Multidisciplinary Interactive Session
How to deal with multifocal adenocarcinoma?

Role of EGFRTKIs in multifocal adenocarcinoma

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Organisers

Partners

Disclosures

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Role of EGFRTKIs in multifocal ADC
Outline

- Clinical characteristics
- Treatment
  - Surgery
  - Systemic
- Conclusions

Clinical characteristics

Multifocal ADC: clinical characteristics

- Up to 8% of NSCLC, multifocal
- Tends to present with intrathoracic metastasis, slow growth rate, longer mOS and increased prevalence in women and never-smokers
- P present with cough, sputum production, chest pain or dyspnea
- Death is characteristically secondary to respiratory failure in the setting of diffuse pulmonary involvement

Multifocal ADC: radiographic patterns

- ***Solitary pulmonary nodules or masses***: lesions vary from having well-defined to irregular borders and are composed of solid soft tissue attenuation, GGO attenuation or a mixture of the two

- ***Localized consolidation***: more typical of mucinous lesions; diffuse parenchymal infiltration often difficult to differentiated from pneumonic or other inflammatory processes

- ***Diffuse disease***: multinodular disease in one or more lobes with the combination of consolidation, satellite nodules and areas of GGO

Multifocal ADC: mucinous *vs* non-mucinous and relationship with molecular alterations

- Non-mucinous tumors, associated with EGFR-mut
  - EGFR-mut positively correlated with acinar predominant tumors

- Mucinous tumors, associated with KRAS-mut
  - However, HER2-mut ***(Zhang CCR 12)*** and CD74-NRG1 fusion alterations, also associated with mucinous lung ADC ***(Fernandez-Cuesta Cancer Discovery 14)***

ROS translocation / crizotinib

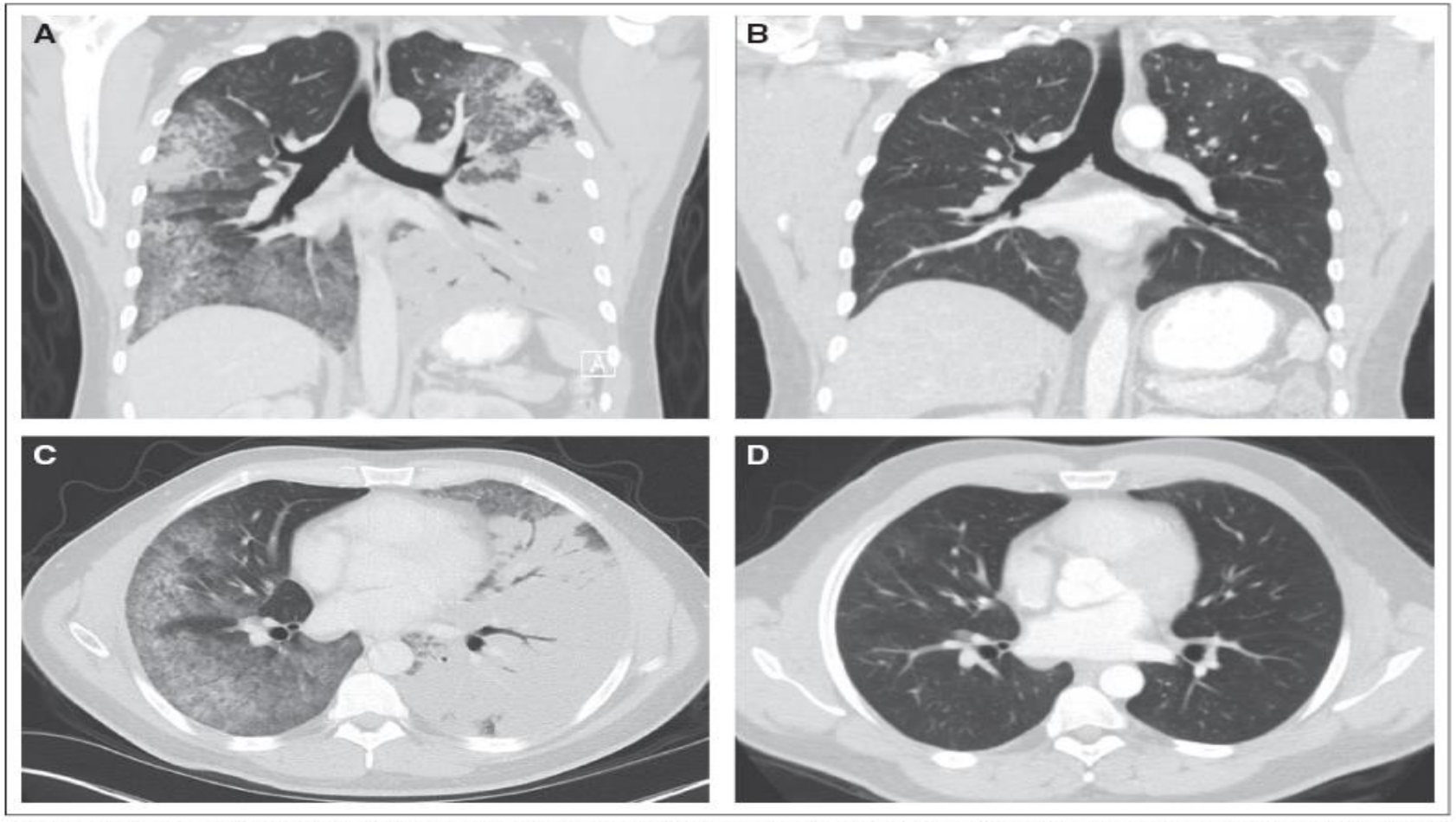


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

EGFR-mut in lung ADC
Relationship with CT characteristics and histologic subtypes

- 153 resected lung ADC / EGFR-mut determined
- At preoperative chest CT, percentage of GGO volume and total tumor volume of each tumor, by a semiautomated algorithm
- Exon 21-mut, more frequent in lepidic-predominant ADC than in other histologic subtypes (OR, 3.44, P = .003)
- % GGO volume in tumors with exon 21-mut, significantly higher than that in EGFRwt (P = .0001) and exon 19-mut tumors (P = .0006)
- Significant trend of prevalence of exon 21-mut increased along with increasing GGO volume (P = .0008)

Multifocal ADC: pathology and molecular features

- Tumor foci are often clonally related

- Analyses of clonal relationship of 78 p (58 ADC and 20 SCC) with multifocal NSCLC lesions ***(Warth Eur Respir J 12)***
  - EGFR-mut detected in synchronous tumors of 4 ADC p
  - KRAS-mut observed in 17 ADC p and 3 SCC / in 6 p KRAS-mut in only 1 nodule
  - In one p, one tumor nodule had KRAS and another EGFR-mut

- Divergent mutation status of KRAS in different nodules in a number of cases
  - Different tumors related to smoking habit?

Treatment

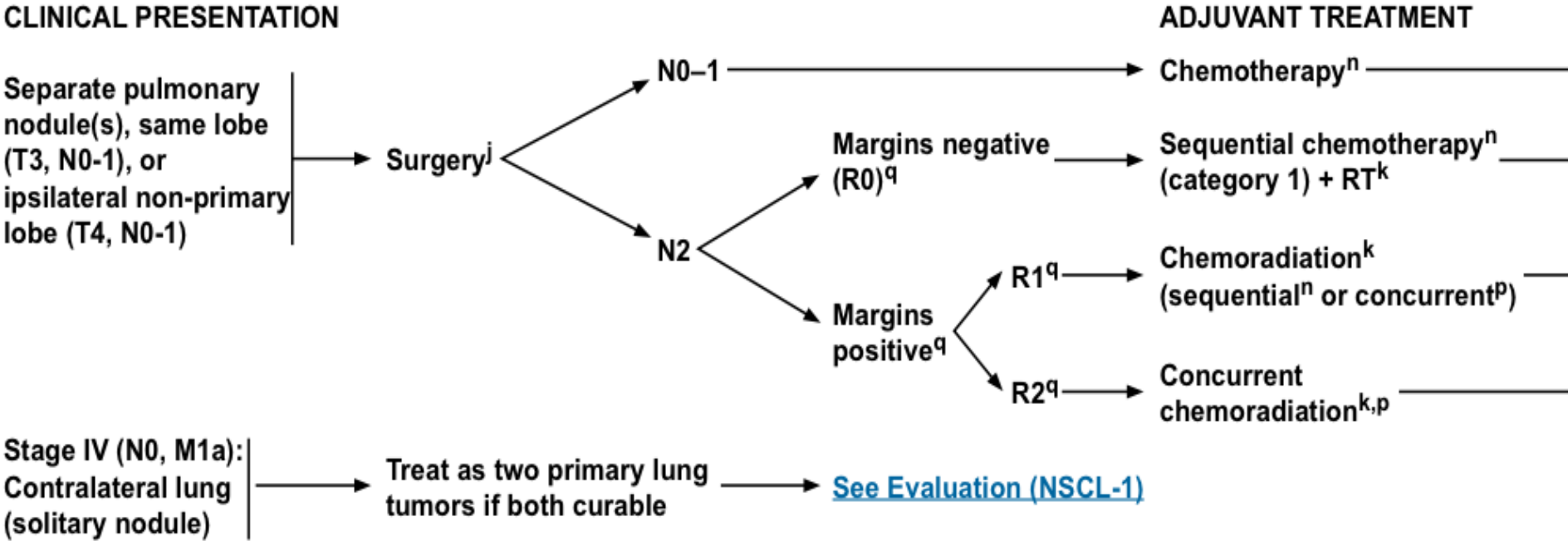
Multifocal ADC: treatment

- No established guidelines for treatment, no prospective information

- Current options include surgery and systemic therapies
  - Fit p with multifocal disease should be referred to an experienced thoracic surgeon

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2015
Non-Small Cell Lung Cancer



Role of EGFRTKIs in multifocal ADC

- Data on systemic approaches, limited
- Dramatic responses in tumors classified as BAC in retrospective analysis
- Gefitinib in 136 p with BAC, 101 untreated, 35 previously treated ***(West JCO 06)***
  - 51% female, 29% never-smoker
  - 17% RR, 6% CR in treatment-naïve p
  - 9% RR with no CRs in pre-treated p
  - 3-yr survival 23%
  - Female / never-smoker associated with improved OS (surrogate of EGFR-mut?)

Role of EGFR TKIs in multifocal ADC

- IFCT-0401 phase II study of gefitinib as 1st-line in advanced ADC with BAC subtype in 88 p
- Disease control achieved in 25 p (29.4%); PR in 11 p (12.9%)
- Median PFS, 2.9 mo
- Median OS, 13.2 mo
- Never smokers / non-mucinous ADC-BAC subtype associated with increased probability of disease control (surrogate of EGFR-mut?)
  - Median PFS for non-mucinous BAC, 11.3 months

Cadranel JTO 09

Role of EGFR TKIs in multifocal ADC

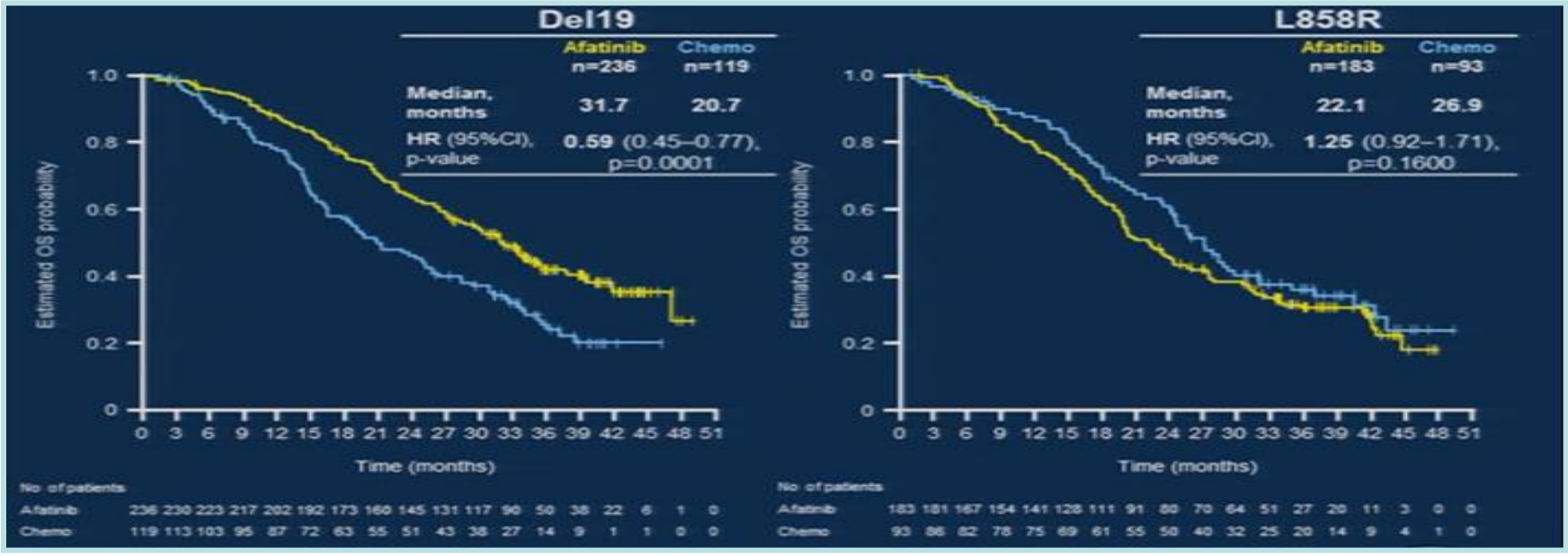
- RR of gefitinib ***(Franklin ASCO 14)***
  - 30% in non-mucinous BAC
  - 0% in mucinous BAC
  - Non-mucinous BAC associated with longer survival (HR 2.85)

- Erlotinib in 101 p, pure BAC (12) or ADC with BAC subtype (89) ***(Miller JCO 08)***
  - 22% RR
  - OS 17 mo
  - 83% RR in EGFR-mut p (18+/81, 22%)
  - 0% RR in KRAS-mut p (18+/80, 22.5%)

1st line EGFRm NSCLC

	EGFR-TKI	Chemo regimen	PFS in TKI arm (m)	HR
IPASS Mok NEJM 09	Gefitinib	Carboplatin + paclitaxel	9.5 vs 6.3	0.48
WJTOG 3405 Mitsudomi Lancet Onc 10	Gefitinib	Cisplatin + docetaxel	9.2 vs 6.3	0.49
NEJ002 Maemondo NEJM 10	Gefitinib	Carboplatin + paclitaxel	10.8 vs 5.4	0.30
EURTAC Rosell Lancet Onc 12	Erlotinib	Doublet platinum based	9.7 vs 5.2	0.37
OPTIMAL Zhou Lancet Onc 11	Erlotinib	Carboplatin + gemcitabine	13.1 vs 4.6	0.16
LUX-LUNG 3 Sequist JCO 13	Afatinib	Cisplatin + pemetrexed	11.1 vs 6.9	0.58
LUX-LUNG 6 Wu Lancet Onc 13	Afatinib	Cisplatin + gemcitabine	11.0 vs 5.6	0.28

LUX-Lung 3/6 impact of driver mutation on combined OS data



- In a combined analysis of LUX-Lung 3/6, OS significantly improved with afatinib vs CT(median 27.3 vs 24.3 mo, HR 0.81 p=0.037) in p with common EGFR mutations (del19/L858R)
- In the EGFR del19 subgroup, OS significantly improved with afatinib vs CT in the combined analysis and in individual studies
- In the EGFR L858R subgroup, neither the individual studies nor the combined analysis showed a significant OS benefit with afatinib

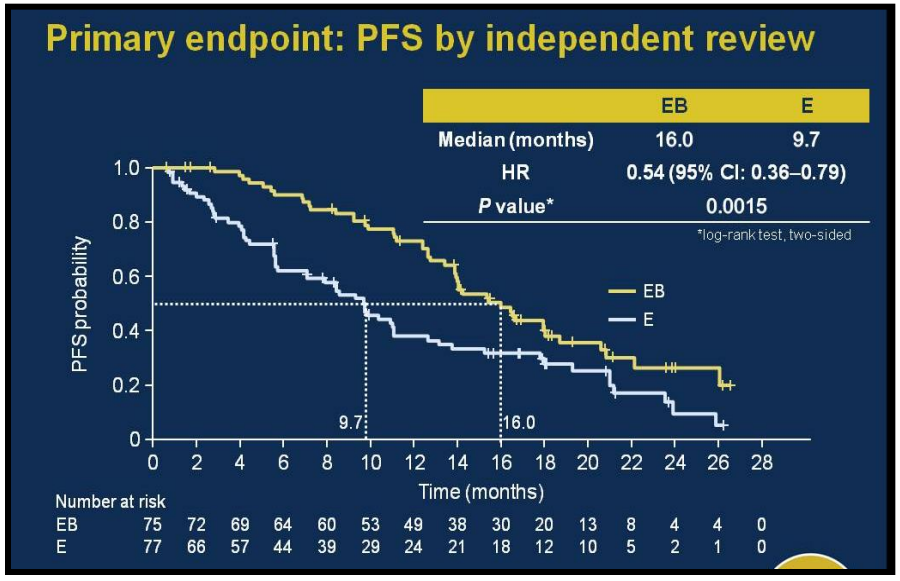
Aspiration study

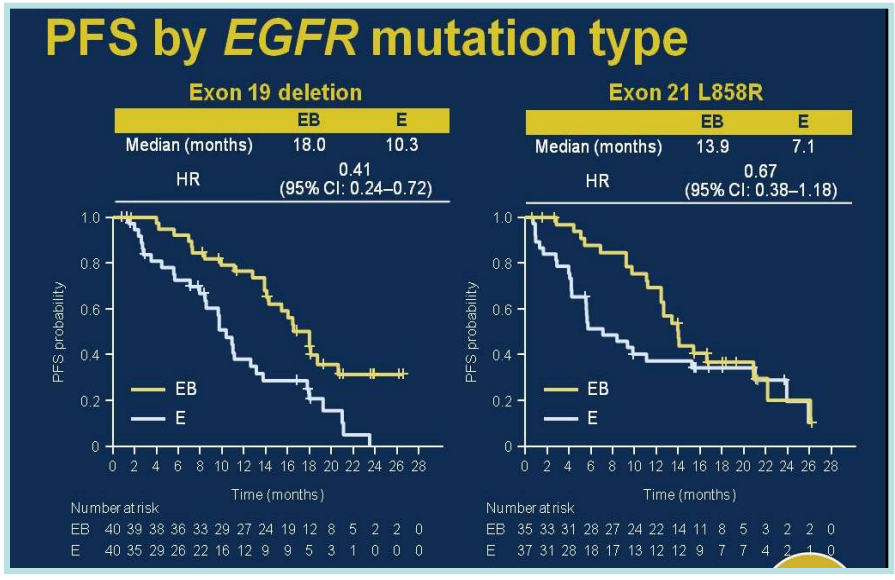
- Phase 2, assess the efficacy of 1st-line E until RECIST PD, efficacy beyond PD if E continued by the investigator
- Primary endpoint: PFS1 (time to RECIST PD/death). Secondary endpoints: PFS2 (time to off-E PD if E was extended beyond RECIST PD)
- 207 p / 150 p RECIST PD
  - PFS1: median 10.8 mo
  - Data from p receiving post-PD E (81 p) median PFS2: 13.0 mo
  - In p receiving post-PD E the difference between PFS1 and PFS2 was 3.7 mo.
- The ASPIRATION data show that continuing E beyond RECIST PD is feasible, with a difference between PFS1 and PFS2 of 3.7 mo in post-PD E

IMPRESS results

- 265 p randomised, 133 in the gefitinib arm and 132 in the placebo arm
- Demographics in the two arms well balanced. However, more p ≥65 years in gefitinib arm and more p with baseline brain metastases in the CT arm
- No statistically significant improvement in PFS for gefitinib *vs* placebo; HR 0.86; p = 0.273. Median PFS 5.4 mo in each arm
- OS was immature (33% of p had died), with better OS for placebo *vs* gefitinib (HR 1.62; p = 0.029)
- No treatment differences found in ORR and DCR

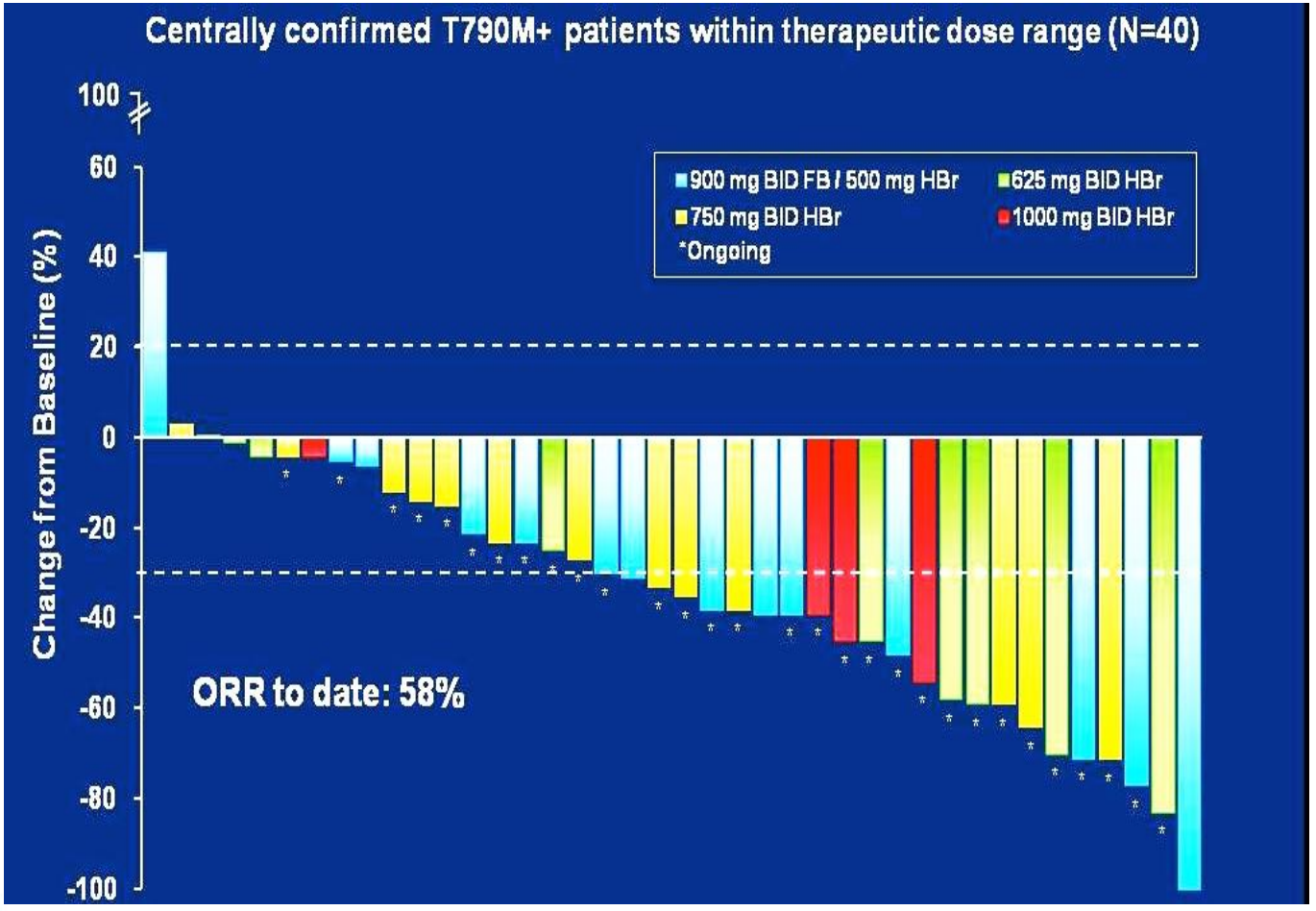
Phase II, randomised, open-label study of erlotinib with or without bevacizumab in p with *EGFR*m+ NSCLC



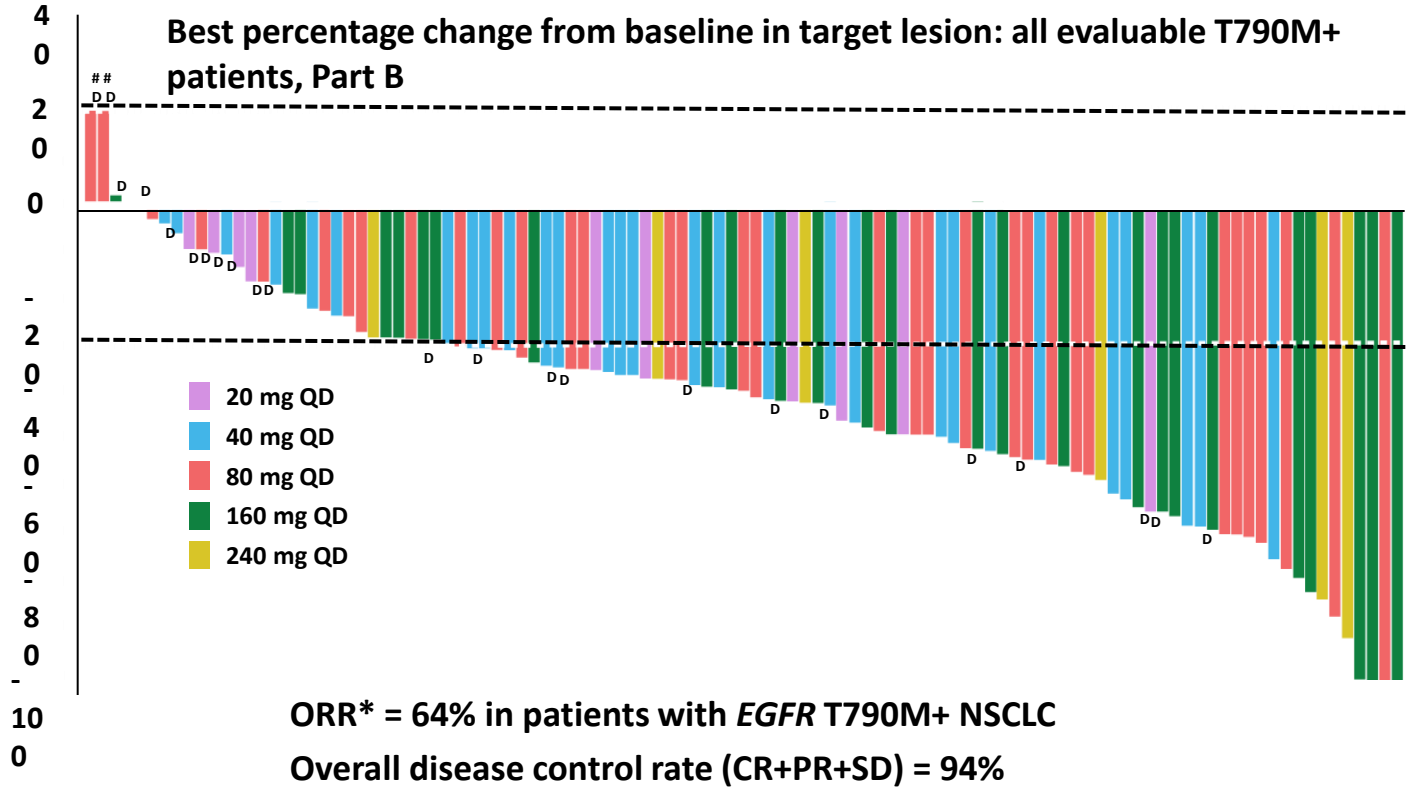


- Median PFS significantly longer in the erlotinib/bevacizumab arm vs the erlotinib arm (16.0 vs 9.7 mo; HR 0.54; p=0.0015])
  - In the EGFR del 19 subgroup: 18.0 vs 10.3 mo
  - in the EGFR L858R subgroup: 13.9 vs 7.1 mo

CO-1686: best response in phase 1 and early phase 2 expansion cohort patients



AZD9291 phase I: response rate in T790M+



ORR* = 64% in patients with *EGFR* T790M+ NSCLC

Overall disease control rate (CR+PR+SD) = 94%

	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

EGFR-mut p with advanced disease: encouraging options

- 1st line, EGFRTKI

- Treatment after EGFRTKI PD
  - For those asymptomatic p with slow PD, maintaining EGFRTKI, valid option
  - For those p switching to chemotherapy, EGFRTKI should be stopped
  - For those p with T790M, T790M inhibitors obtain > 50% RR

- No conclusive information regarding:
  - Which EGFRTKI to be used in 1st line
  - Need to individualize treatment according to mutation type
  - Bevacizumab use in combination with EGFRTKI

Role of EGFRTKIs in multifocal ADC: final thoughts

- No prospective data
- If surgery is ruled out, assessment of EGFR-mut, mandatory
- A clear need to genotype the tumor
  - In many cases, tumor sample obtained by fine-needle aspiration
  - If insufficient tumor for EGFR-mut determination, consider trucut or videotoracoscopy
- If EGFR-mut negative, other molecular determinations may be considered, KRAS, HER2, ROS1
- For those p with EGFR-mut and unsuitable for surgery, EGFRTKI, standard of care

Thanks!!!

15-18 April 2015, Geneva, Switzerland

Organisers

IASLC
International Association for the Study of Lung Cancer

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