

ESMO Clinical Practice Guidelines

Lung Cancer Discussion

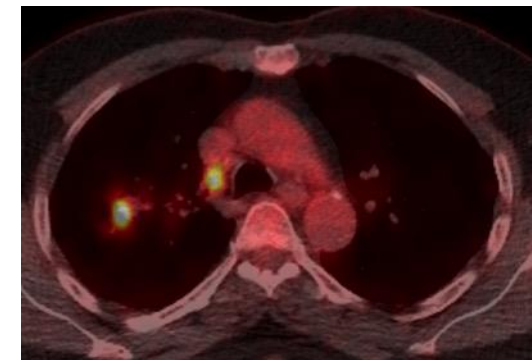
Prof Tetsuya Mitsudomi
Department of Thoracic Surgery
Kinki University Faculty of Medicine
Osaka-Sayama, Japan

Disclosures: Tetsuya Mitsudomi

- I have acted as consultant/advisor for Roche/Chugai, AstraZeneca, Pfizer, Novartis, Boehringer Ingelheim, Clovis, Bristol Myers Squibb/Ono, MSD
- I have received honoraria from Chugai, Taiho, AstraZeneca, Pfizer, Eli Lilly, Boehringer Ingelheim, Bristol Myers Squibb/Ono

Case...discussion points

- Treatment of cN2(discrete, single N2)disease
- Treatment of lung cancer with EGFR mutation (Del 19). Choice of TKI
- Treatment of acquired resistance due to T790M



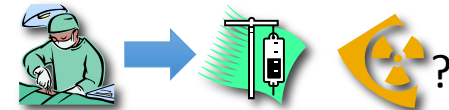
what are the optimal multi-modality combinations for the different stage III disease sub-stages?

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt¹, D. De Ruyscher², W. Weder³, C. Le Péchoux⁴, P. De Leyn⁵, H. Hoffmann⁶, V. Westeel⁷, R. Stahel⁸, E. Felip⁹, S. Peters¹⁰ & Panel Members[†]

incidental IIIA(N2) (unforeseen N2)

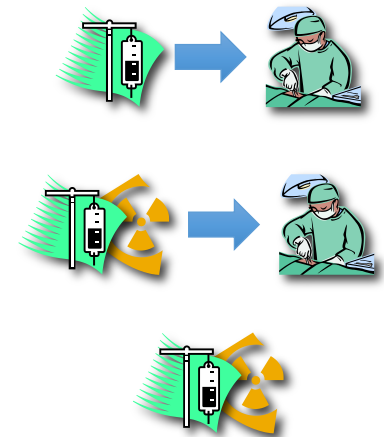
Recommendation 4.1: If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant chemotherapy [I, A]. In case of complete resection, addition of post-operative radiotherapy is not routinely recommended, but may be an option following individual risk assessment [V, C].



potentially resectable IIIA(N2) disease

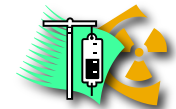
preoperative diagnosis of IIIA(N2)

Recommendation 4.2.1: Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].

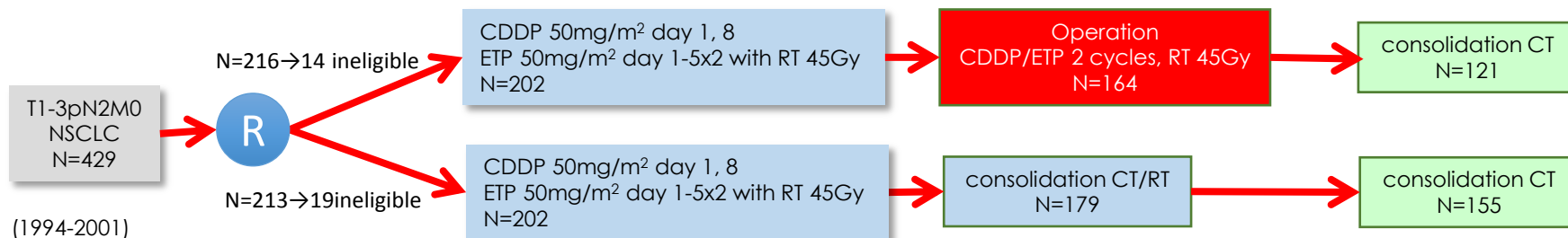


unresectable IIIA (N2) disease and IIIB disease patients

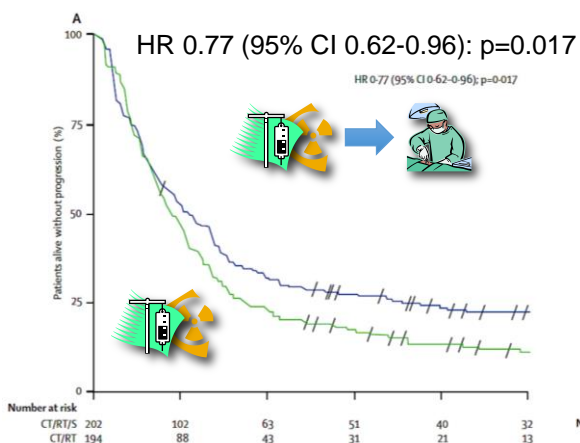
Recommendation 4.3: Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible—for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A].



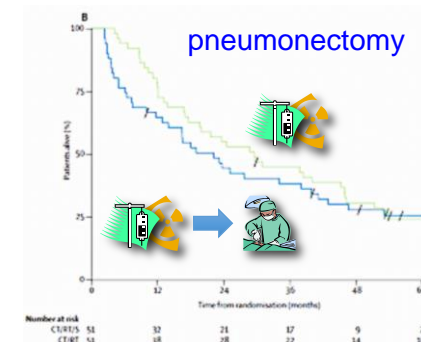
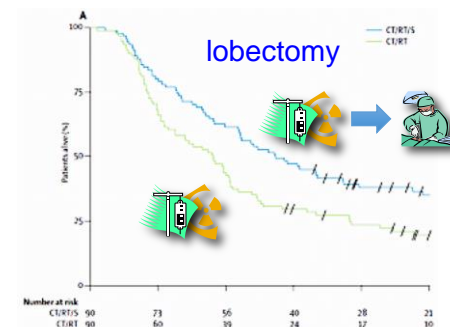
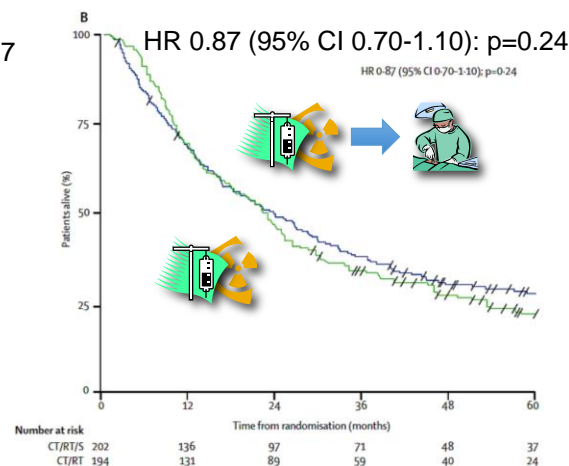
Radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC: a phase III randomized controlled trial (INT0139) Albain et al., Lancet 2009



Progression free survival



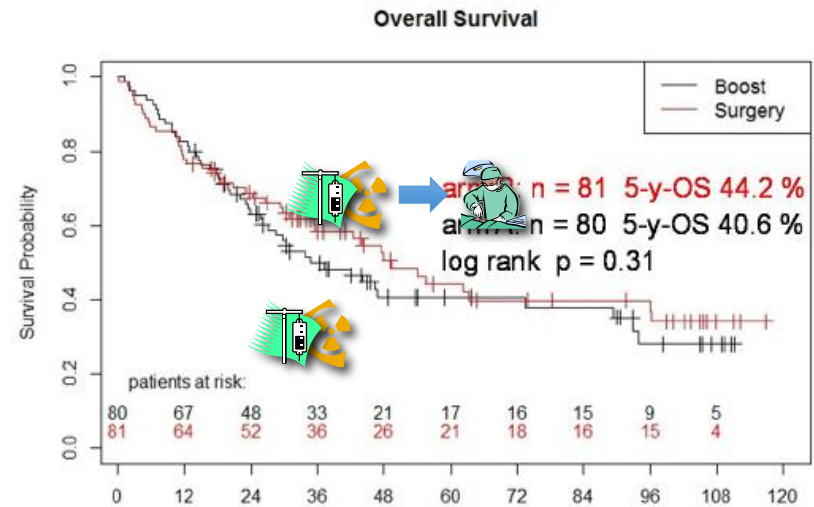
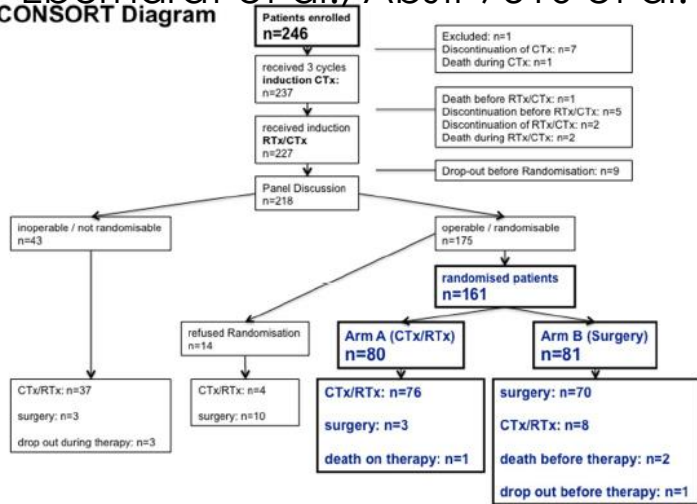
Overall survival (primary endpoint)



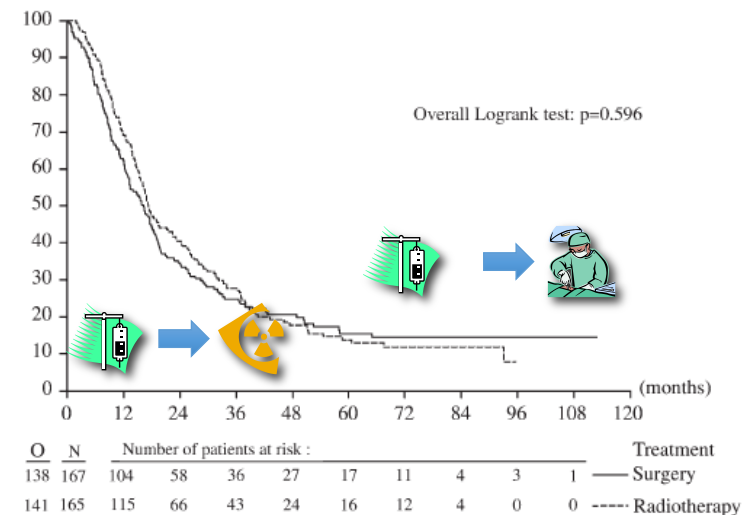
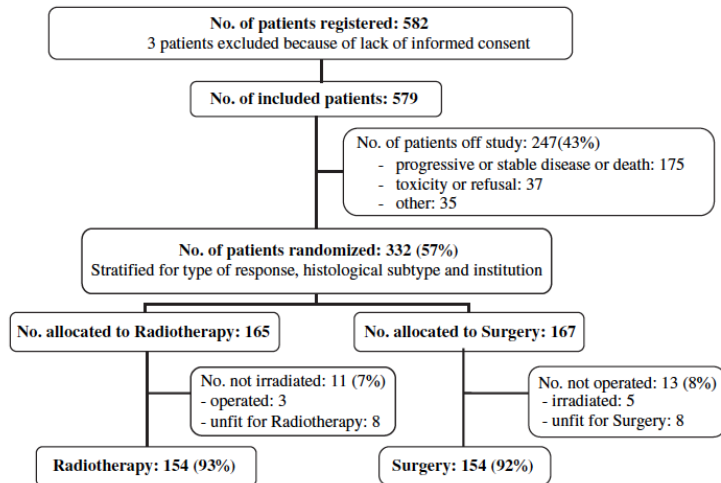
Phase III study of surgery vs. definitive concurrent chemoradiotherapy boost in patients with operable (stage IIIA(N2)/selected IIb (sel IIIB) NSCLC following induction chemotherapy and concurrent CRTx (ESPA-TUE).

Eberhardt et al., Abstr 7510 et al. ASCO 2014

CONSORT Diagram



Randomized controlled trial of resection vs. radiotherapy after induction chemotherapy in stage IIA-N2 NSCLC (EORTC)
van Meerbeeck et al., J Natl Cancer Inst, 2007

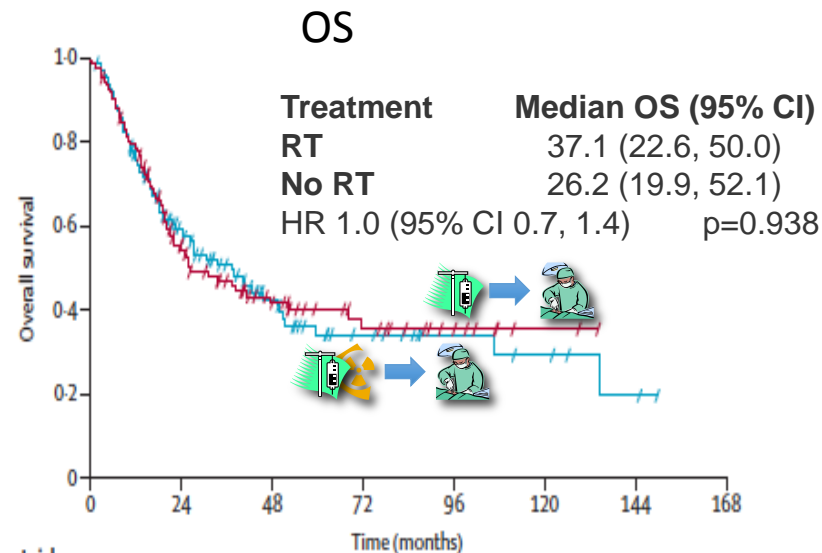
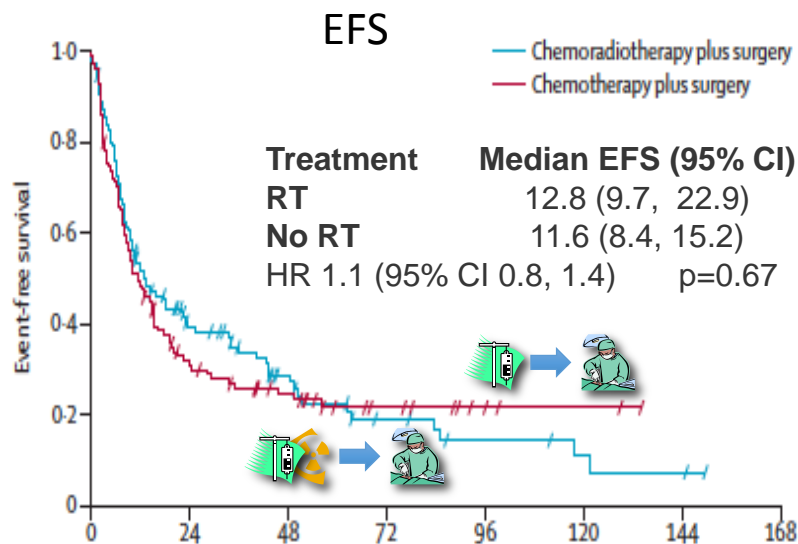
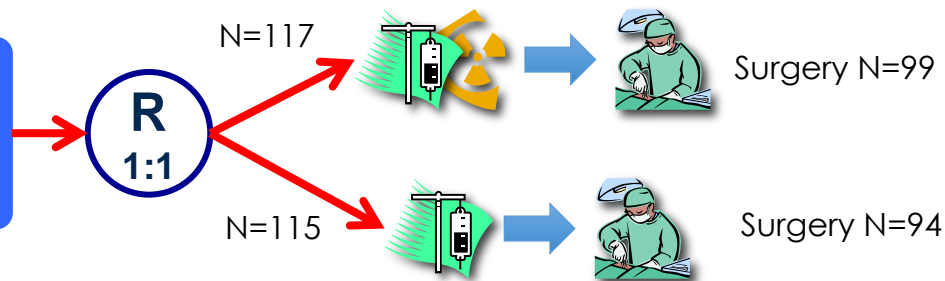


Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial SAKK 16/00 trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

Lancet 2015; 386: 1049-56

- Resectable stage IIIA/N2 NSCLC
- PS 0-1
- Adequate organ function (n=232)



Interpretation Radiotherapy did not add any benefit to induction chemotherapy followed by surgery

Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data

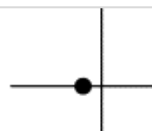
NSCLC Meta-analysis Collaborative Group*

The Lancet, 2014; 383, 1561 - 1571

Clinical stage (IA, IB, II, III)

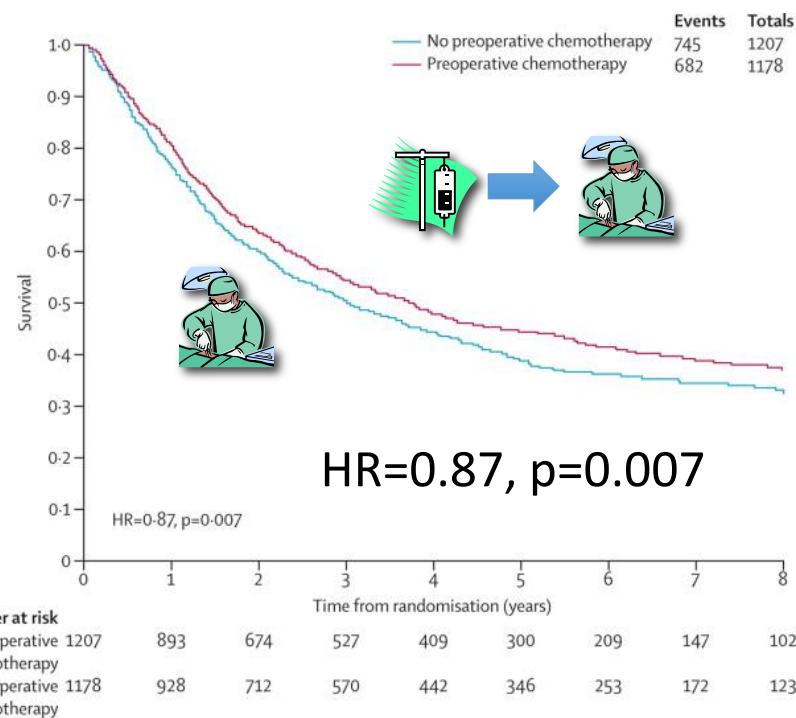
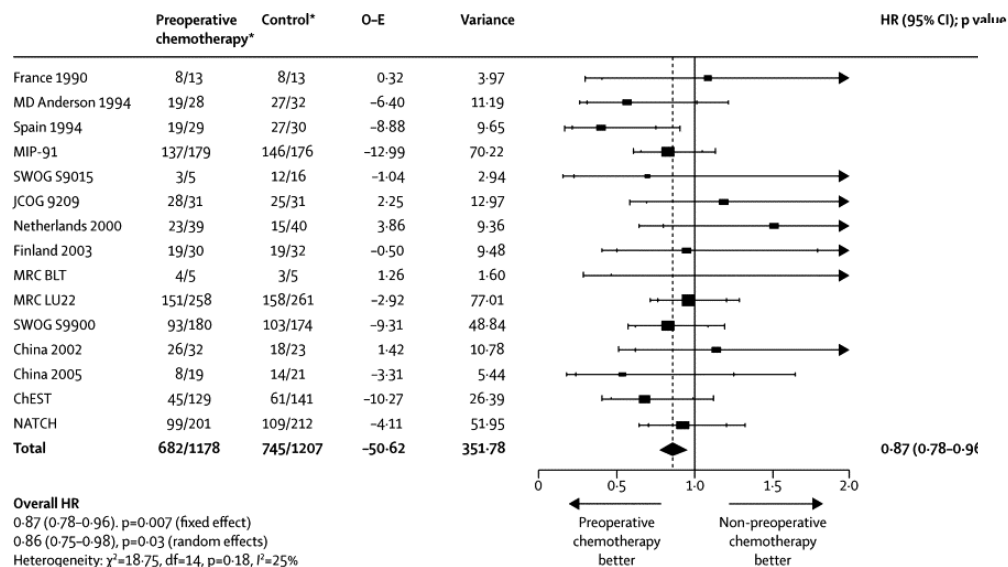
9 trials, 2171 patients

Greater treatment effect
with higher clinical stage



Greater treatment effect
with lower clinical stage

0.96 (0.83-1.12), $p=0.64$,
heterogeneity $p=0.22$





Treatment of Stage III Non-small Cell Lung Cancer

**Diagnosis and Management of Lung Cancer,
3rd ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines**

*Nithya Ramnath, MD; Thomas J. Dilling, MD; Loren J. Harris, MD, FCCP;
Anthony W. Kim, MD, FCCP; Gaetane C. Michaud, MD, FCCP;
Alex A. Balekian, MD, MSHS; Rebecca Diekemper, MPH;
Frank C. Detterbeck, MD, FCCP; and Douglas A. Arenberg, MD, FCCP*

2013 ACCP guidelines

Discrete mediastinal node involvement

In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA),

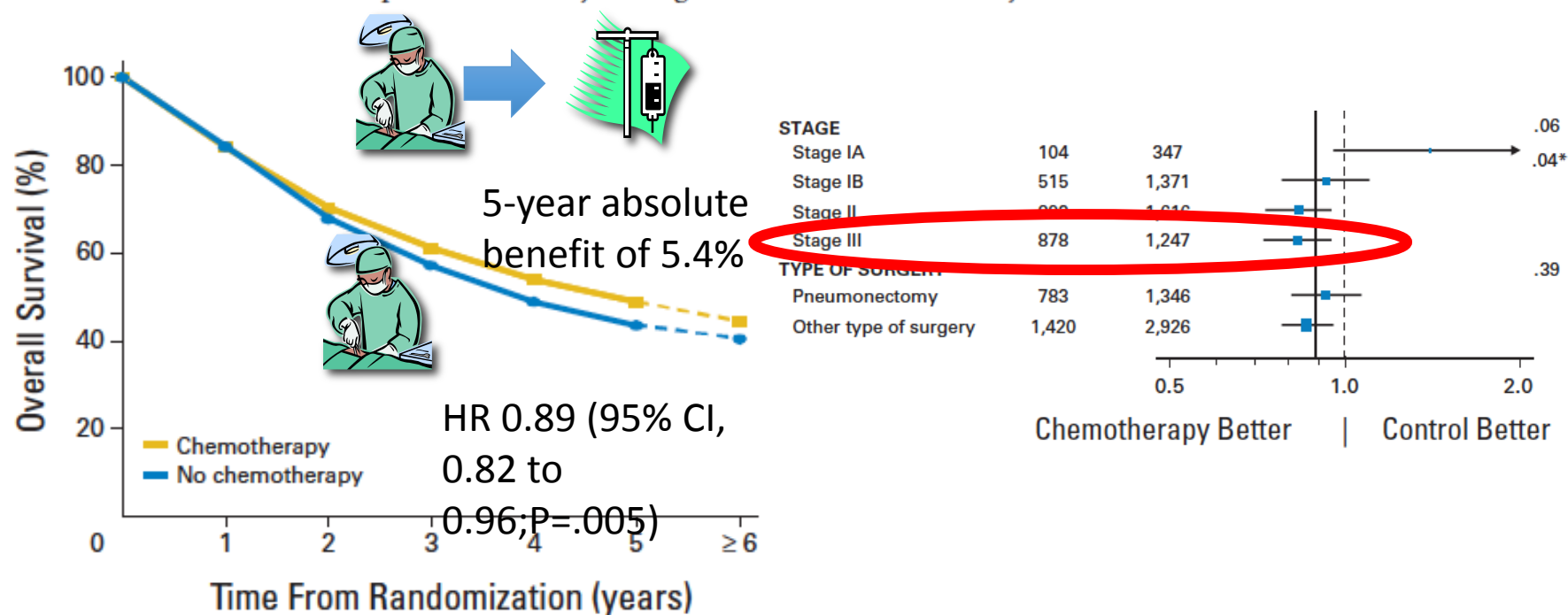
3.5.2. either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A) .

3.5.3. primary surgical resection followed by adjuvant therapy is not recommended (Grade 1C) .

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

A



Deaths / person years

by period

Control

Chemotherapy

Years 0-3

966 / 5,155

857 / 5,181

Years 4-5

239 / 1,668

203 / 1,817

Years ≥ 6

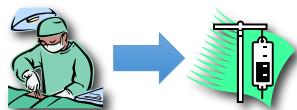
49 / 720

76 / 790

However, how many of these patients were discrete N2 is unknown

SINGAPORE
2015ESMO
ASIA18-21 DECEMBER
SINGAPORE

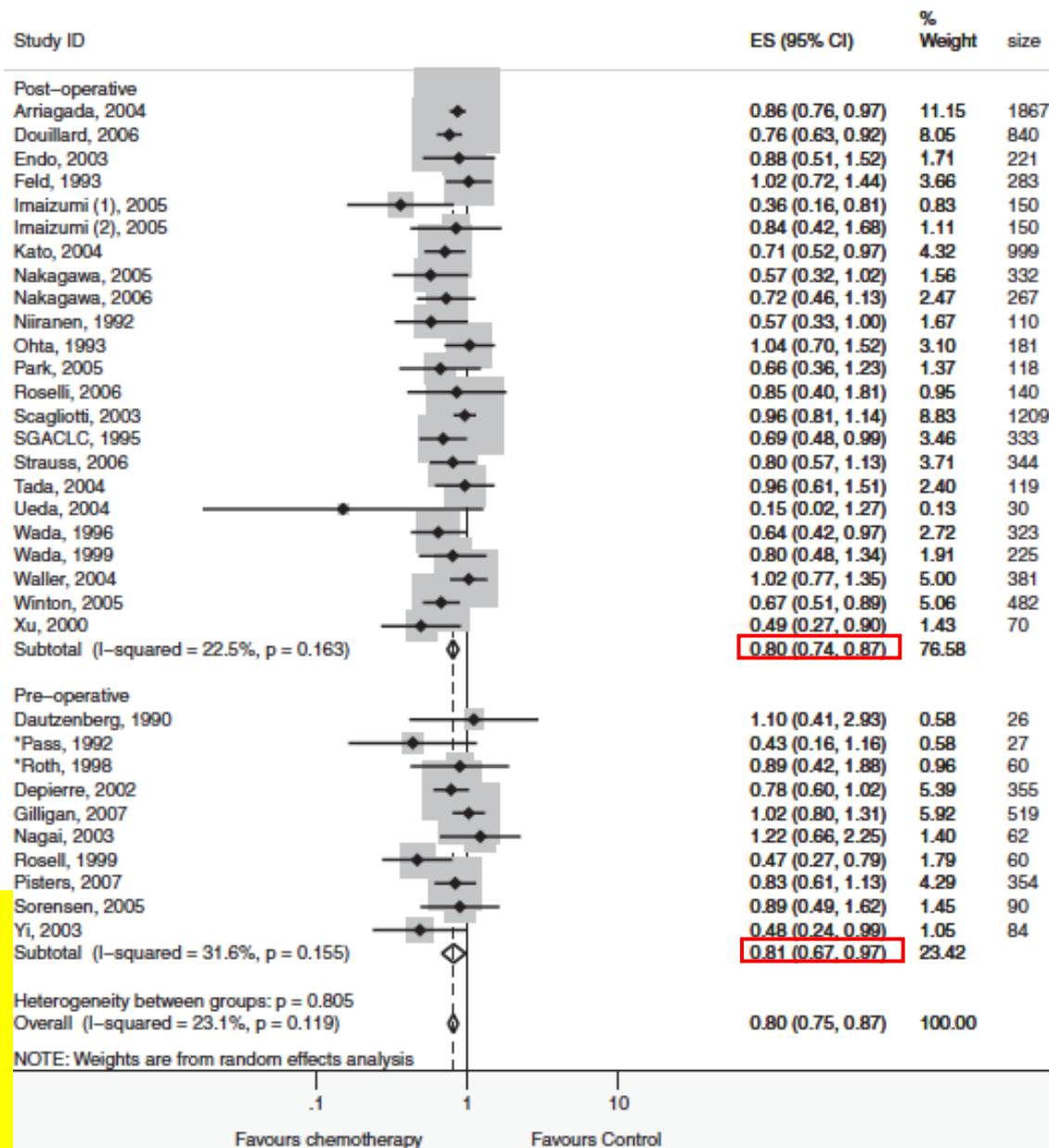
Preoperative vs. postoperative chemotherapy in patients with resectable NSCLC: Systematic review of indirect comparison meta-analysis of randomized trials Lim et al., J Thorac Oncol, 4:1380-1388, 2009



12/24 included N2



10/10 included N2



Conclusions: the relative hazards of postoperative CTx compared with preoperative CTx was 0.99 (0.81–1.21; p = 0.91).
In patients with resectable lung cancer, there was no evidence of a difference OS and DFS between postoperative versus preoperative CTx

Peri-operative chemo/radiotherapy for N2 disease



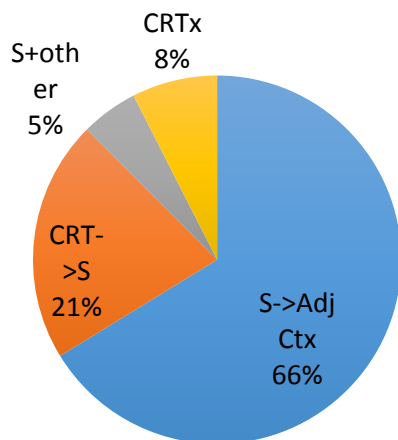
Something is better than nothing !?
However N2 is very heterogeneous...
Patient subsets between the trials are not same



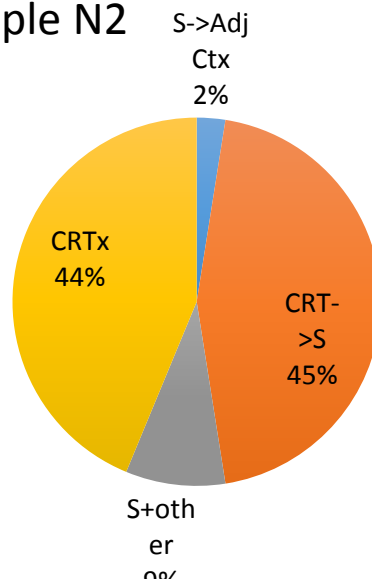
JCOG Lung cancer group questionnaire survey (2013)

Courtesy of Dr. Horinouchi

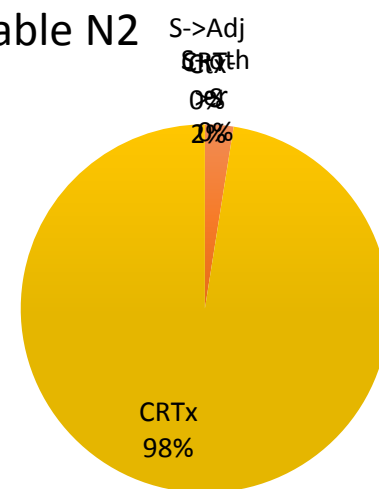
Single N2



Multiple N2



Unresectable N2

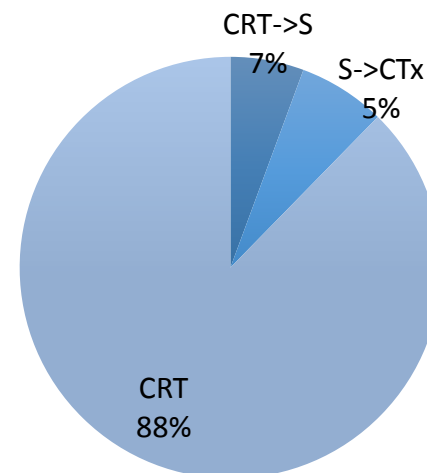


Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non-Small-Cell Lung Cancer

Matthew Koshy, MD,*† Stacey A. Fedewa, MPH,‡ Renu Malik, MD,† Mark K. Ferguson, MD,§¶

Wickii T. Vigneswaran, MD,§ Lawrence Feldman, MD,|| Andrew Howard, MD,*† Khaled Abdelhady, MD,#
Ralph R. Weichselbaum, MD,*† and Katherine S. Virgo, PhD, MBA‡**

Journal of Thoracic Oncology® • Volume 8, Number 7, July 2013

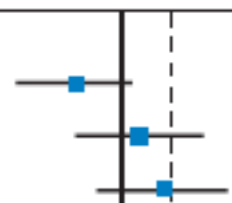


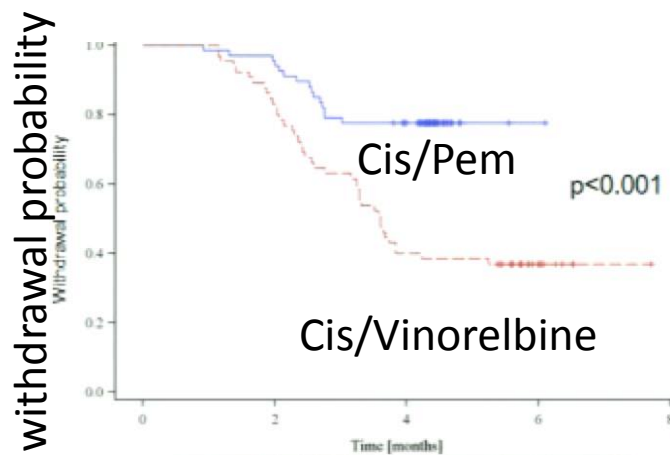
- Q2: Should the patient receive adjuvant therapy?

A2: Cisplatin-Pemetrexed for 4 cycles

What is the most appropriate regimen for adjuvant platinum doublet?

Overall Survival

Category	No. Events / No. Patients		Hazard Ratio	Probability of interaction/ trend* test
ASSOCIATED DRUGS				.11
Cisplatin + vinorelbine	935	1,888		Pignon et al., 2008
Cisplatin + 1 other drug	742	1,373		
Cisplatin + 2 other drugs	713	1,323		



Randomized P-II trial on early stage NSCLC adjuvant CTx with Cis/Pem vs. Cis/Vnr: TREAT

Conclusion: Adjuvant chemotherapy with CPx is safe and feasible with less toxicity and superior dose delivery compared with CVb.

Recurrence after 15months

- mediastinal nodes, liver and bone mets with EGFR gene exon 19 deletion
- Q4: What would be the appropriate therapy?
A4: The patient received afatinib, resulting in significant response

clinical practice guidelines

Annals of Oncology 00: 1–13, 2014

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

M. Reck^{1,2}, S. Popat^{3,4}, N. Reinmuth^{1,2}, D. De Ruyscher⁵, K. M. Kerr⁶, S. Peters⁷ & on behalf of the ESMO Guidelines Working Group*

- First-line treatment with a TKI (erlotinib, gefitinib, or afatinib) is the preferred treatment of patients with tumours bearing an activating (sensitising) EGFR mutation [I, A].

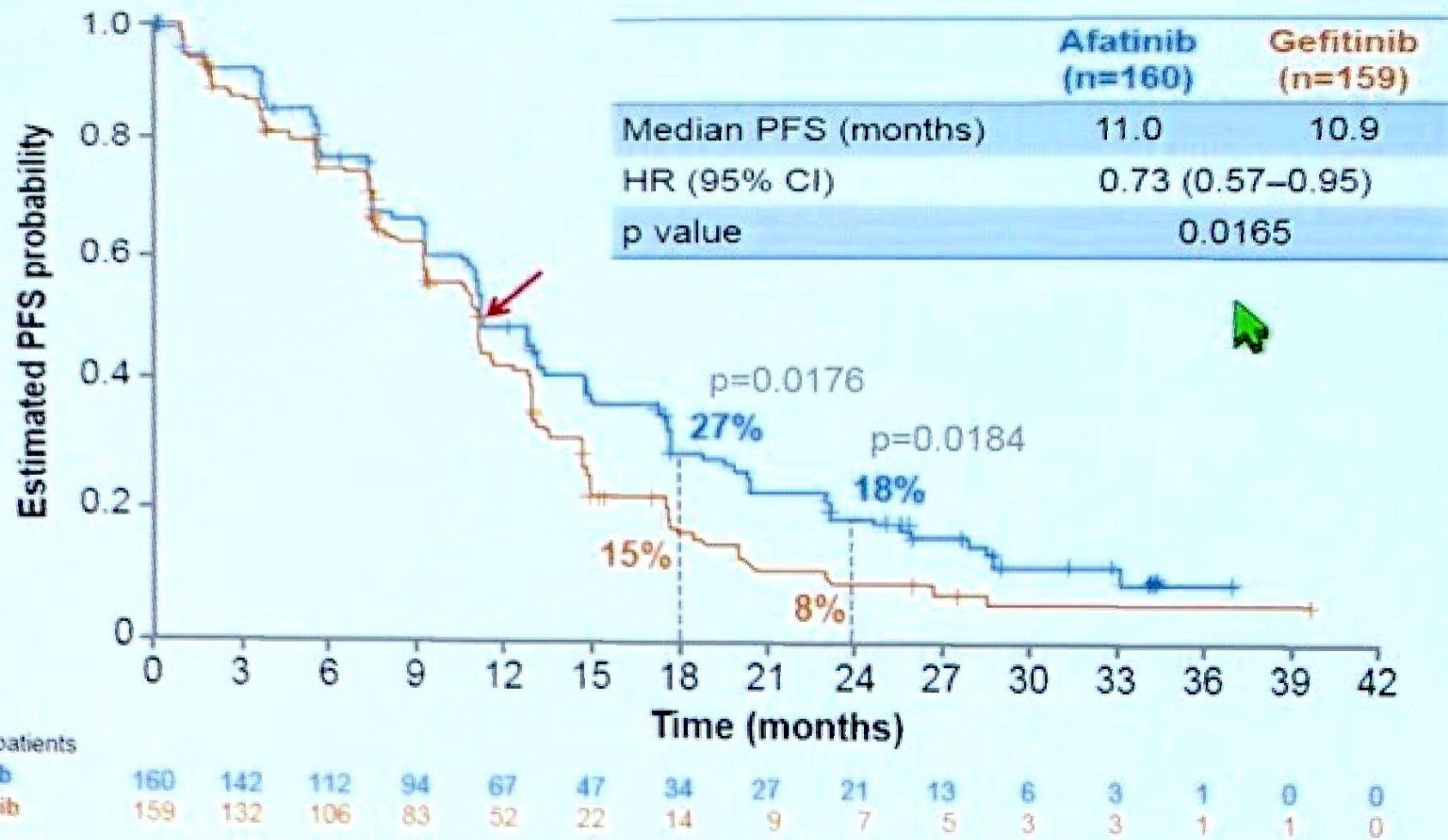
Choice of EGFR TKI?

Phase III studies comparing chemotherapy with EGFR-TKIs for EGFR mu+ patients

study	subject	EGFR-TKI	N	PFS		HR PFS(95%CI)	OS	
				TKI	CTx		TKI	CTx
NEJ002	Japanese	gefitinib	228	10.8	5.4	0.32 (0.24-0.44)	27.7	26.6
WJTOG3405	Japanese	gefitinib	172	9.6*	6.6	0.52 (0.38-0.72)	35.5	38.8
OPTIMAL	Chinese	erlotinib	154	13.7*	4.6	0.16 (0.10-0.26)	22.7	28.9
EURTAC	European	erlotinib	173	10.4*	5.1	0.3 7(0.25-0.54)	22.9	20.8
Lux Lung 3	Caucasian 26% Asian 72%	afatinib	345	11.1 (13.6*)	6.9	0.58 (0.43-0.78)	28.2 (31.6*)	28.2 (28.2*)
Lux Lung 6	Asian	afatinib	365	11.0	5.6	0.28 80.20-0.39)	23.1 (23.6*)	23.5 (23.5*)

Lux Lung 7 Park et al, ESMO Asia 2015

PFS by independent review



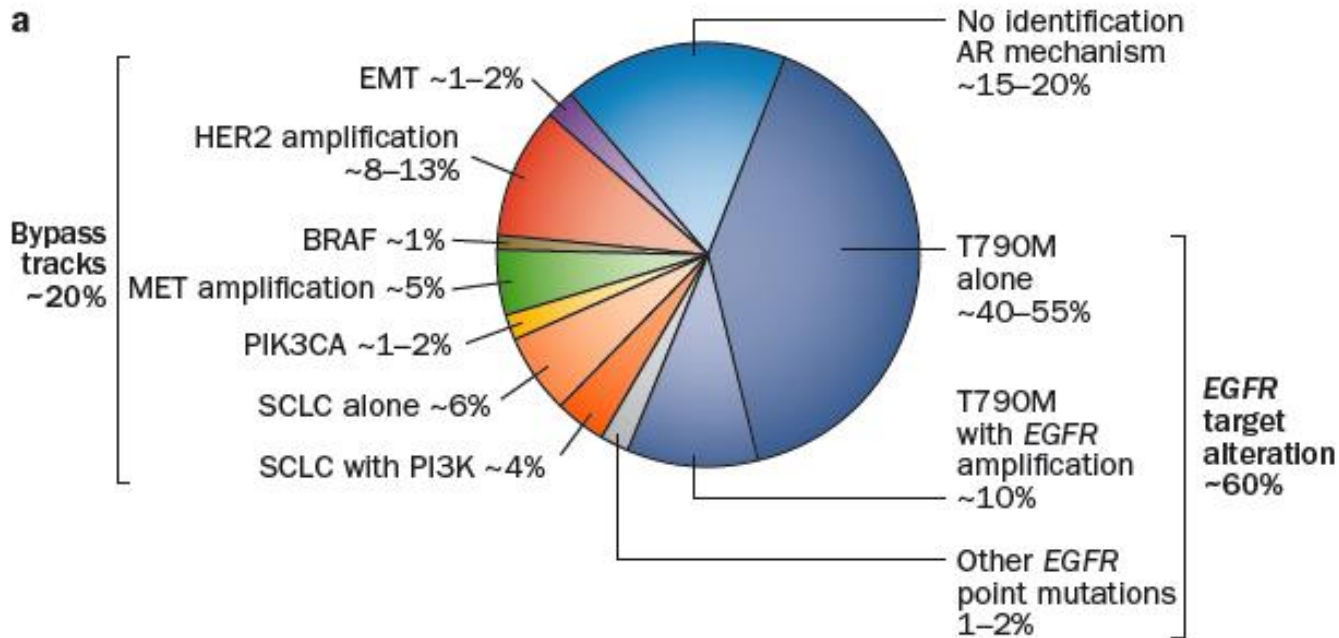
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2015

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ASIA

18-21 DECEMBER
SINGAPORE

Acquired resistance after 14 months

- brain and liver mets with T790M
Patient is receiving AZD9291 (osimertinib)
- Benefit of the 3rd generation EGFR-TKI?

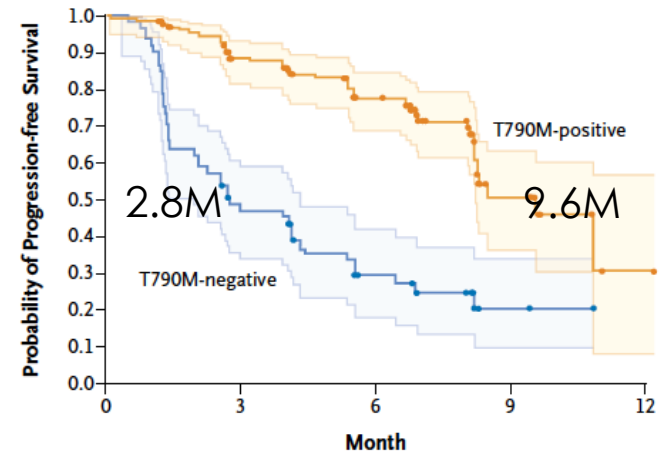
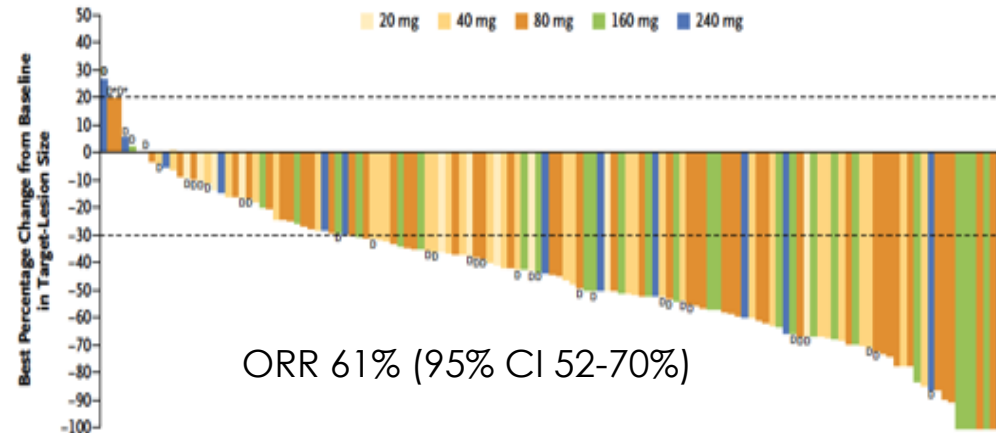


AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., David Planchard, M.D., Ph.D., Yuichiro Ohe, M.D., Suresh S. Ramalingam, M.D., Myung-Ju Ahn, M.D., Ph.D., Sang-We Kim, M.D., Ph.D., Wu-Chou Su, M.D., Leora Horn, M.D., Daniel Haggstrom, M.D., Enriqueta Felip, M.D., Ph.D., Joo-Hang Kim, M.D., Ph.D., Paul Frewer, M.Sc., Mireille Cantarini, M.D., Kathryn H. Brown, Ph.D., Paul A. Dickinson, Ph.D., Serban Ghorghiu, M.D., and Malcolm Ranson, M.B., Ch.B., Ph.D.



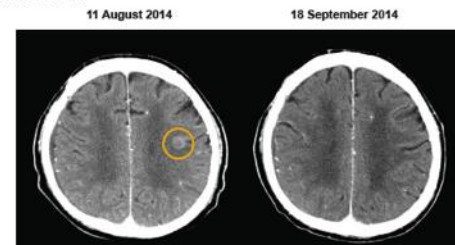
B EGFR T790M–Positive



No. at Risk					
T790M-positive	138	100	70	14	1
T790M-negative	62	27	13	3	0

AZD9291 activity in patients with EGFR-mutant advanced NSCLC and brain metastases: data from Phase II studies
Ahn et al., ECCO/ESMO 2015

Figure 3. Evidence of shrinkage of brain metastases following treatment with AZD9291



Summary

- N2 disease is very heterogeneous
 - discrete ~ bulky N2 disease is associated with poor prognosis
 - Treatments are still controversial
 - New modality?
 - Surgery + EGFR-TKI for FISH/IHC (RADIANT), Surgery + chem /Bev (E1505), Surgery+ MAGE(MAGRIT) all negative!!
 - Ongoing
 - Surgery+ TKI for EGFR mu/ALK fusion
 - Surgery +PD-1/PD-L1 Ab
- Patients with EGFR mutation
 - Choice of different TKI for different EGFR mutation is still controversial
 - Molecular testing at the time of recurrence is a must
 - 3rd Generation EGFR TKI has promising activity for T790M mediated resistance

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W. E. E. Eberhardt¹, D. De Ruyscher², W. Weder³, C. Le Péchoux⁴, P. De Leyn⁵, H. Hoffmann⁶,
V. Westeel⁷, R. Stahel⁸, E. Felip⁹, S. Peters¹⁰ & Panel Members[†]



CHEST

Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Treatment of Stage III Non-small Cell Lung Cancer

Diagnosis and Management of Lung Cancer,
3rd ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines

Nithya Ramnath, MD; Thomas J. Dilling, MD; Loren J. Harris, MD, FCCP;
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potentially resectable IIIA(N2) disease

preoperative diagnosis of IIIA(N2)

Recommendation 4.2.1: Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].

3.5.1. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), it is recommended that the treatment plan should be made with the input from a multidisciplinary team (Grade 1C).