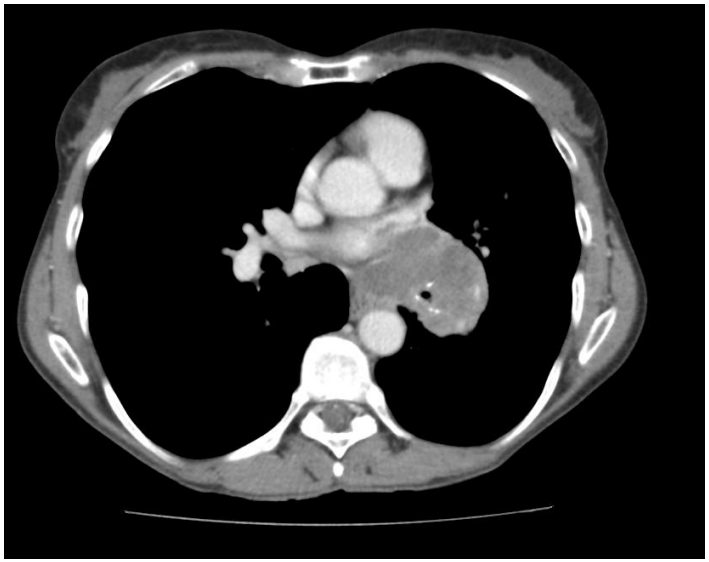
Systemic treatment with future impact on stage III



Prof. Solange Peters, MD-PD
Oncology Department & Ludwig Instutute
Lausanne
Switzerland

Disclosures

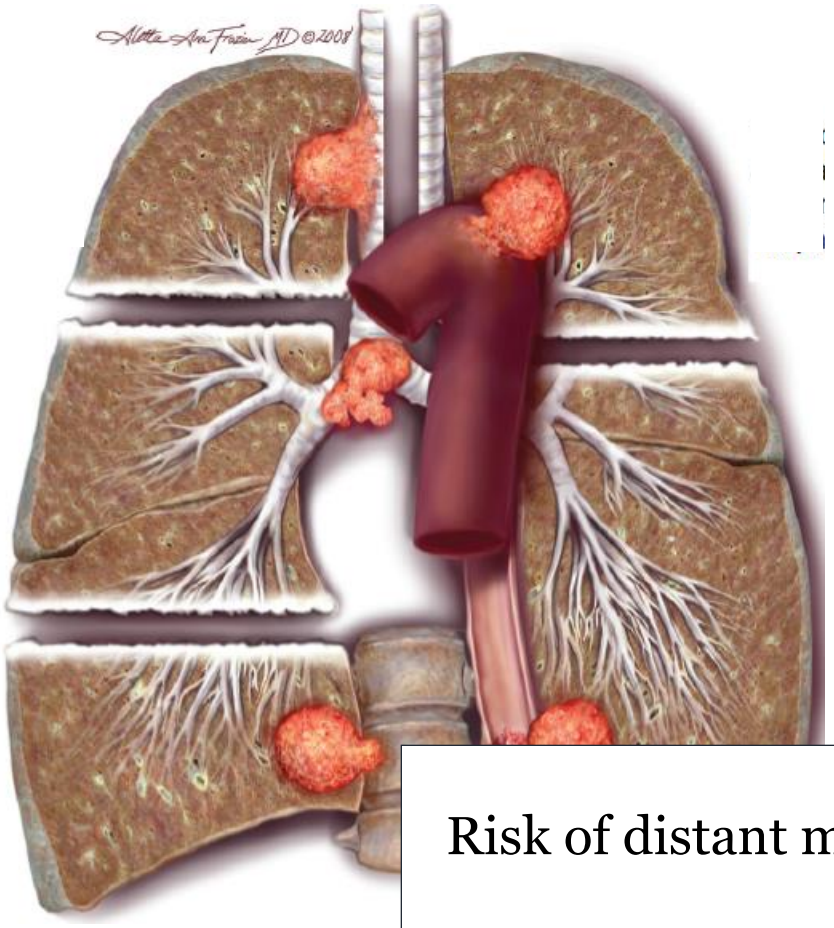
I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly, MSD, AstraZeneca, Pfizer, Novartis, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, Amgen, Clovis, Tesaro, Cellgene, Debiopharm, for which I received honoraria.

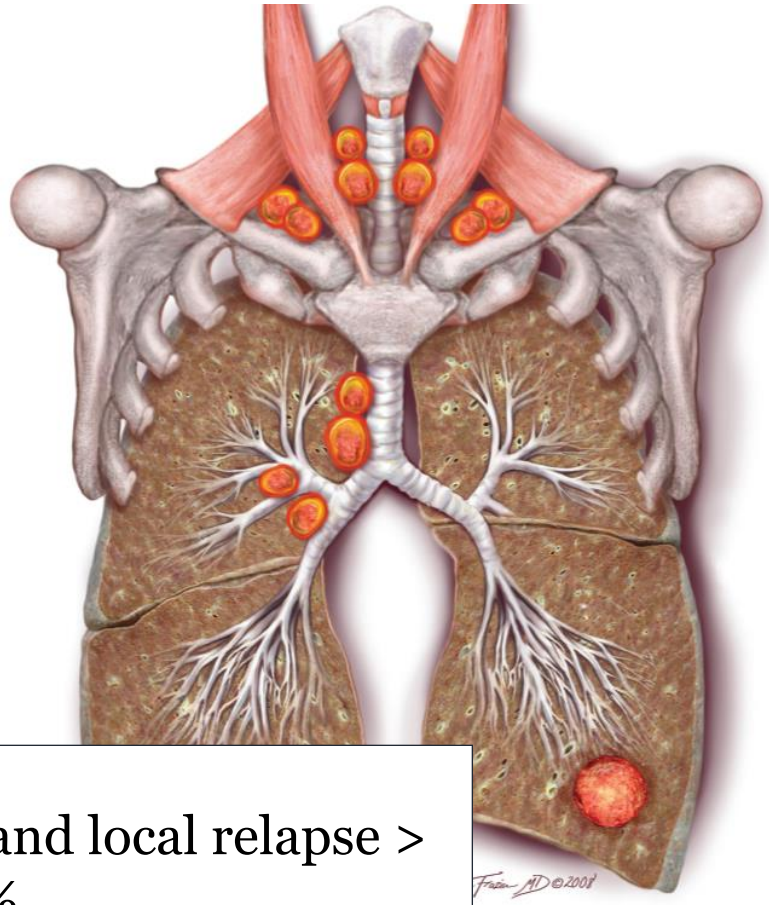
I declare no conflict of interest.

The problem of stage III heterogeneity

T3/T4 disease



N2/N3 disease



Risk of distant mets and local relapse > 60%

Some more complexity

Table 2. Patient subsets and sub-stages included into stage III non-small-cell lung cancer

IASLC/UICC 7	Definition	TNM subsets	Description	Robinson classification
IIIA	Incidental N2	T1–3 N2	N2 found at surgery	
	(unforeseen N2)		Microscopic N2 (final pathology)	IIIA1
			Microscopic/macroscopic N2 (frozen section)	IIIA2
IIIA	Potentially resectable N2	T1–3 N2	Minimal N2/single station at staging	IIIA3
IIIA	Potentially resectable N2	T1–3 N2	Pancoast tumour subsets, T3-4 N1, T3 N2 selective	–
	But: risk of incomplete resection		centrally located IIIA(N2)	IIIA3
IIIA	Unresectable N2	T1–3 N2	Bulky and/or multilevel N2 at staging	IIIA4
IIIA	Potentially resectable T4	T4 N0–1	Pulmonary artery, carina, spine, trachea, vena cava, right	–
	But: risk of incomplete resection		atrium	
IIIB	Unresectable T4	T4 N0–1	Oesophagus, heart, aorta, pulmonary veins	–
		T4 N2		
IIIB	Unresectable N3	T1–4 N3	N3 nodes at staging	

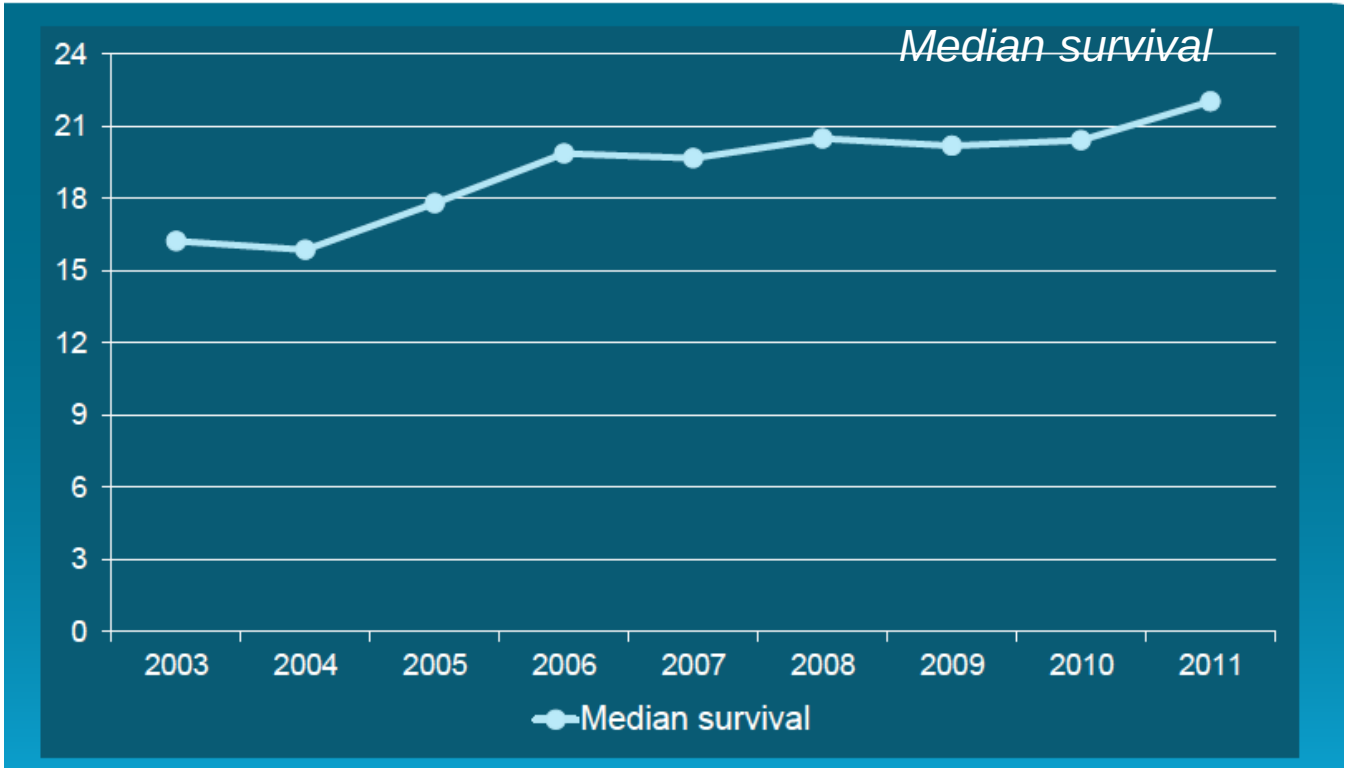
Efficient recruitment in stage III clinical trials ***is strongly limited by****:*

- *Heterogeneity of stage III disease*
- *Adoption of very variable local standards*

Eberhardt and Peters, Ann Oncol 2015

Stage III NSCLC: population outcomes

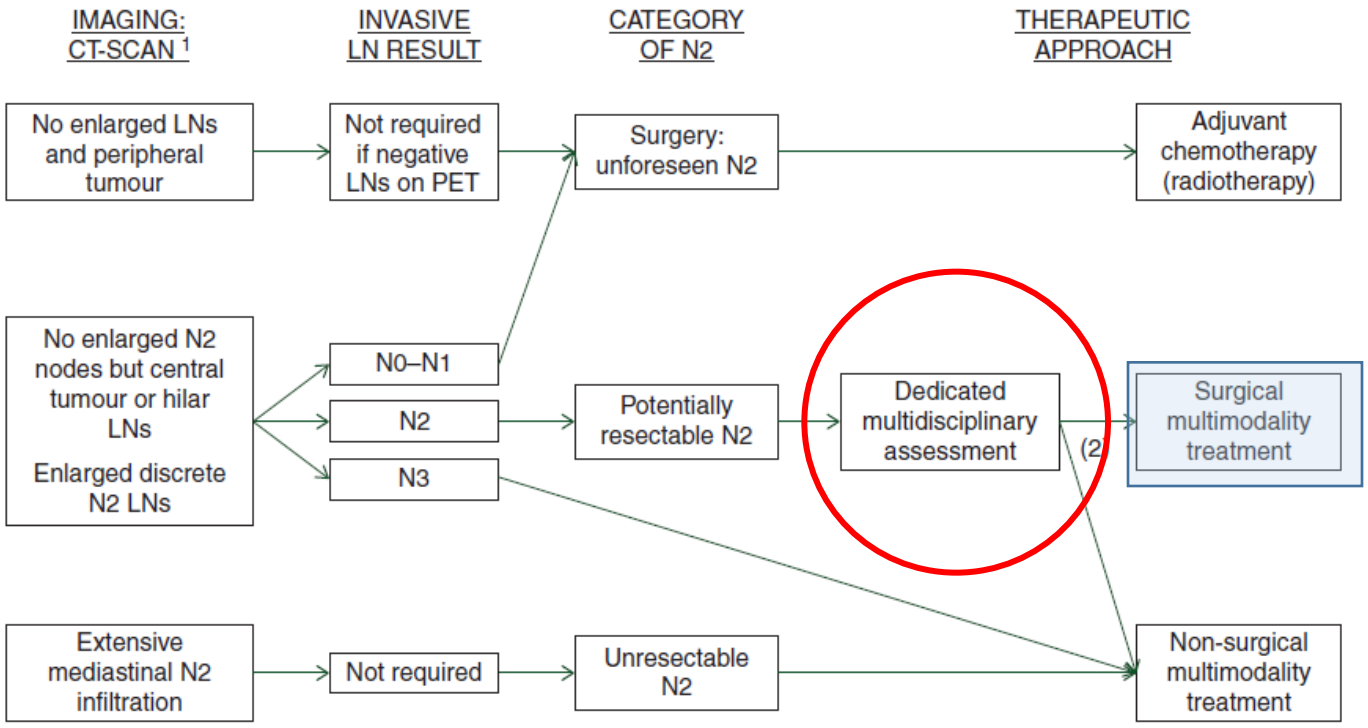
- Netherlands Cancer Registry (2003-2012)
- 22 700 patients with Stage III
- 45% underwent chemo-radiotherapy (2012)



IMRT = intensity modulated radiotherapy

Damhuis R et al, ELCC 2014

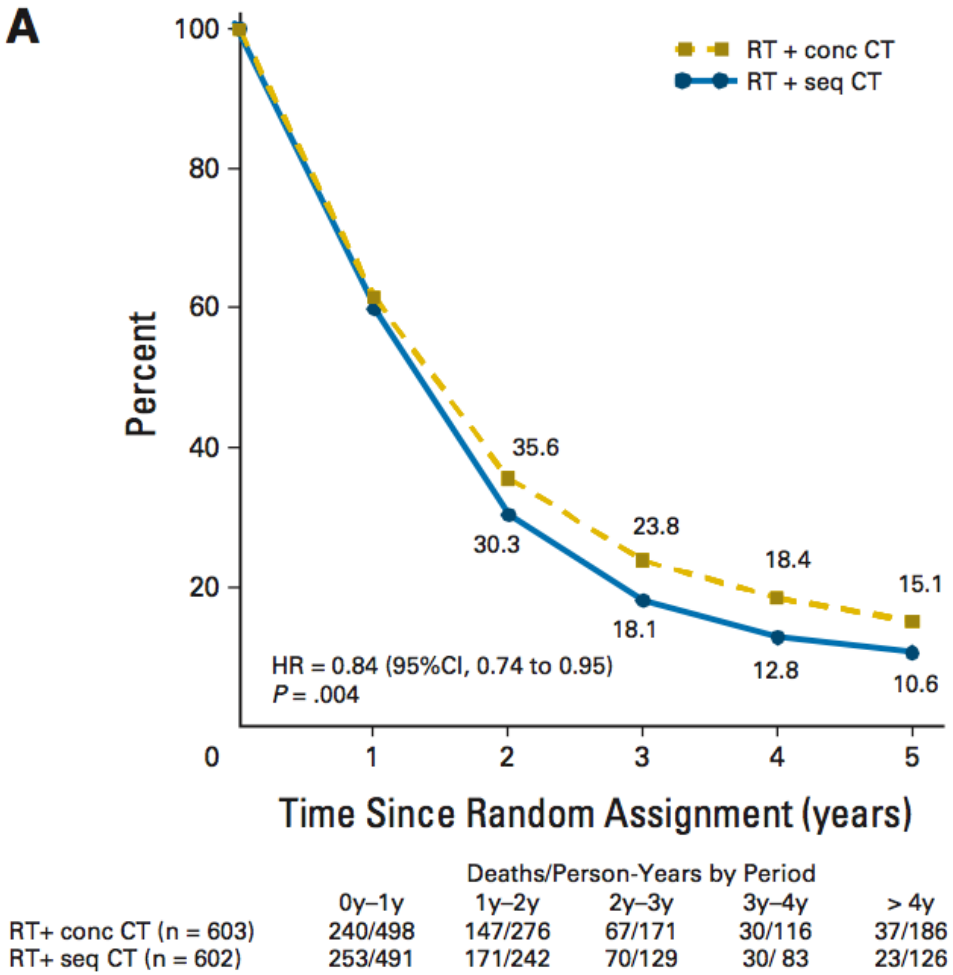
Current ESMO stage 3 NSCLC Consensus



[1] Category discription according to C
see text for more details.
[2] See text for factors involved in the

1) Chemotherapy
2) Targeted therapy (EGFR, VEGF, Metformin)
3) Immunotherapy

Most stage III patients are treated with induction or concurrent CT-RT



OS Benefit: HR=0.84 (0.74-0.95)

Local progression: HR=0.77 (0.62-0.95); absolute 6% benefit at 3yrs

Distant progression: HR=1.04 (.086-1.25); no absolute difference

Aupérin, JCO 2010

Optimal chemotherapy regimen remains to be defined in this context

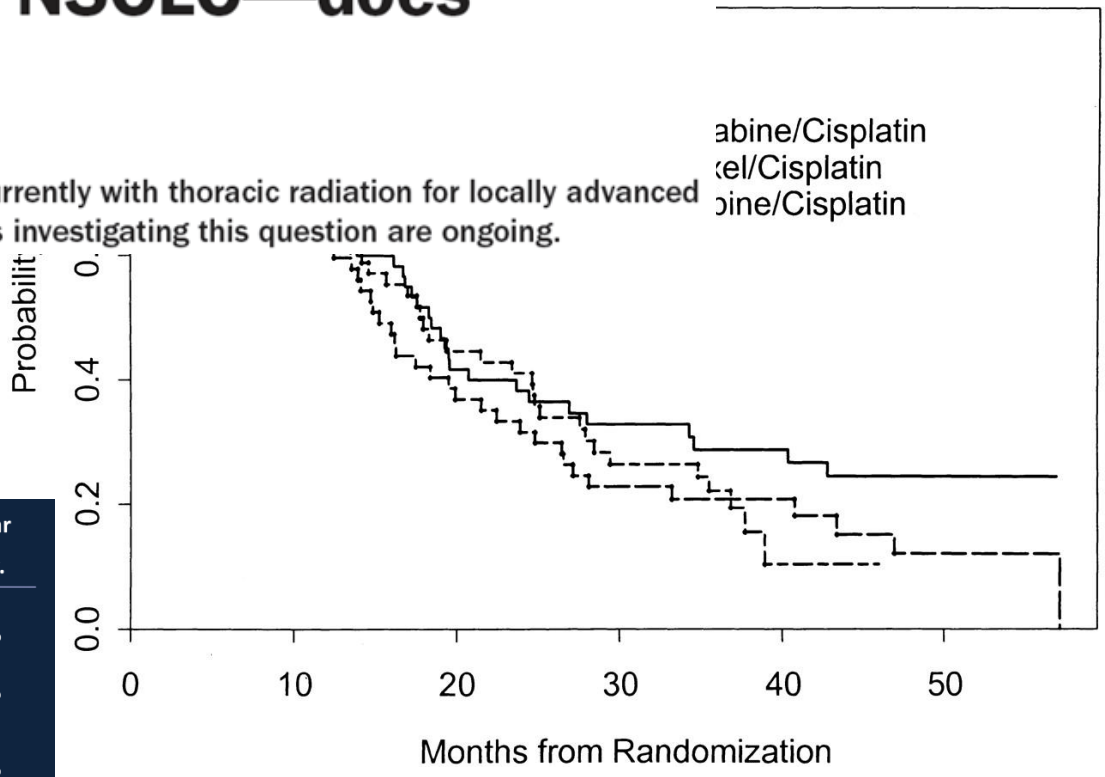
MEDICAL ONCOLOGY

Chemoradiotherapy for NSCLC—does a 'standard' exist?

Allen M. Chen and Primo N. Lara Jr

The optimal chemotherapy regimen to be used concurrently with thoracic radiation for locally advanced non-small-cell lung cancer remains uncertain. Studies investigating this question are ongoing.

	Response after CT	Resp. after concom. CT/RT	Med survival	1 year Surv.
NVB - CDDP	44%	73%	17.7 m	65%
TXL - CDDP	33%	67%	14.8 m	62%
GEM - CDDP	40%	74%	18.3 m	68%



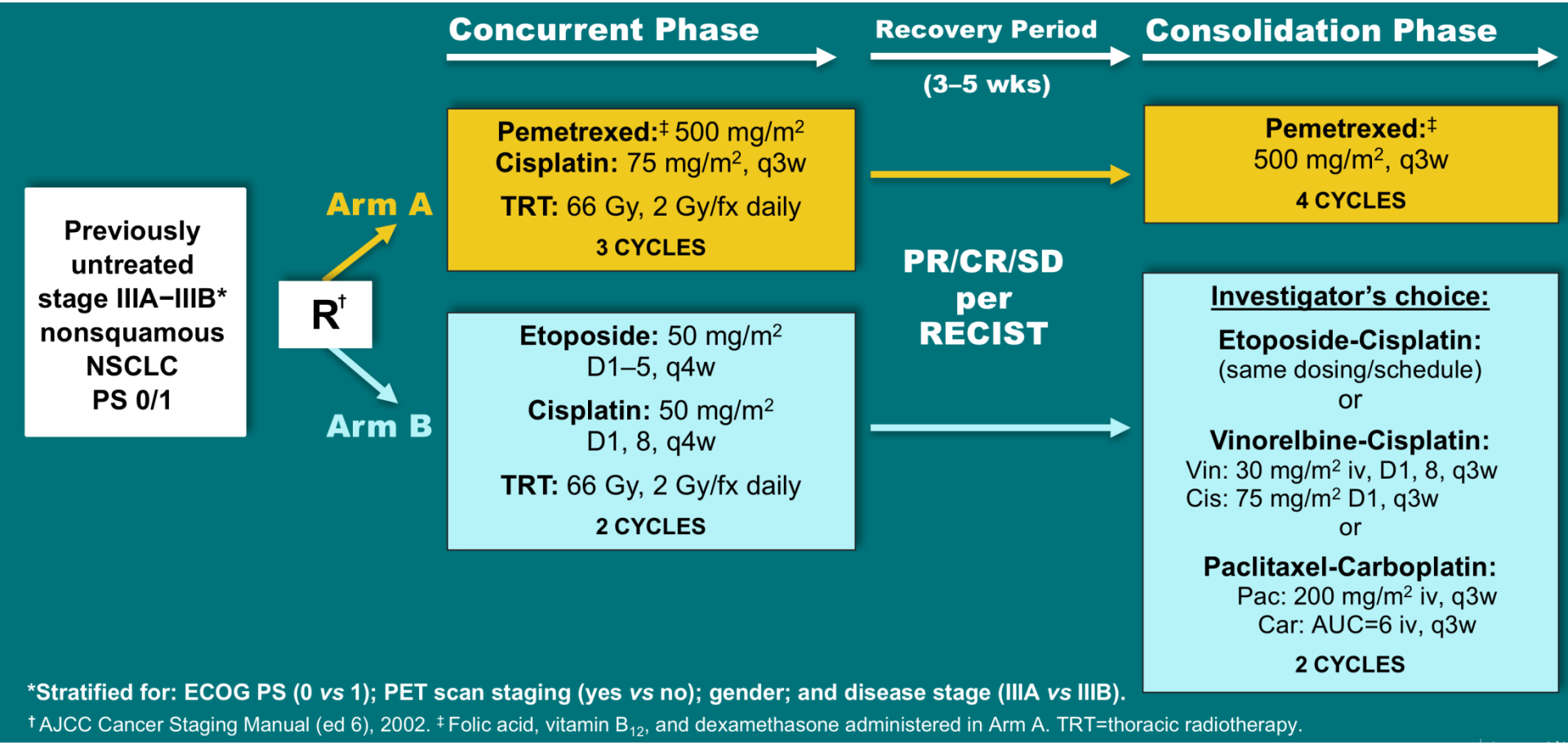
Vokes, J. Clin. Oncol., 2002

What about weekly paclitaxel/carboplatin (+ 2 consolidation cycles?)

- Most commonly used regimens in US : cisplatin/etoposide (PE) and carboplatin/paclitaxel (CP)
- Only meta-analysis: 3194 patients from 32 studies in the PE arm, and 3789 patients from 51 studies in CP
- No significant difference in overall survival (19.8m vs. 18.4m)
- PE was associated with higher grade 3/4 hematological toxicities than CP

Steuer, ASCO 2015

Pemetrexed/Cisplatin and Versus PE and RT in Stage III Non Predominantly Squamous (PROCLAIM)

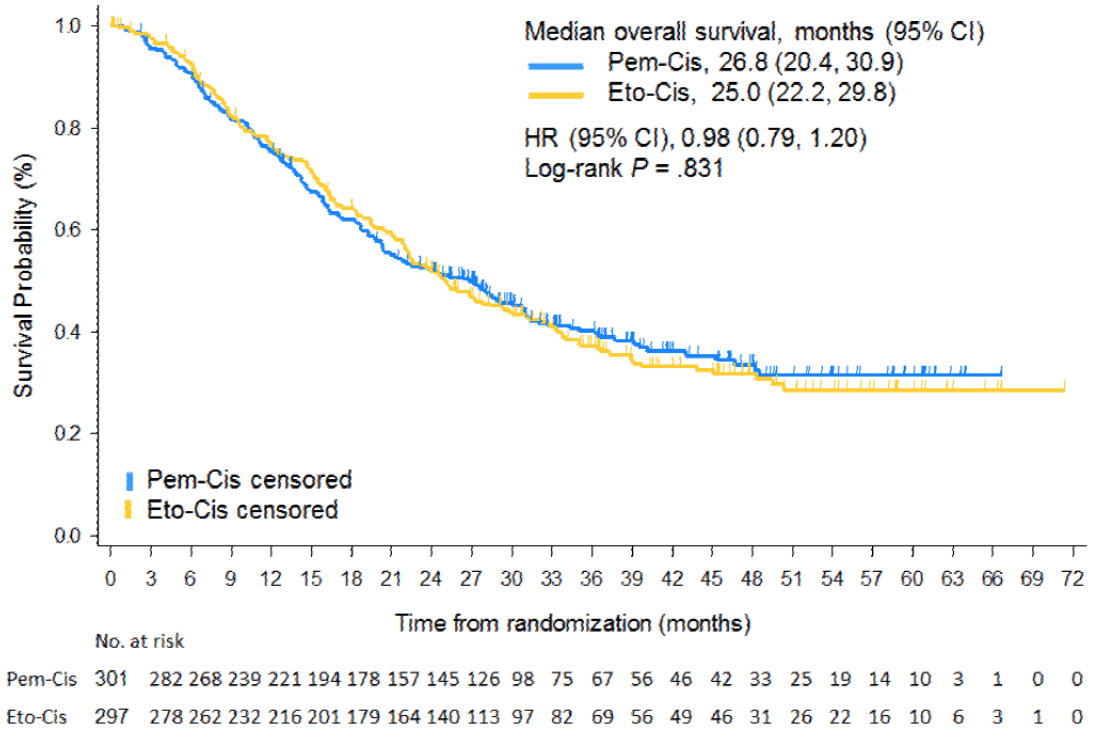


*Stratified for: ECOG PS (0 *vs* 1); PET scan staging (yes *vs* no); gender; and disease stage (IIIA *vs* IIIB).

† AJCC Cancer Staging Manual (ed 6), 2002. ‡ Folic acid, vitamin B_{12}, and dexamethasone administered in Arm A. TRT=thoracic radiotherapy.

Senan, JCO 2016

Pemetrexed/Cisplatin and Versus PE and RT in Stage III Non Predominantly Squamous (PROCLAIM)



- The Pem-Cis arm had a significantly lower incidence of drug-related grade 3–4 AEs (all events combined), including neutropenia, during the overall treatment period.

Senan, JCO 2016

No role for Induction chemotherapy

Study	Year	Strategy	No.	MST	3 yr OS
CALGB 39801	2006	Induction→Concurrent	184	14 mo	23%
		Concurrent alone	182	12 mo	19%
Korea	2007	Induction→Concurrent	67	13 mo	<25%
		Concurrent alone	67	18 mo	NR
CALGB 9431	2002	Induction→Concurrent	62	18 mo	28%
		Induction→Concurrent	58	15 mo	19%
		Induction→Concurrent	55	18 mo	23%
RTOG 9801	2007	Induction→Concurrent	118	17 mo	27%
		Induction→Concurrent	121	18 mo	28%
NCI/RTOG/MDA	2007	Induction→Concurrent	188	14 mo	~25%
		Induction→Concurrent	191	16 mo	~25%

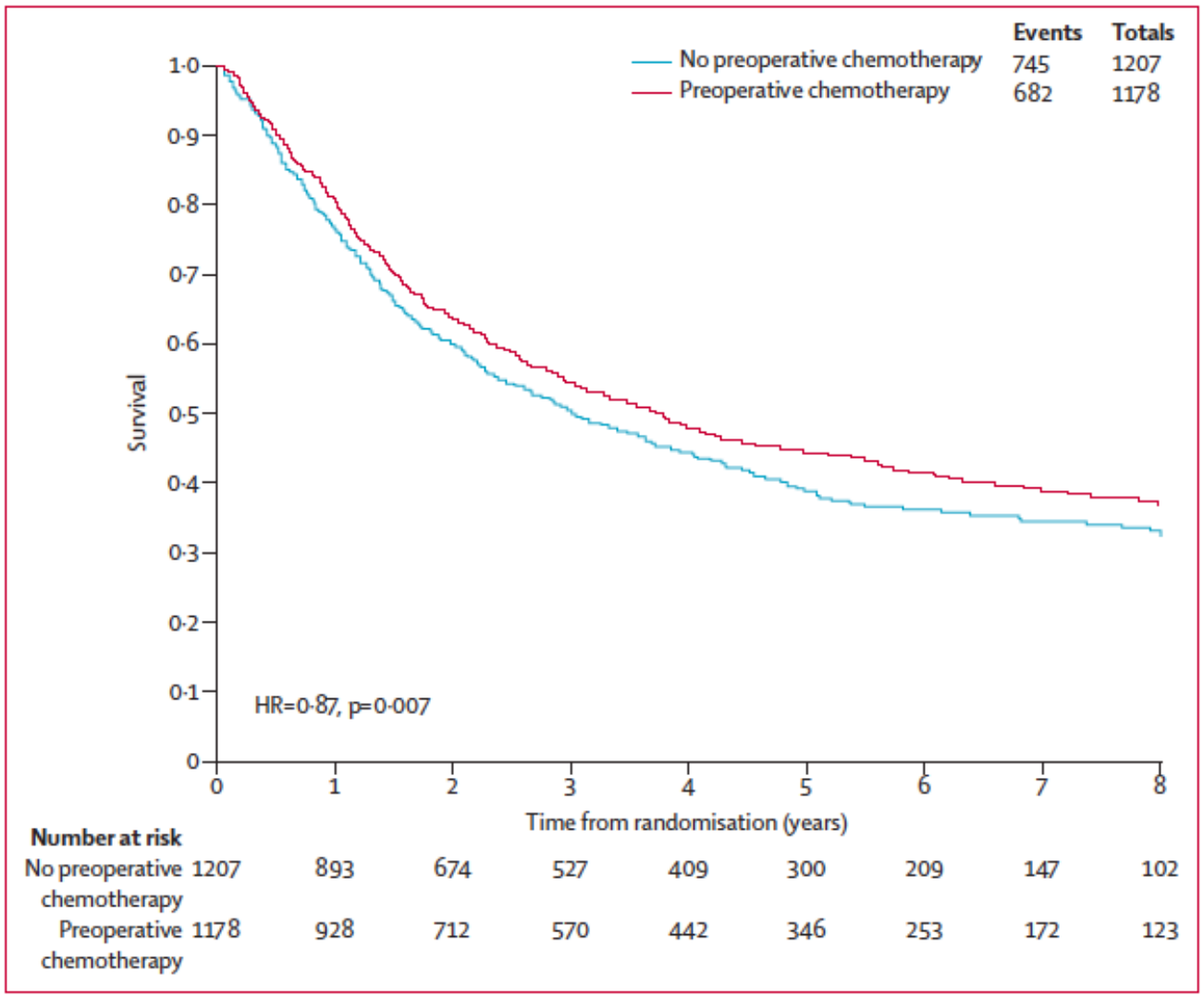
Modified form Hanna, ASCO 2015

No role for Consolidation chemotherapy

Study	Year	Strategy	No.	MST	3/4 yr OS
HOG/USO	2007	EP/XRT	203	23.2	26.1%
		EP/XRT→Docetaxel		21.2	27.1%
GILT	2012	PVino/XRT	165	20.8	25.3%
		PVino/XRT→PVino		18.5	21.4%
Park	2014	P/Docetaxel/XRT	419	20.6	NR
		P/Docetaxel/XRT→ P/Docetaxel		21.2	

Modified form Hanna, ASCO 2015

Surgery in stage IIIA NSCLC
Place of induction chemotherapy

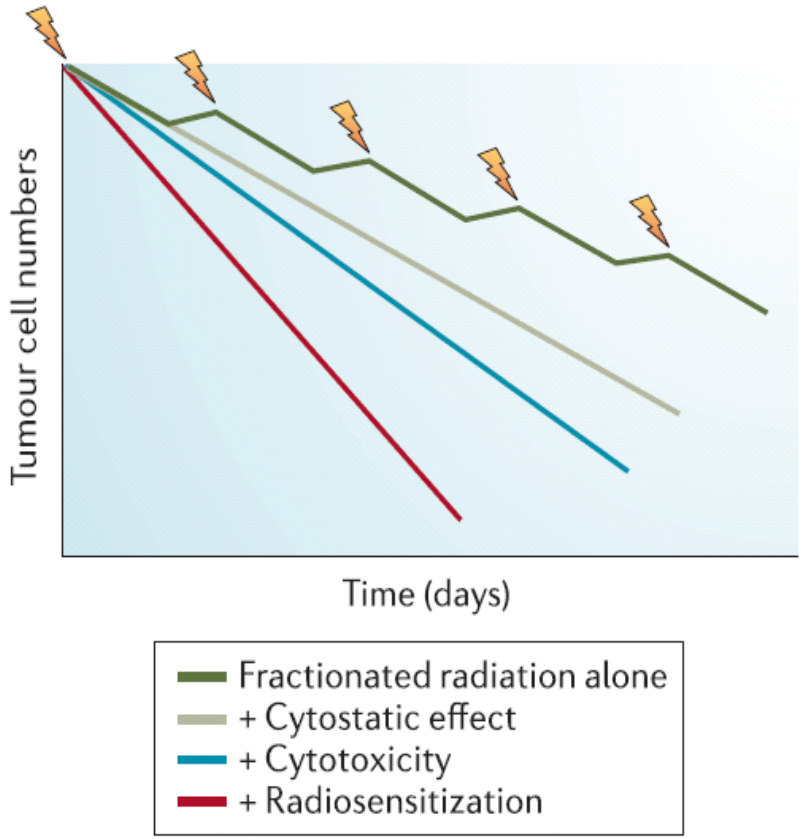


Absolute survival improvement at 5 years of 5% for all stages, from 20% to 25% in stage III (98% stages IIIA)

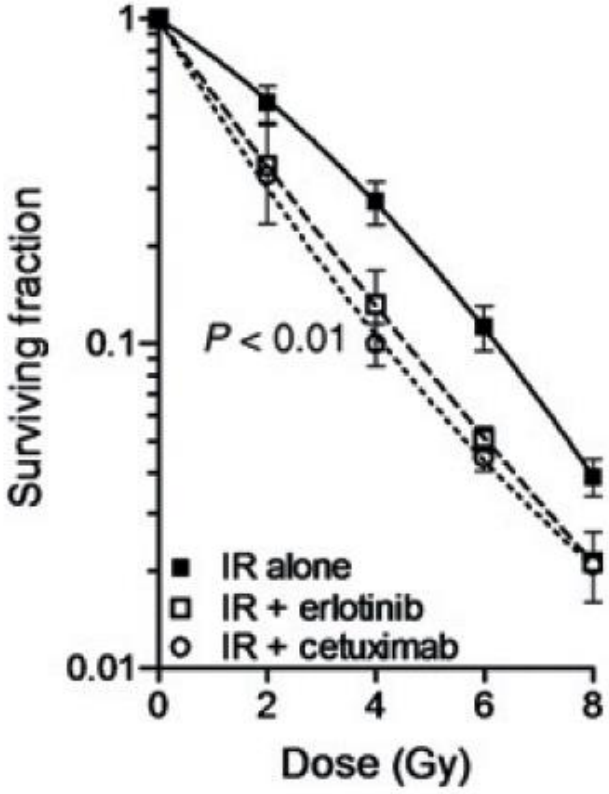
NSCLC Meta-analysis Collaborative Group, Lancet 2014

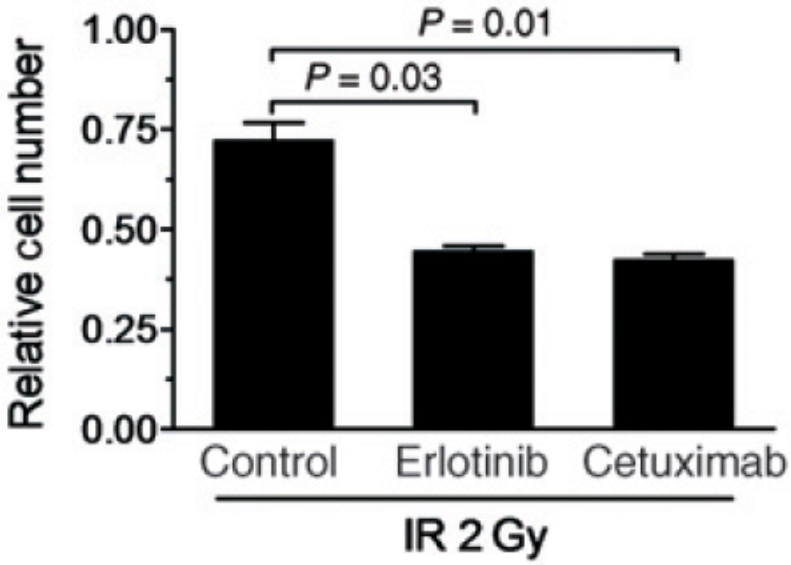
Targeted agents in stage III: Rationale

Agents that are know to enhance RT-induced tumour cell killing while having moderate effect on normal tissues should be considered in combination with thoracic RT



EGFR inhibition and RT in A549 cells





Wang , Cancer Res 2011

Evaluating 74 Gy and cetuximab: Factorial design RTOG 0617

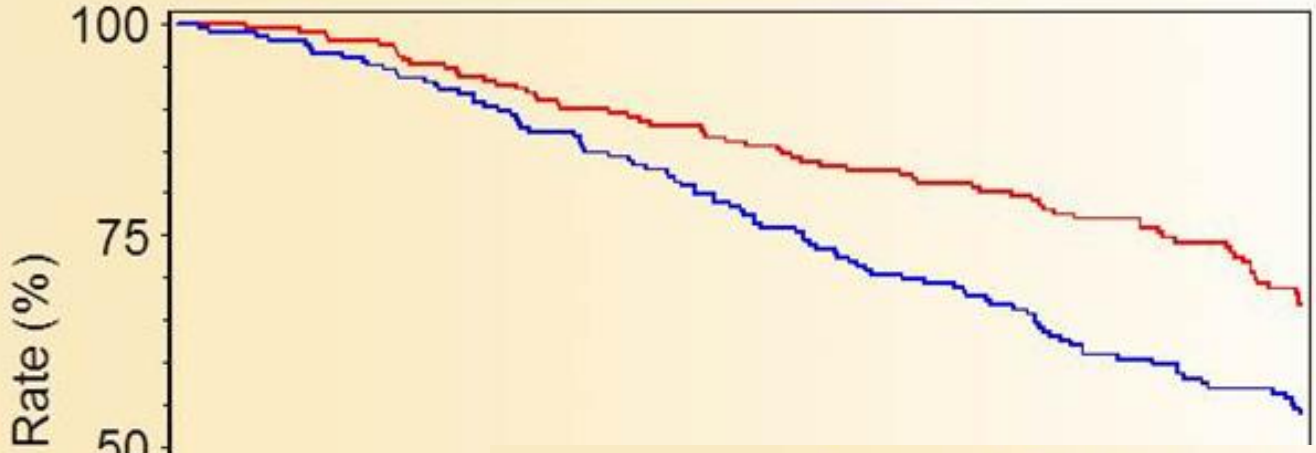
Schema

STRATIFY	RANDOMIZE	Concurrent Treatment	Consolidation Treatment
RT Technique 1. 3D-CRT 2. IMRT **Zubrod** 1. 0 2. 1 **PET Staging** 1. No 2. Yes **Histology** 1. Squamous 2. Non-Squamous		**Arm A** Concurrent chemotherapy* RT to **60 Gy**, 5 x per wk for 6 wks	Arm A Consolidation chemotherapy*
		Arm B Concurrent chemotherapy* RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm B Consolidation chemotherapy*
		Arm C Concurrent chemotherapy* and **Cetuximab** RT to **60 Gy**, 5 x per wk for 6 wks	Arm C Consolidation chemotherapy* and Cetuximab
		Arm D Concurrent chemotherapy* and **Cetuximab** RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel

Bradley, Lancet Oncol 2015

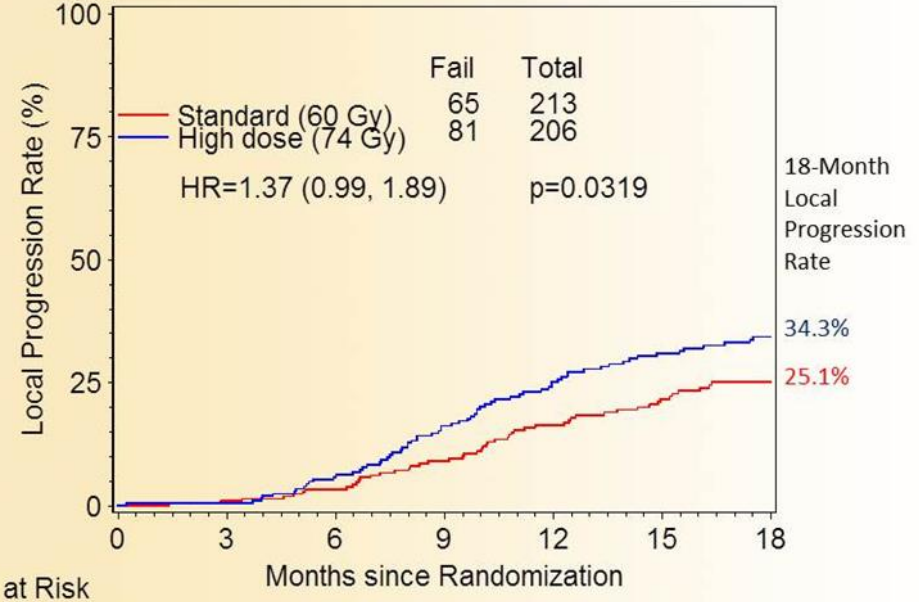
Overall Survival



Patients at Risk

Standard	213	207
High dose	206	197

Local Failure



Patients at Risk

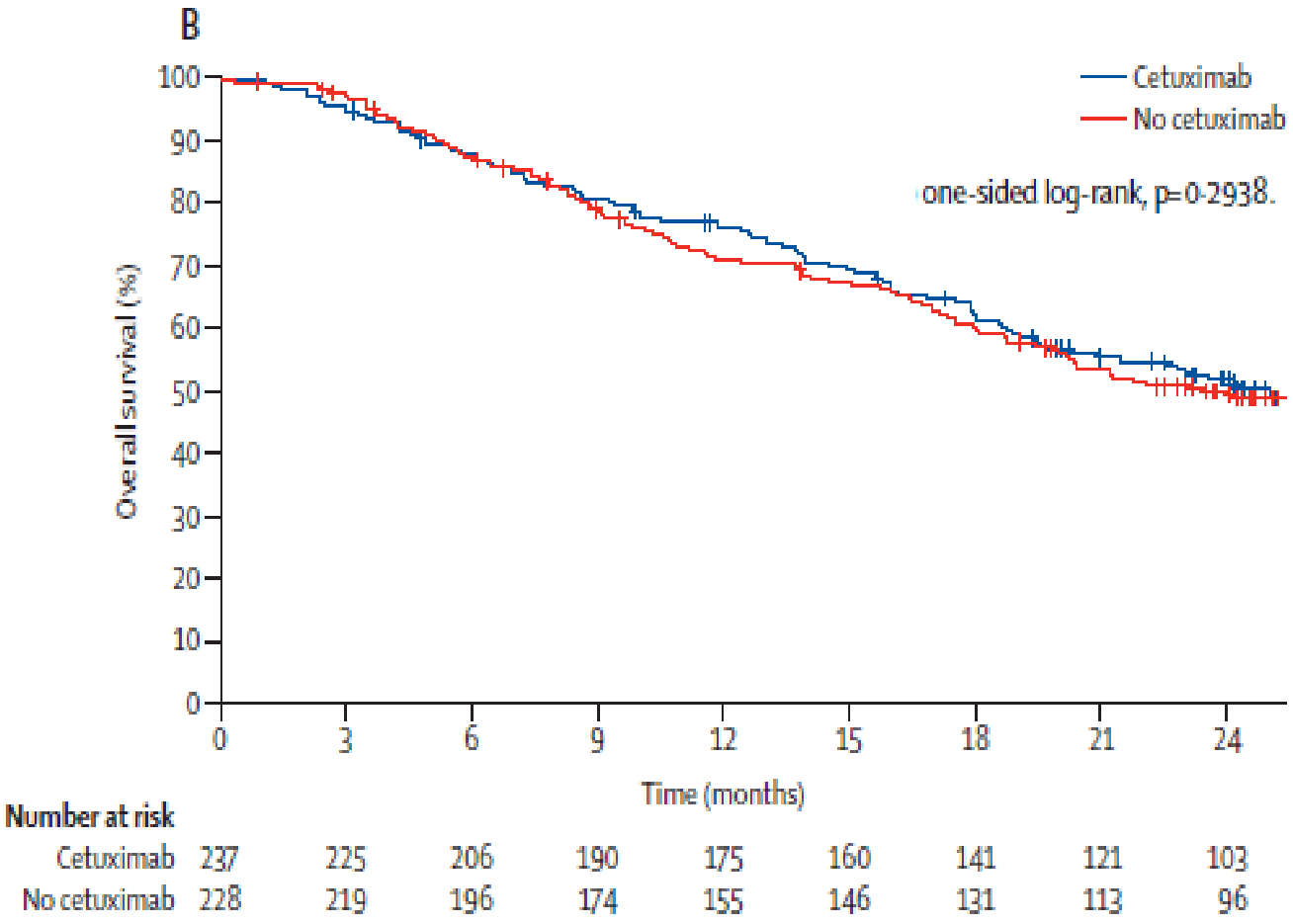
Standard	213	205	187	165	137	113	85
High dose	206	197	170	134	105	80	62

Summary of Adverse attributed to Treatment

	Cetuximab (n=237) Grade			No Cetuximab (n=227) Grade		
	3	4	5	3	4	5
Worst non-hematologic	130 (54.9%)	26 (11.0%)	11 (4.6%)	91 (40.1%)	18 (7.9%)	6 (2.6%)
Combined*	167 (70.5%)			115 (50.7%)		
Worst overall	117 (49.4%)	74 (31.2%)	11 (4.6%)	93 (41.0%)	57 (25.1%)	7 (3.1%)
Combined*	202 (85.2%)			157 (69.2%)		

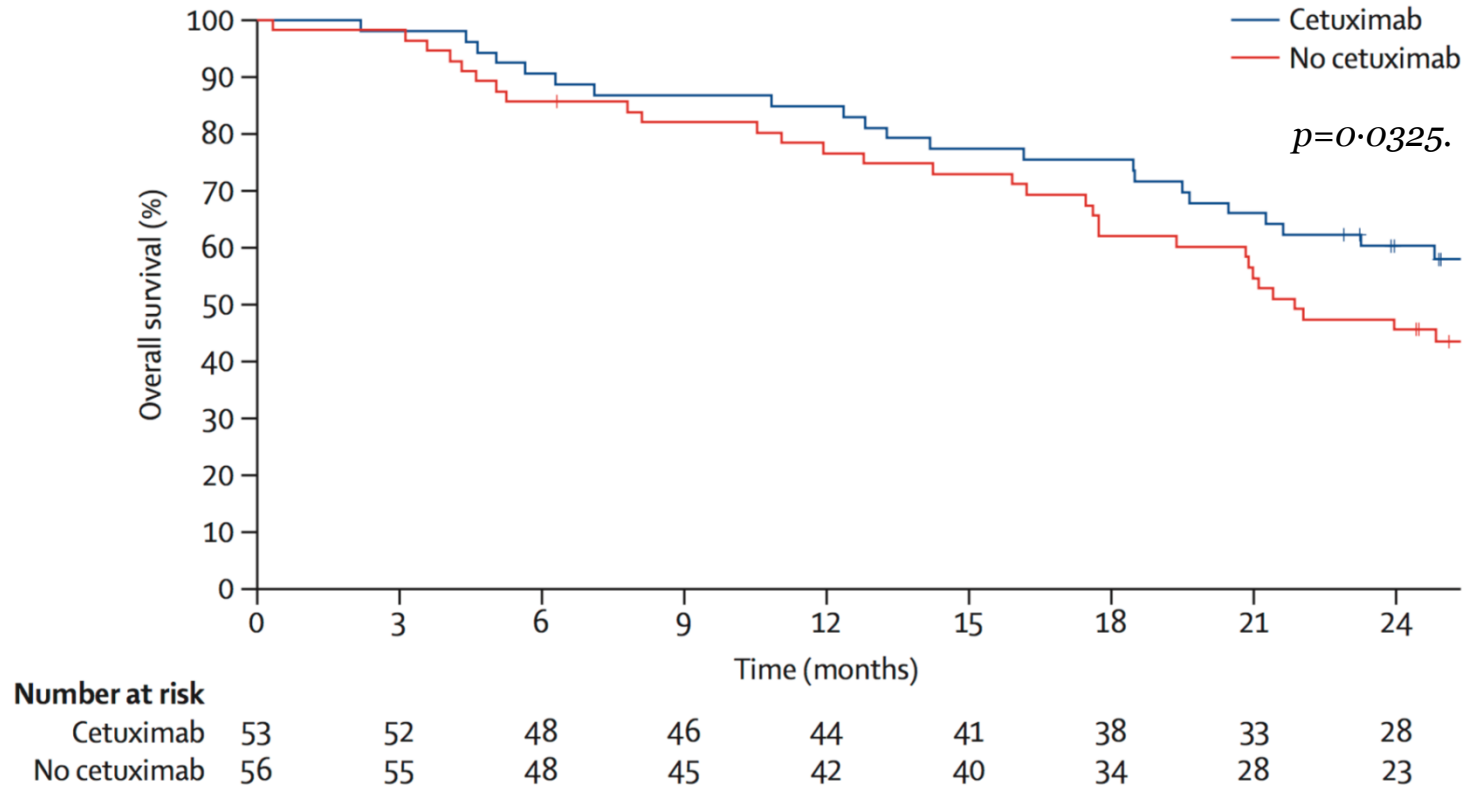
*$p<0.0001$

Concurrent cetuximab: RTOG 0617



Bradley, Lancet Oncol 2015

RTOG 0617: EGFR expression (H score ≥200) and Cetuximab interaction for OS



- H score ≥200 more common in squamous histology (p=0·0003)
- < 200: OS cetuximab 19·5 months vs 29·6 mos
- ≥ 200: OS cetuximab 42·0 vs 21·2 mos

Bradley, Lancet Oncol 2015

Erlotinib and radiotherapy in unselected NSCLC: A prospective phase II study

Single-institution Phase II study

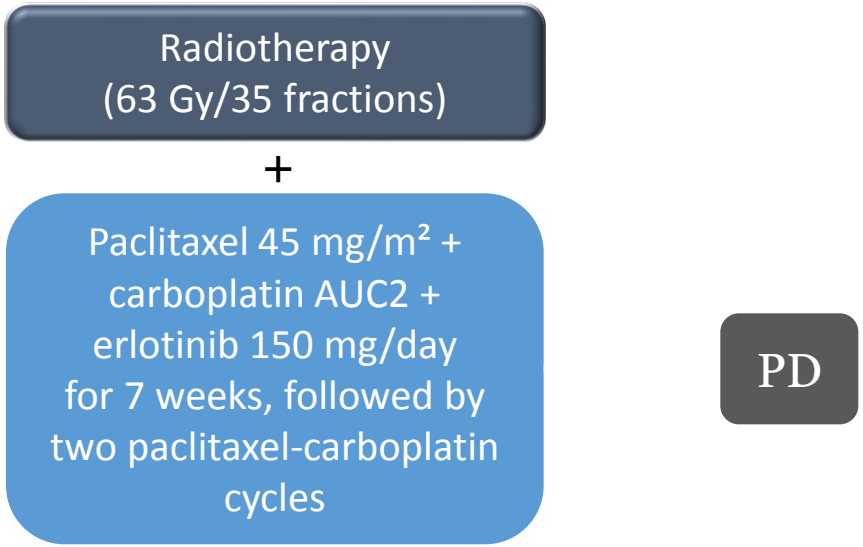
Key patient inclusion criteria

- Previously untreated, locally advanced, inoperable, stage III NSCLC
- Karnofsky's performance status >70

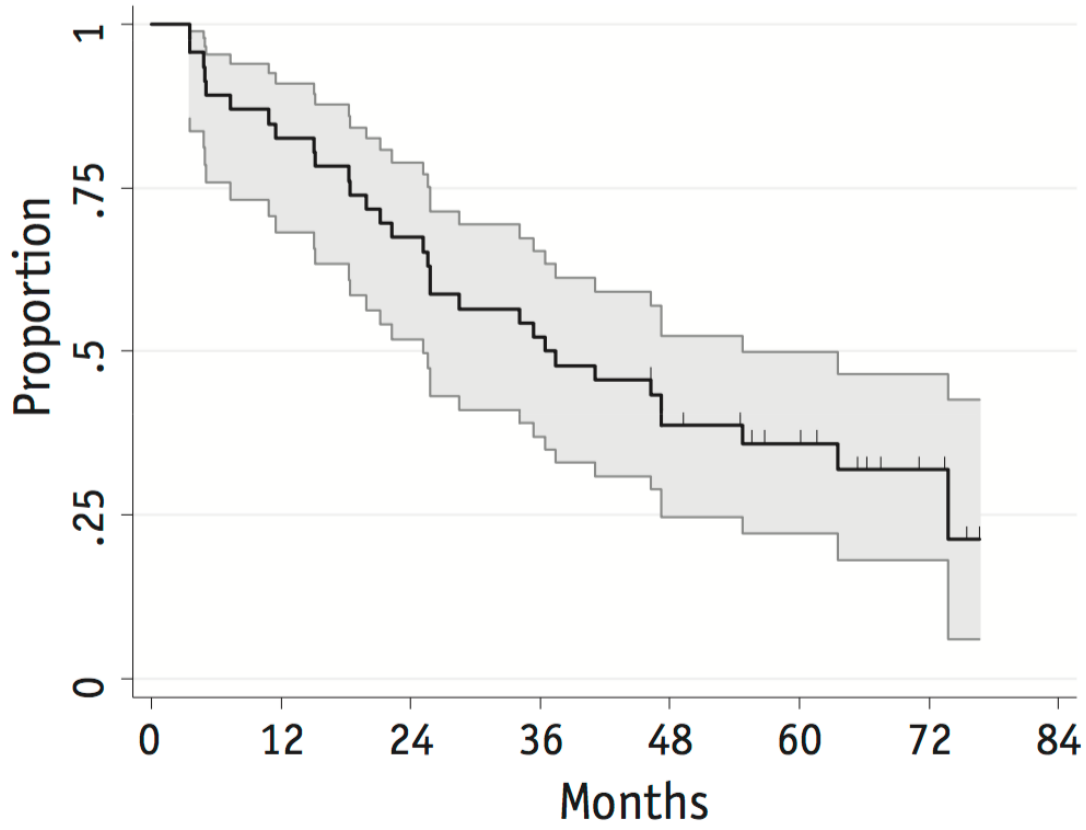
(n=46, 37 EGFR WT)

Primary endpoint

- Time to progression



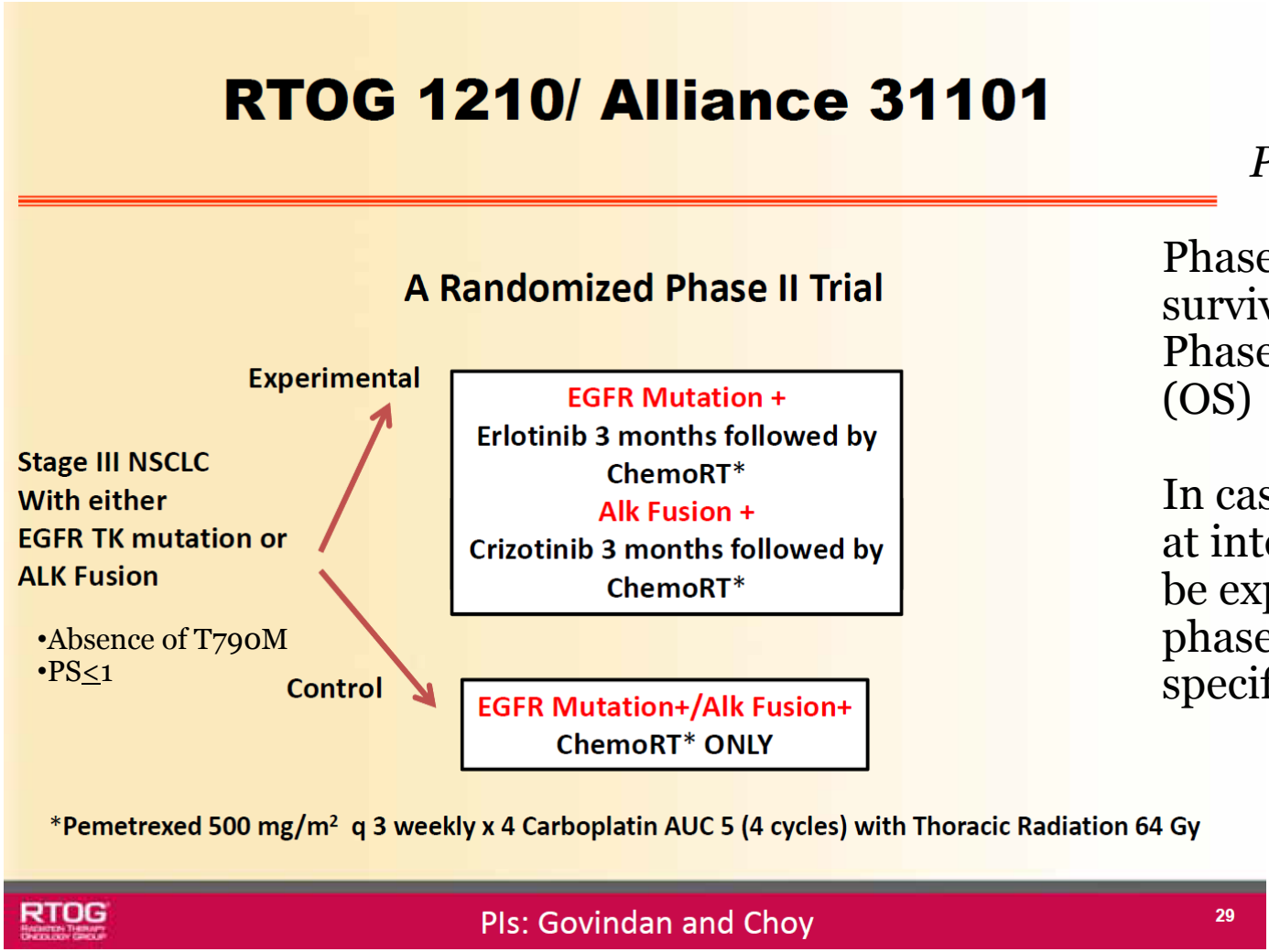
Komaki et al. Int J Radiation Oncol Biol Phys 2015



Median OS 36.5 months [34.1 months for WT EGFR and 41.1 months for mutated EGFR]
Incidence and severity of toxicity were also low- only 1 grade 4 event (pneumonitis)

Komaki et al. Int J Radiation Oncol Biol Phys 2015

EGFR TKI and radiotherapy in EGFR mutated NSCLC? RTOG 1210/Alliance 31101



Primary endpoint

Phase II: Progression-free survival (PFS)
Phase III: Overall survival (OS)

In case of PFS superiority at interim, the study will be expanded into its phase III portion for that specific mutation

Bevacizumab and radiotherapy

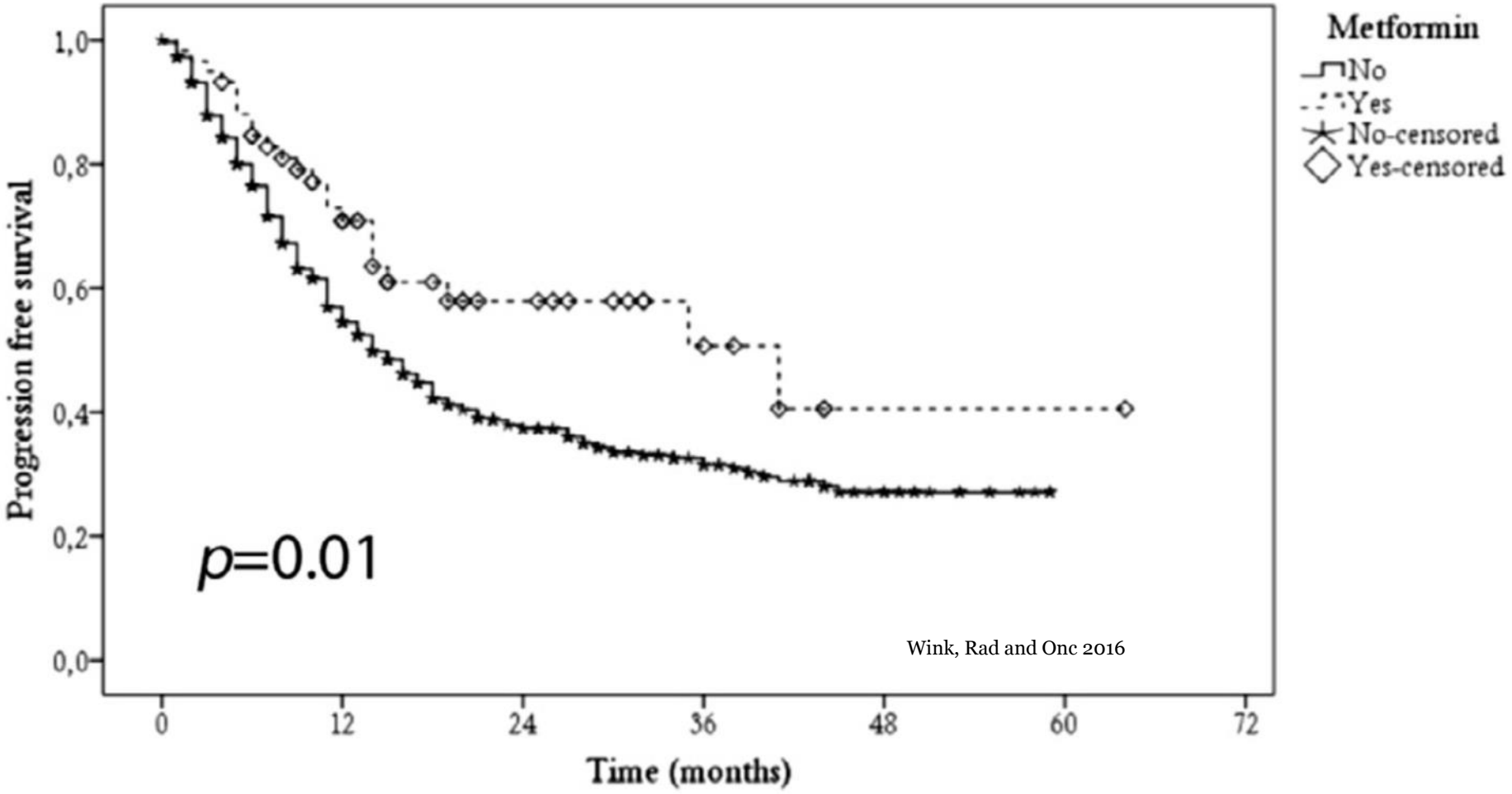
- Two independent phase II clinical trials in NSCLC and SCLC using bevacizumab in combination with chemotherapy and radiation.

- In each trial, tracheoesophageal fistulae development were reported.

- Related morbidity and mortality prompted early trial closures, US FDA warnings, and a change in bevacizumab labeling.

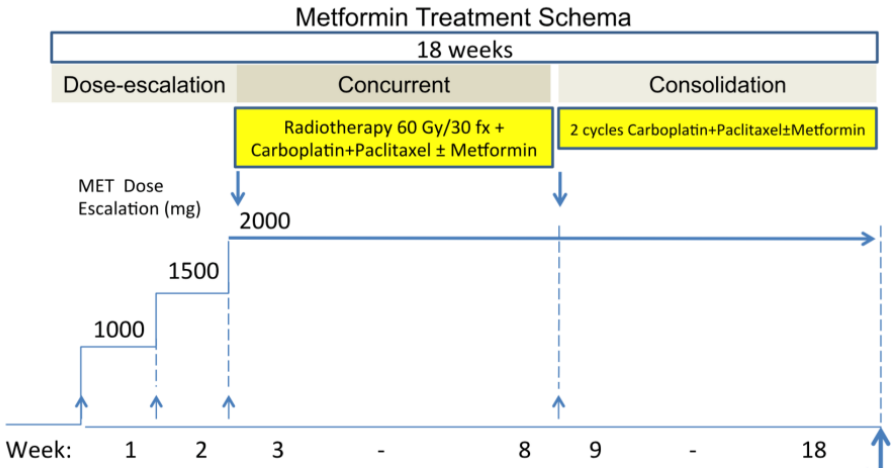
Spigel, JCO 2010

Metformin as a PI3K blocker with chemoradiation in stage III?



Metformin as a PI3K blocker with chemoradiation in stage III?

168 pts randomized to CRT (carbo/paclitaxel) +/- 2000mg of concurrent metformin & as maintenance for 10 weeks.
Designed to detect a 15% improvement in PFS at 12 months.

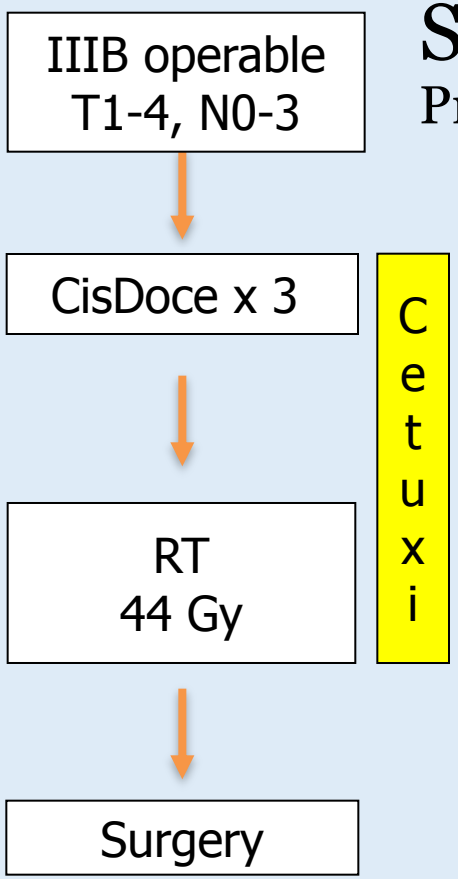


NCT02186847

- ALMERA : Phase II trial, 94 pts randomised to 63Gy RT plus concurrent Cisplatin-based chemotherapy +/- concurrent Metformin and continuing for a total of 12 months. Designed to detect a 20% improvement in PFS at 12 months.

NCT02115464

What about surgical stages IIIB: Cetuximab?



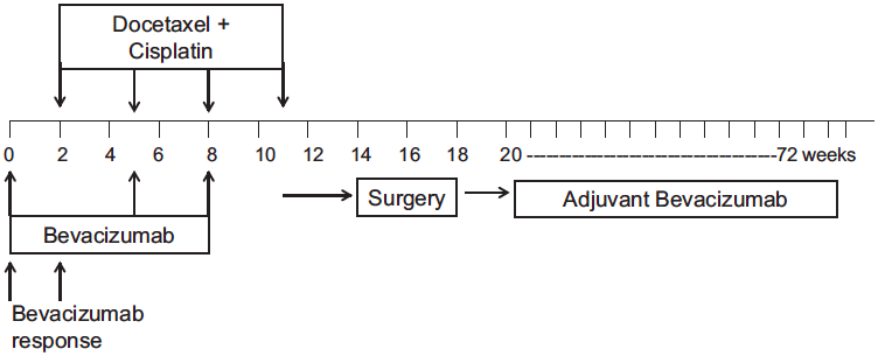
SAKK 16/08 (recruited)

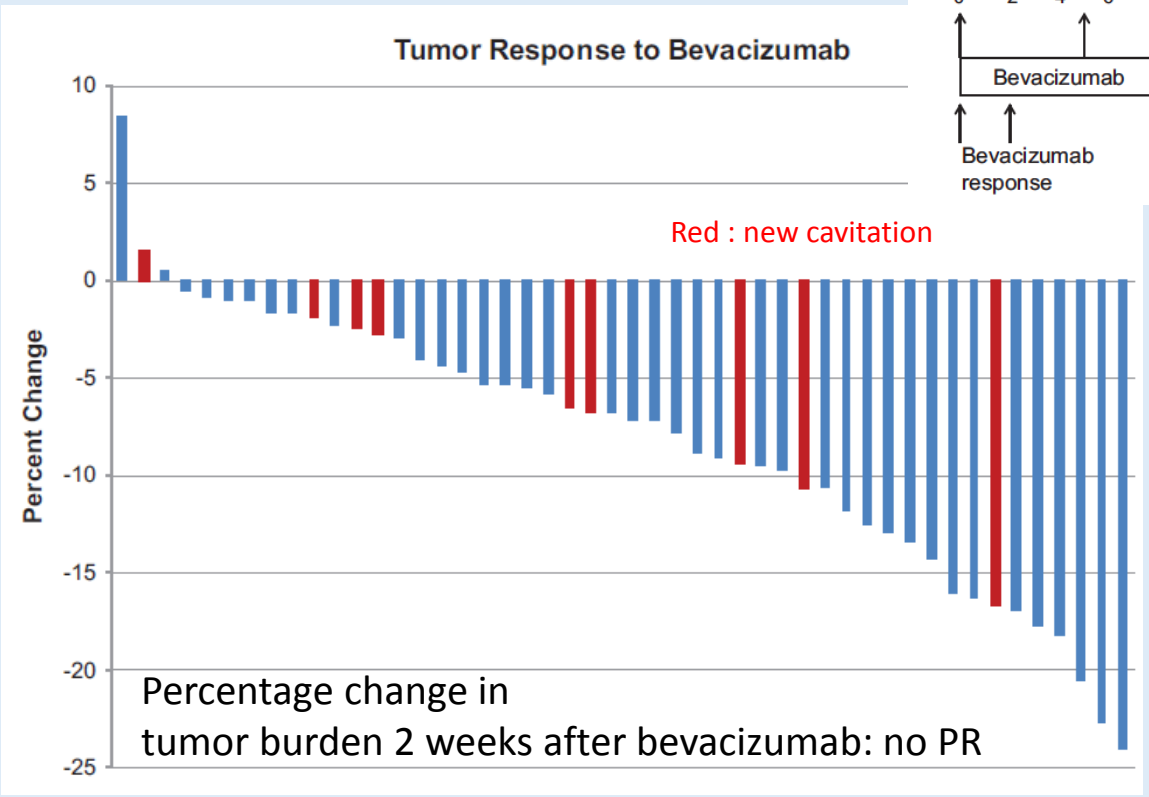
Preoperative CT-RT plus concomittant Cetuximab in III.

- N = 69
- PFS1y (1. EP)
- Exclusion of supraclavicular N, malignant effusion, infiltration of aorta, esophagus, myocardium
- Cetuxi 400mg/m2 -> 250mg/m2/wk
- Interim safety analysis conducted after 25 pts

What about surgical stages III: Bevacizumab?

Phase II Trial of Neoadjuvant Bevacizumab Plus Chemotherapy and Adjuvant Bevacizumab in Patients with Resectable Nonsquamous Non–Small-Cell Lung Cancers

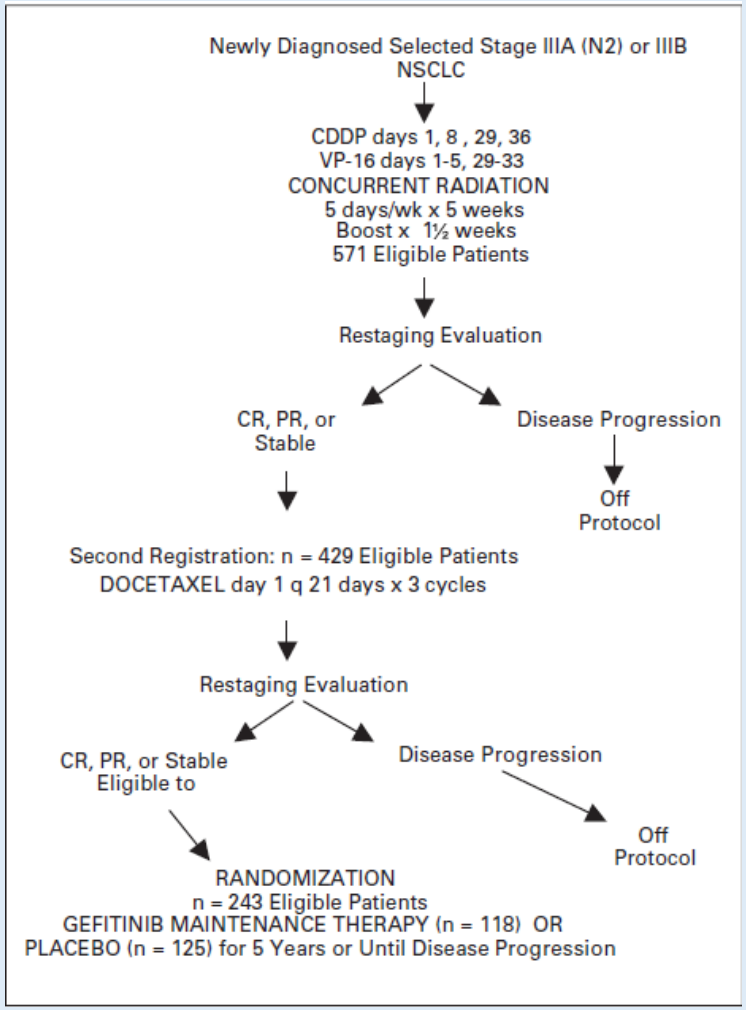




This study failed to meet its primary endpoint (an increase from the reported 33% to a goal of 50% pathological downstaging.

Chaft, JTO, 2013

Maintenance gefitinib: unselected patients: SWOG 0023



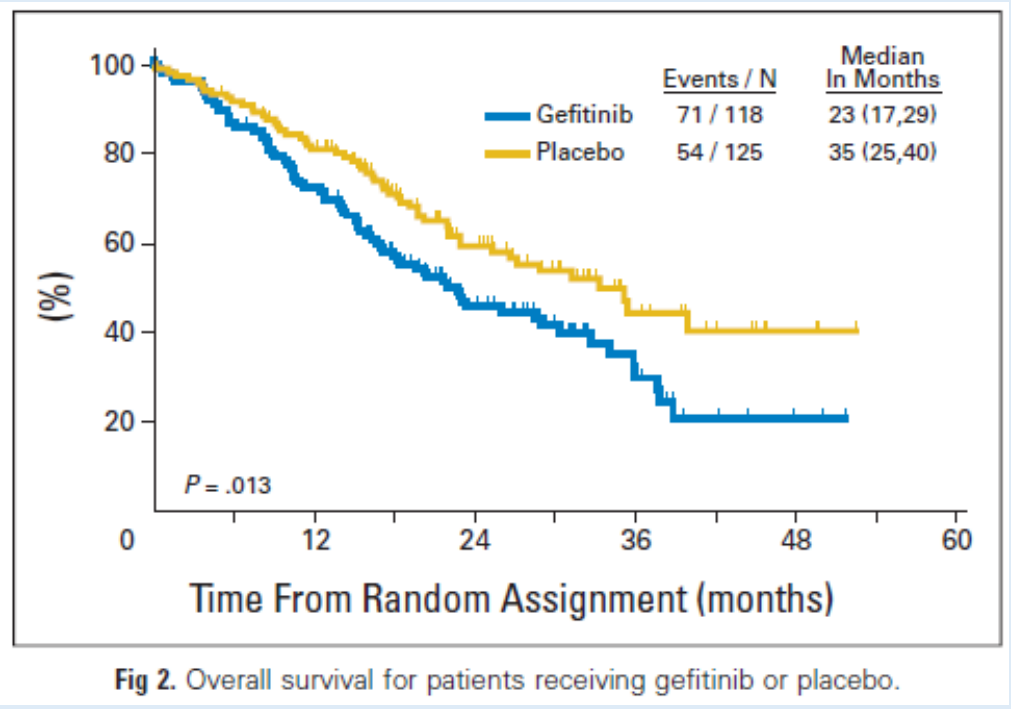


Fig 2. Overall survival for patients receiving gefitinib or placebo.

Deaths related to progressive disease

Kelly JCO 2008

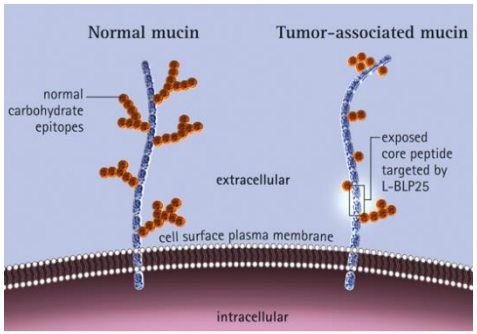
Immunotherapy for stage III NSCLC

Rationale for radiotherapy and immunotherapy

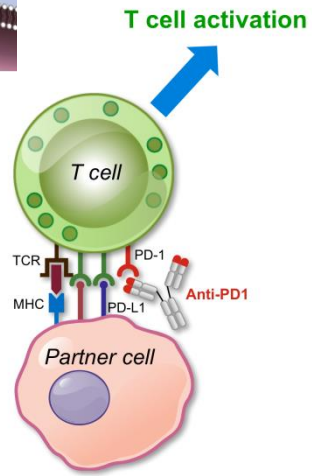
- Antigen release
- Antigen specific T cell activation and proliferation
- Increase in antigen-presenting and tumour cells PD-L1 expression

Attempts in the clinic

- START trial (Stimuvax®; L-BLP25)



- Ongoing checkpoint inhbitors-based trials



Stimuvax® after chemoradiation in stage III NSCLC

- 1,239 patients were included in the primary analysis population (median age 61 years; 39% stage IIIA and 61% IIIB; 65% concurrent and 35% sequential chemoradiotherapy)

	L-BLP25 + BSC	Placebo +BSC	HR (95% CI)	p value
OS, months				
All patients	**25.6**	**22.3**	**0.88 (0.75–1.03)**	**0.123**
Concurrent chemo/RT	**30.8**	**20.6**	**0.78 (0.64–0.95)**	**0.016**
TTP, months				
All patients	**10.0**	**8.4**	**0.87 (0.75–1.00)**	**0.053**

- L-BLP25 maintenance therapy in stage III NSCLC was well tolerated, but did not significantly prolong OS except in the subgroup of patients treated with a concurrent chemoradiotherapy strategy

Butts, Lancet Oncol 2014

Stimuvax® after chemoradiation in stage III NSCLC

BLP25 Liposome Vaccine and Bevacizumab After Chemotherapy and Radiation Therapy in Treating Patients With Newly Diagnosed Stage IIIA or Stage IIIB Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2014 by Eastern Cooperative Oncology Group

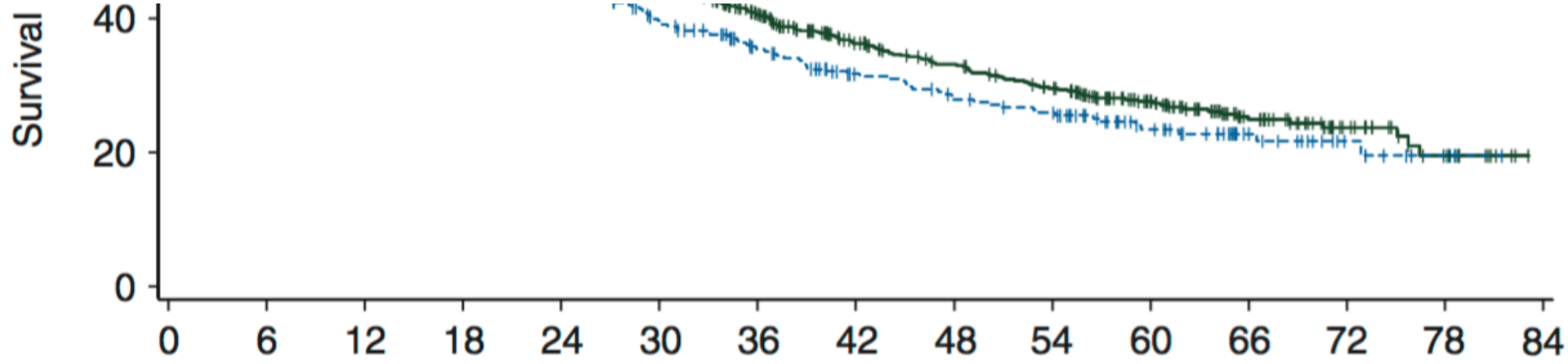
Sponsor:
Eastern Cooperative Oncology Group

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
Eastern Cooperative Oncology Group

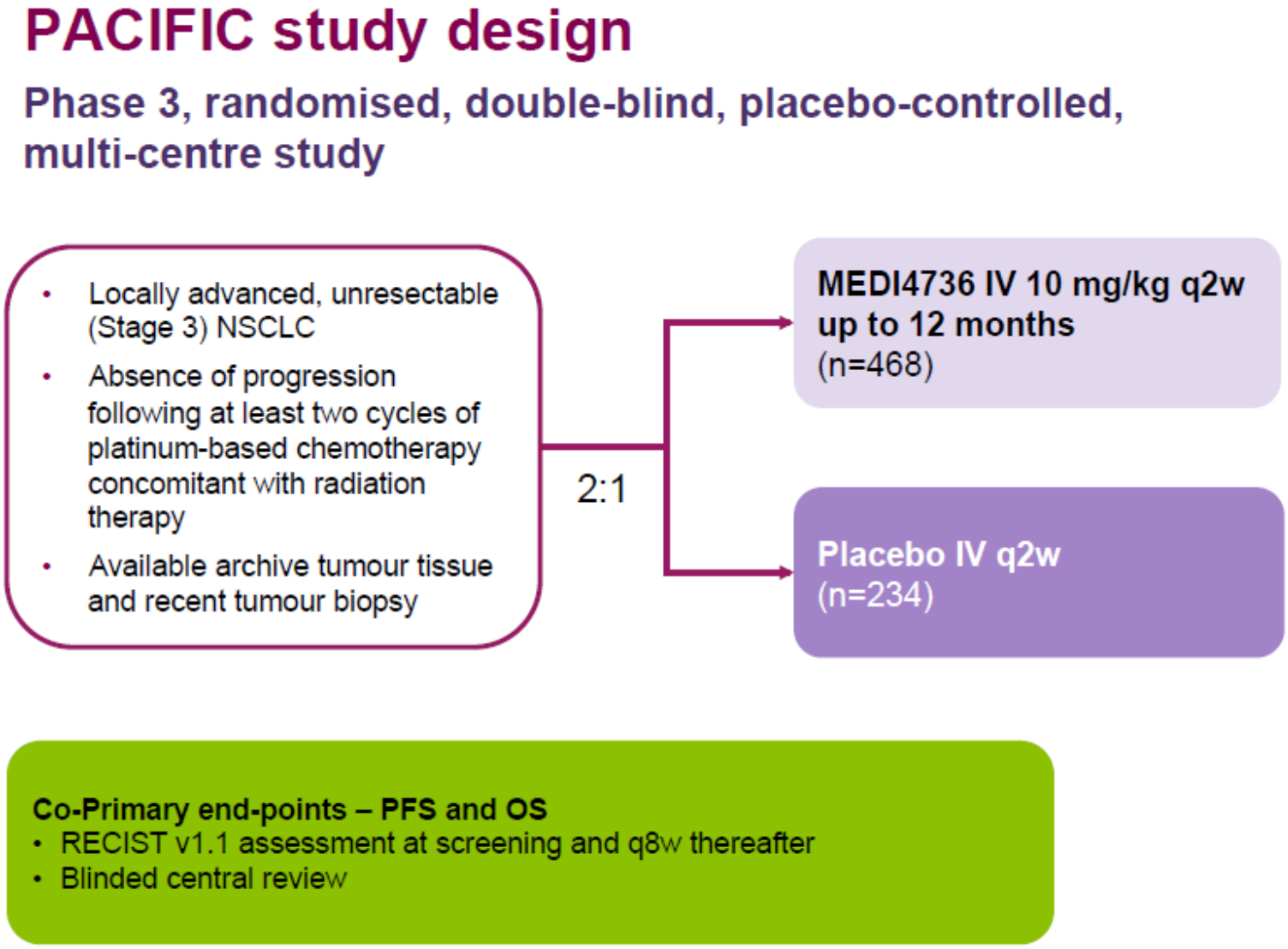
ClinicalTrials.gov Identifier:
NCT00828009

First received: January 22, 2009
Last updated: September 16, 2014
Last verified: September 2014
History of Changes

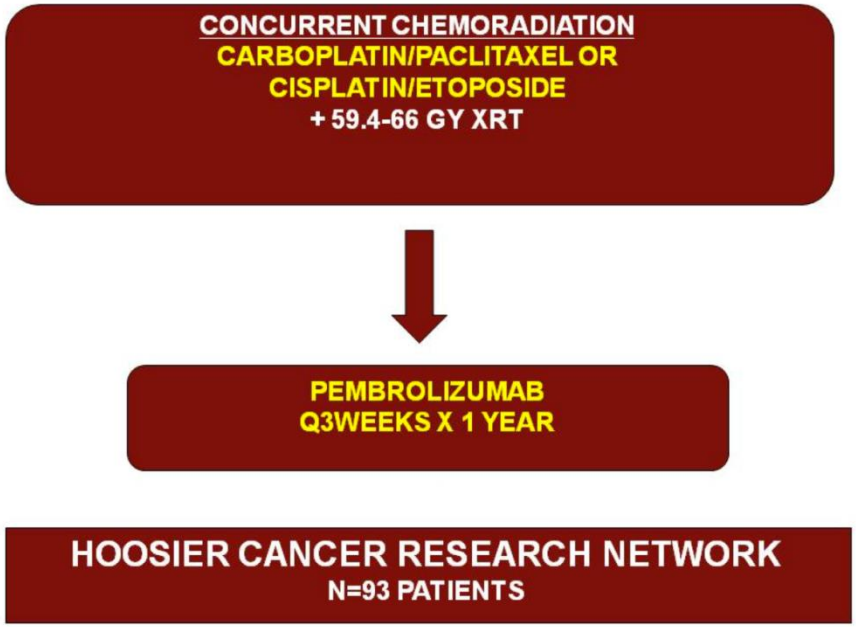


Mitchell, Ann Oncol 2015

Blocking PD1/PD-L1 pathway in stage III NSCLC



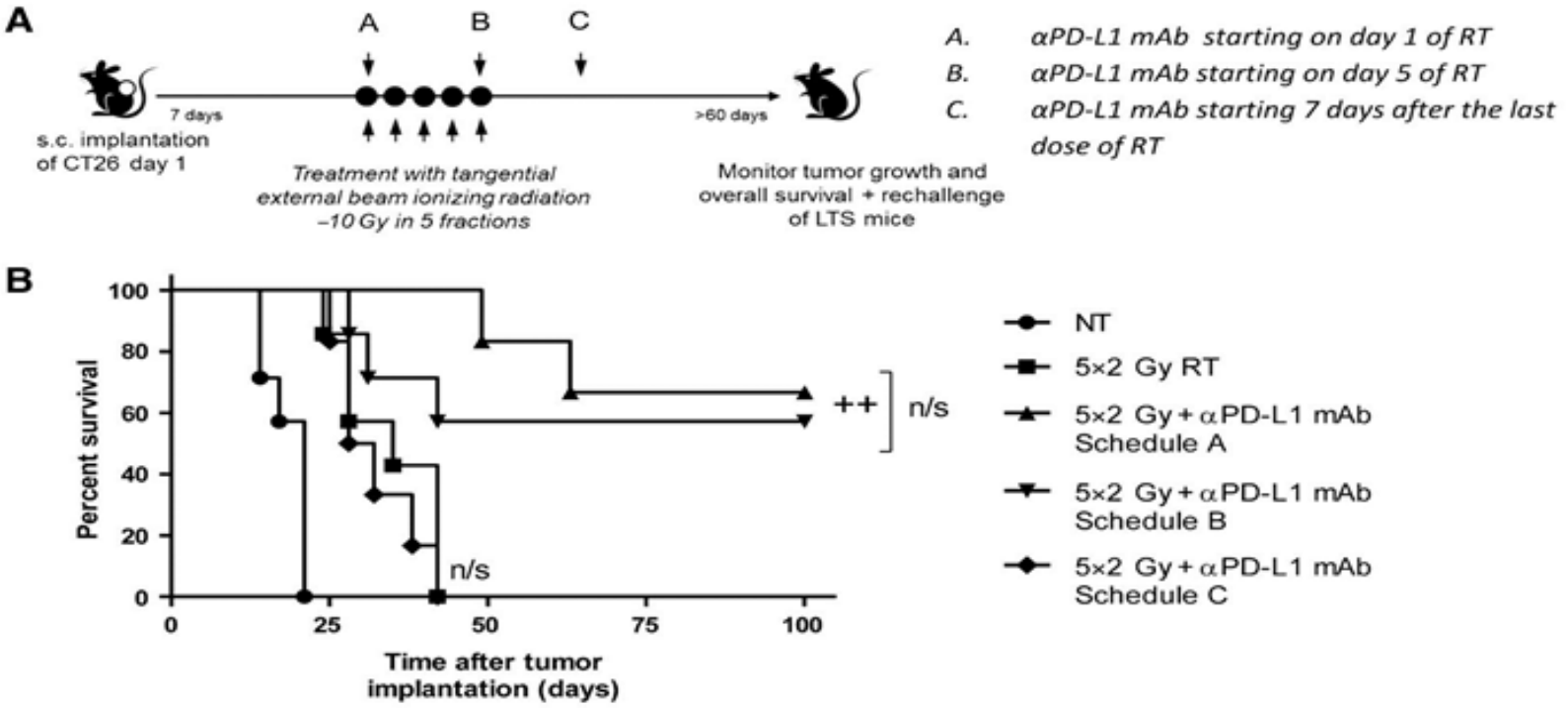
Blocking PD1/PD-L1 pathway in stage III NSCLC



NCT02525757: Chemotherapy + Radiation with MPDL3280A right after completion or after a 3-4 week rest period (MD Anderson)

Rtog3505 / checkmate 209-333 : Phase III trial of Nivolumab following stage III chemoradiation will be posted will be posted next month on clinicaltrials.gov

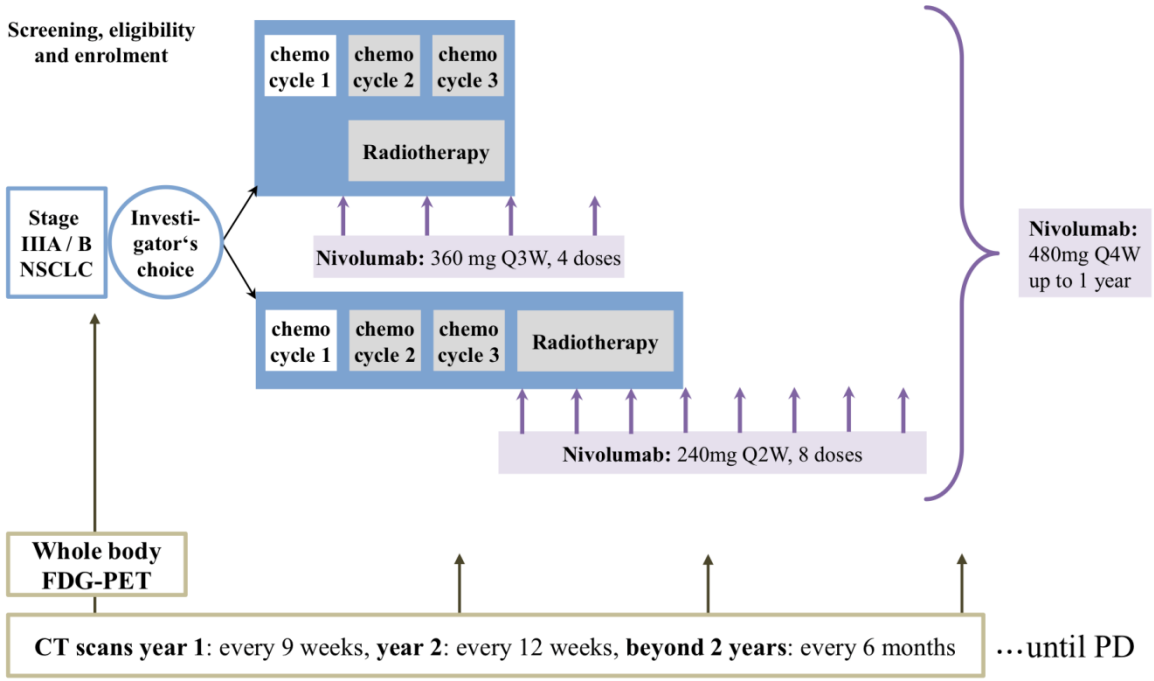
Blocking PD1/PD-L1 pathway in stage III NSCLC



Dosing schedule is critical to outcome with radiotherapy potentiation only observed with concurrent but not sequential αPD-L1 mAb therapy.

Dovedi CCR 2014

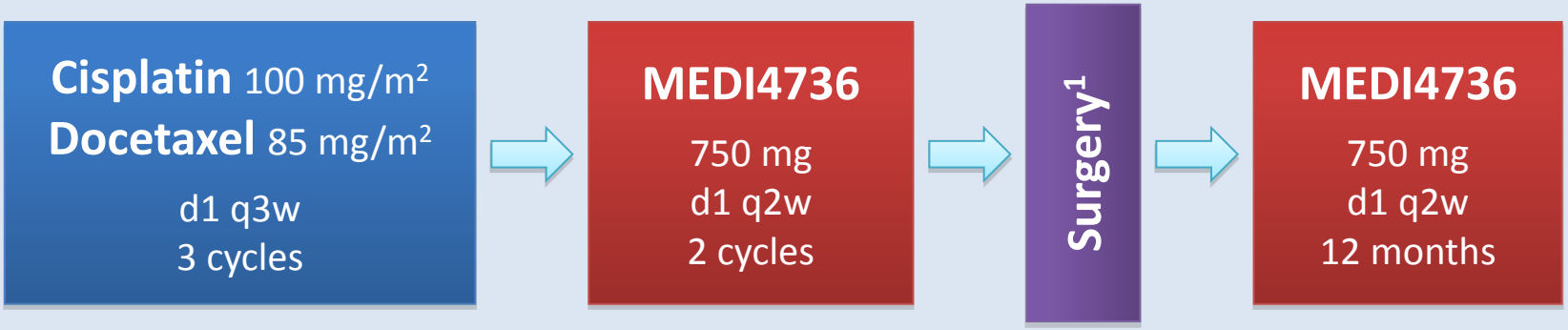
Blocking PD1/PD-L1 pathway in stage III NSCLC: alternative scheduling? ETOP phase 2 Nicolas trial



NCT02621398: Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-IIIB Non-Small Cell Lung Cancer (Phase 1; New Jersey, not yet recruiting)

Neoadjuvant checkpoint blockade in stage IIIA

- Stage IIIA(N2) NSCLC
- Resectable disease
- ECOG PS 0-1
- Available tissue
- N=68



[1]Postoperative Radiotherapy for patients with R1/R2 resection

Interim safety analysis

•After 25 operated patients

•If 30-day postoperative mortality >10% → need of IDMC

Primary endpoint

–Event-free survival (EFS) at 12 months

50 YEARS SAKK
WE BRING PROGRESS TO CANCER CARE

Thanks for your attention…