941: a phase III study



Lu, J Natl Cancer Inst 2010;102:859-865

Chemoradiotherapy and AE-941: a phase III study

	% of patients		
Toxic effect	AE-941	Placebo	*P*
Dyspnea	26	31	.57
Neutropenia	20	26	.43
Esophagitis	20	15	.38
Fatigue	14	17	.71
Pneumonitis[†]	8	12	.49
Febrile neutropenia[‡]	6	8	.79

Lu, J Natl Cancer Inst 2010;102:859-865

RT and targeted agents in stage IV NSCLC

15-18 April 2015, Geneva, Switzerland

Organisers

Partners

Can I treat brain metastases in NSCLC EGFR M+ patient with WBRT and concurrent erlotinib/gefitinib?

Randomized Trial of Erlotinib Plus Whole-Brain Radiotherapy for NSCLC Patients With Multiple Brain Metastases

Siow Ming Lee, Conrad R. Lewanski, Nicholas Counsell, Christian Ottensmeier, Andrew Bates, Nirali Patel, Christina Wadsworth, Yenting Ngai, Allan Hackshaw, Corinne Faivre-Finn

Manuscript received April 30, 2013; revised April 23, 2014; accepted April 28, 2014.

20Gy/5fr.
SAFE

VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Erlotinib Plus Concurrent Whole-Brain Radiation Therapy for Patients With Brain Metastases From Non–Small-Cell Lung Cancer

James W. Welsh, Ritsuko Komaki, Arya Amini, Mark F. Munsell, Wyatt Unger, Pamela K. Allen, Joe Y. Chang, Jeffrey S. Wefel, Susan L. McGovern, Linda L. Garland, Su S. Chen, Jamie Holt, Zhongxing Liao, Paul Brown, Erik Sulman, John V. Heymach, Edward S. Kim, and Baldassarre Stea

35Gy/14fr.
SAFE

Drug Design, Development and Therapy

Dovepress

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ORIGINAL RESEARCH

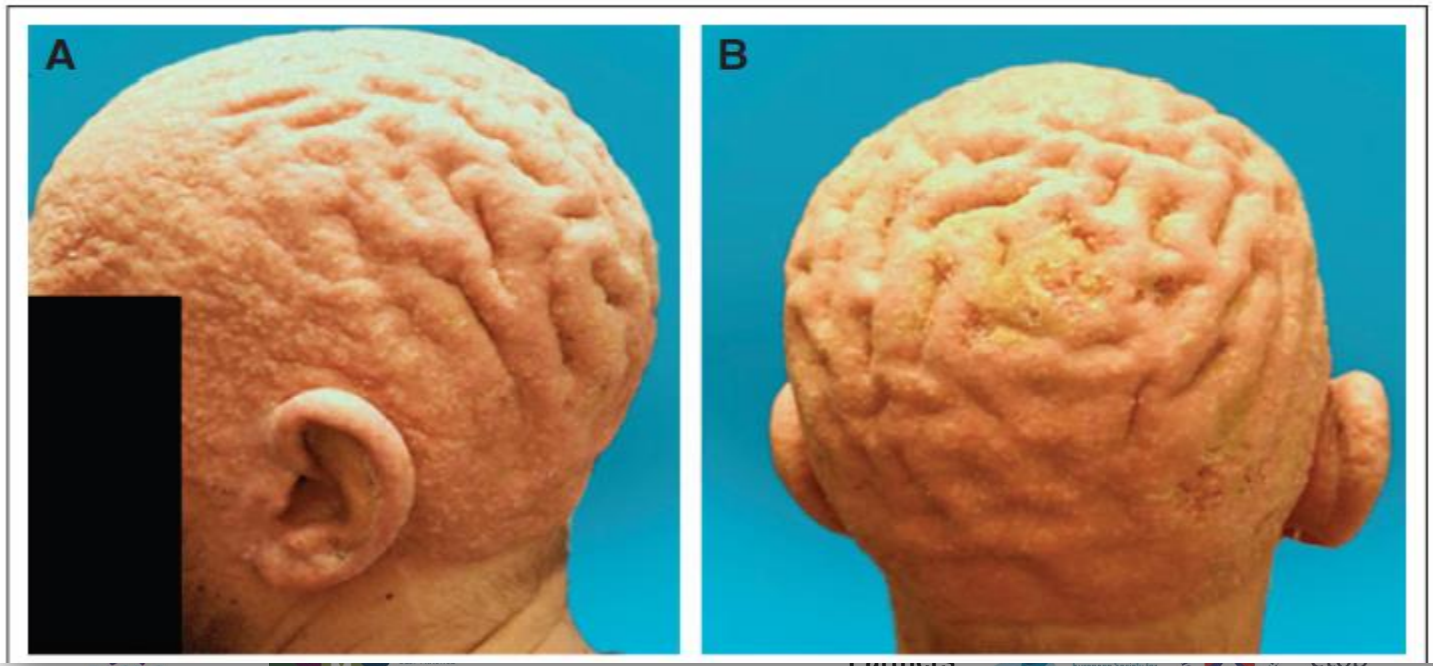
Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma

30Gy/10fr.
SAFE

BRAF kinase inhibitors + RT (BRAF mutant melanoma)

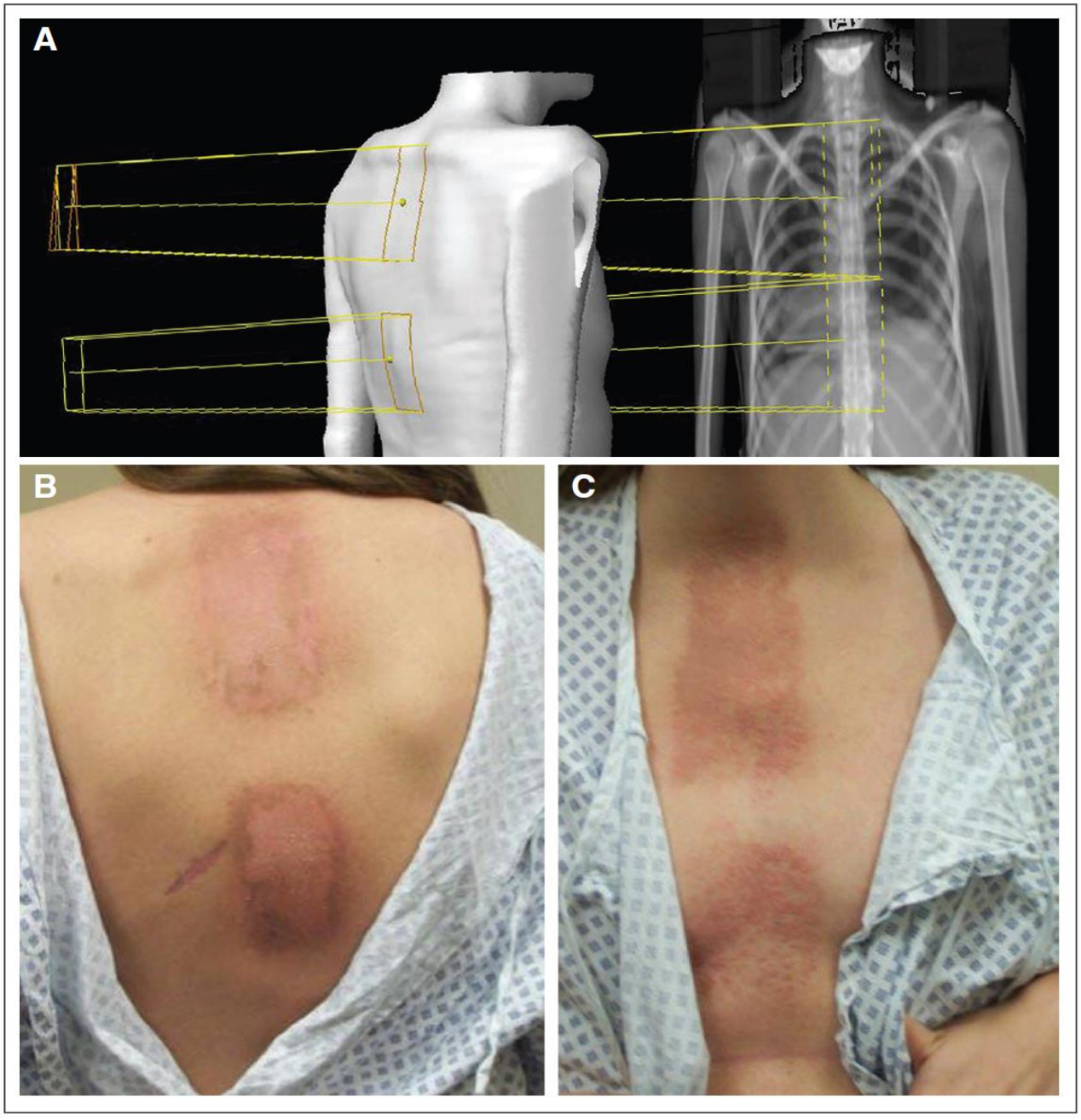
vemurafenib and WBRT Cutis Verticis Gyrata

pain
erythema,
hyperkeratosis
hypertrophy of the scalp



Harding et al.
JCO 2014

BRAF kinase inhibitor vemurafenib + RT (melanoma)



Anker et al.
JCO 2013

Take-home messages

- Use of EGFR inhibitors or angiogenesis inhibitors and concurent radio(chemo)therapy in stage III NSCLC results in increased RT-related toxicities
- In palliative setting, concurrent RT and targeted agents should be used only if there is sufficient evidence of safety

Acknowledgment

- Prof. Jacek Jassem
- Prof. Barbara Jereczek-Fossa