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The two faces of MET

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Disclosure

- **Participation in sponsored conferences and advisory boards for Roche and Pfizer**

The two faces of MET

Efficacy and safety of crizotinib in patients with advanced *MET*-amplified non-small-cell lung cancer (NSCLC)
ABSTRACT #8001

Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial
ABSTRACT #8000

Efficacy and safety of crizotinib in patients with advanced *MET*-amplified non-small-cell lung cancer (NSCLC)

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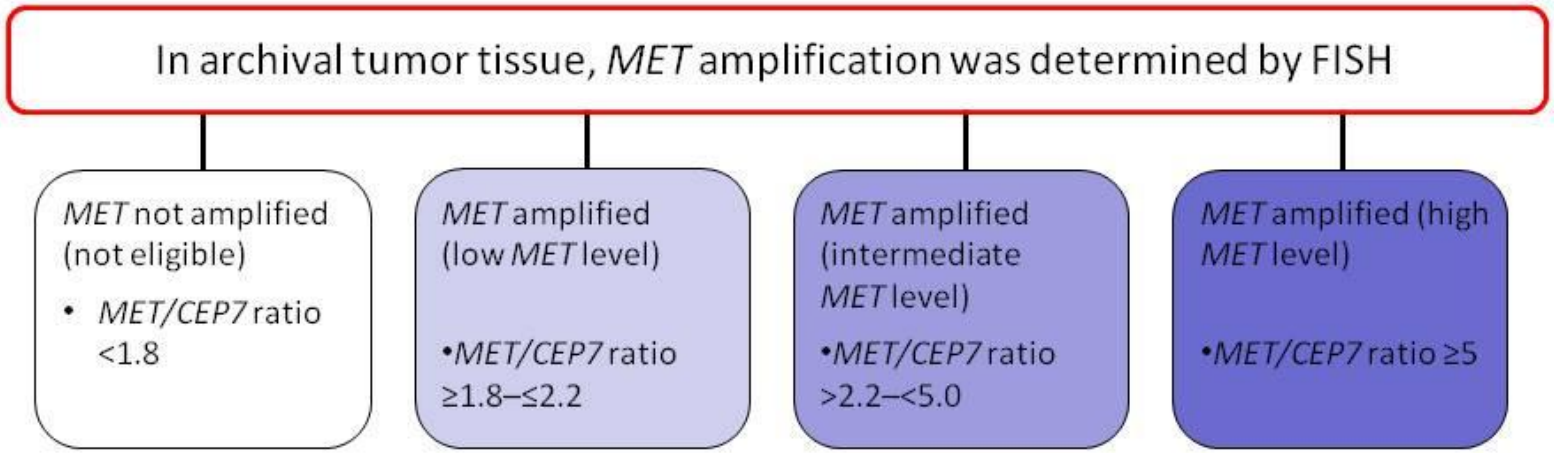
Presented By Federico Cappuzzo at 2014 ASCO Annual Meeting

Patient eligibility: NSCLC *MET* amplification cohort

- Patients (≥18 years) had histologically confirmed advanced NSCLC, and
  - measurable disease per RECIST v1.0
  - adequate organ function
  - resolution of acute toxic effects of prior therapies or surgical procedures (CTCAE Grade ≤1)
  - received no prior MET- or HGF-targeted therapies



CEP7, chromosome 7 centromere signal; CTCAE, Common Toxicity Criteria for Adverse Events
FISH, fluorescence in-situ hybridization; RECIST, Response Evaluation Criteria In Solid Tumors

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Patient and disease characteristics

	Low *MET*, n=2	Intermediate *MET*, n=6	High *MET*, n=6	Total, N=14[a]
Median age, years (range)	52 (42–63)	55 (48–73)	67 (46–79)	61 (42–79)
Male, n (%)	1 (50)	2 (33)	3 (50)	6 (43)
Race, n (%)				
White	2 (100)	5 (83)	6 (100)	13 (93)
Black	0	1 (17)	0	1 (7)
Histology				
Adenocarcinoma	2 (100)	5 (83)	6 (100)	13 (93)
Other[b]	0	1 (17)	0	1 (7)
ECOG PS, n (%)				
0	1 (50)	2 (33)	2 (33)	5 (36)
1	1 (50)	4 (67)	3 (50)	8 (57)
2	0	0	1 (17)	1 (7)
Smoking status, n (%)				
Never smoker	1 (50)	1 (17)	0	2 (14)
Ex-smoker	1 (50)	4 (67)	6 (100)	11 (79)
Smoker	0	1 (17)	0	1 (7)

[a]Three additional subjects enrolled into the *MET*-amplified NSCLC cohort were subsequently confirmed not to meet eligibility criteria (*MET/CEP7* ratio was below the lower *MET* level category and 1 patient had a *MET* mutation); they were not included in the efficacy analysis. [b]Poorly differentiated.

MET amplification categories are classified as follows: low *MET/CEP7* ratio ≥1.8 to ≤2.2; intermediate *MET/CEP7* ratio >2.2 to <5; high *MET/CEP7* ratio ≥5.

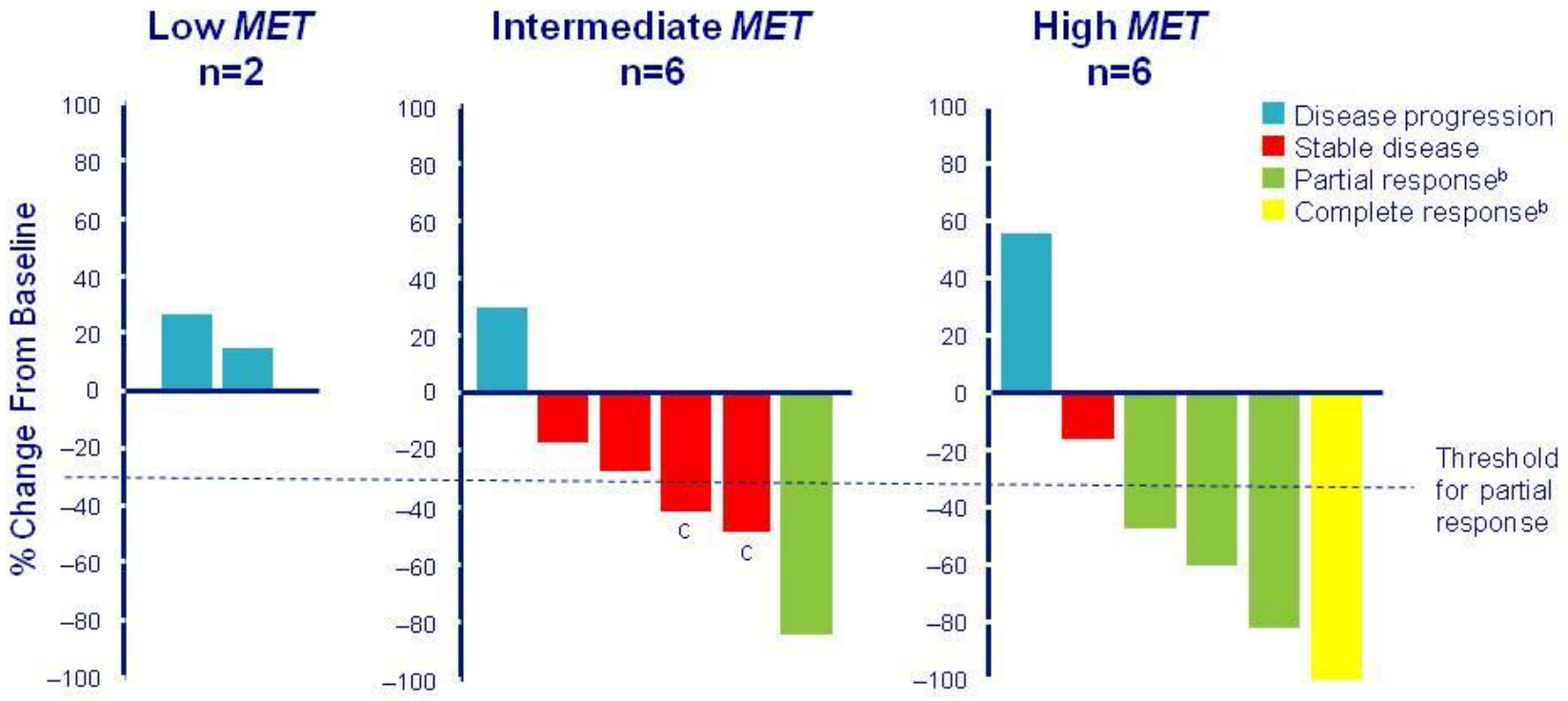
Clinical characteristics of *MET* amplified NSCLC

Characteristic	N	%
Total amplified (ratio ≥2.2)	16	100
Squamous	5	31.2
Non-squamous	11	68.8
Never smokers	0	0
Current/former	15	93.7
Smoking unknown	1	6.3

Cappuzzo F et al., J Clin Oncol 2009

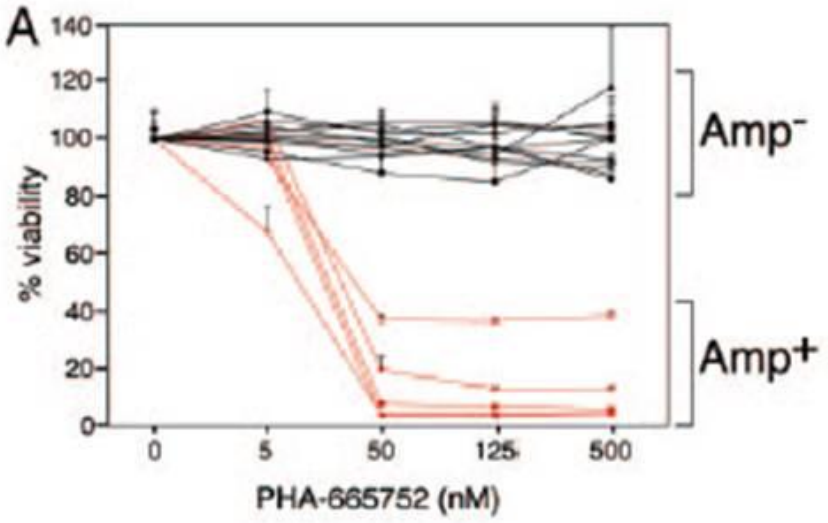
Tumor Shrinkage Seen in Intermediate and High *MET* Cohorts

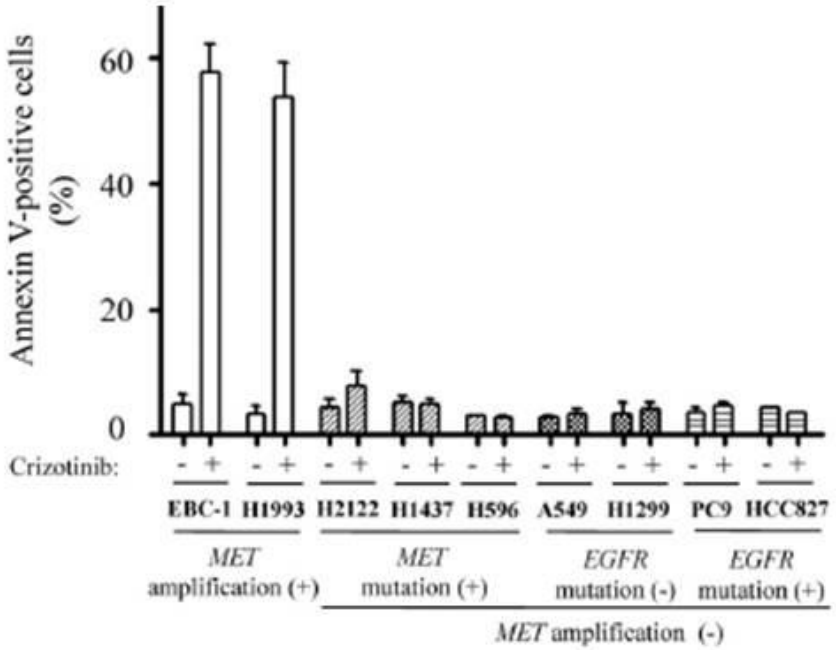
Best percent change from baseline in target tumor lesions[a] by patient



[a]Confirmed objective responses.
[b]Based on investigator assessment.
[c]Two patients in the intermediate *MET* group had an unconfirmed PR that was not confirmed in a second assessment.

Sensitivity to anti-Met agents only in presence of high levels of *MET* amplification

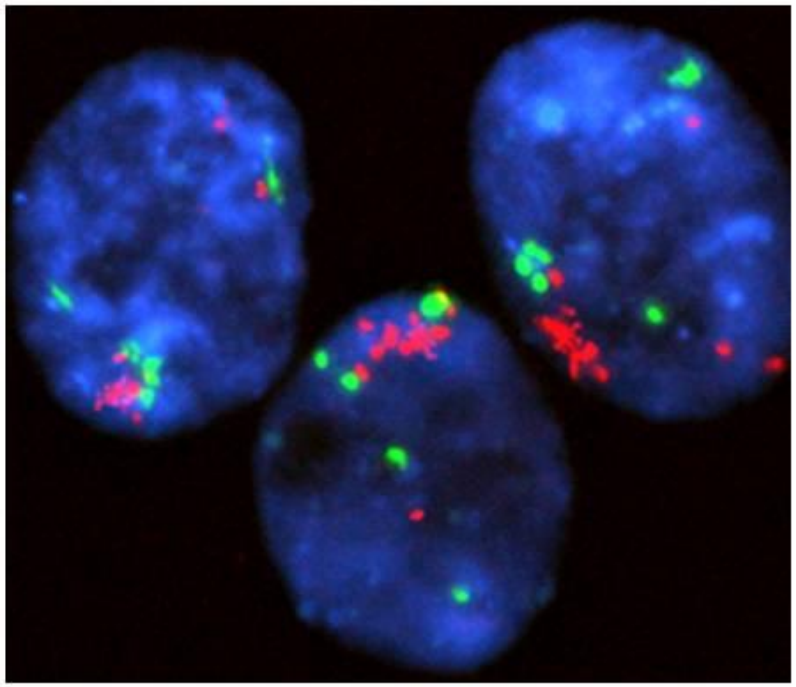




Smolen GA et al., PNAS 2006, Tanizaki J et al., JTO 2011

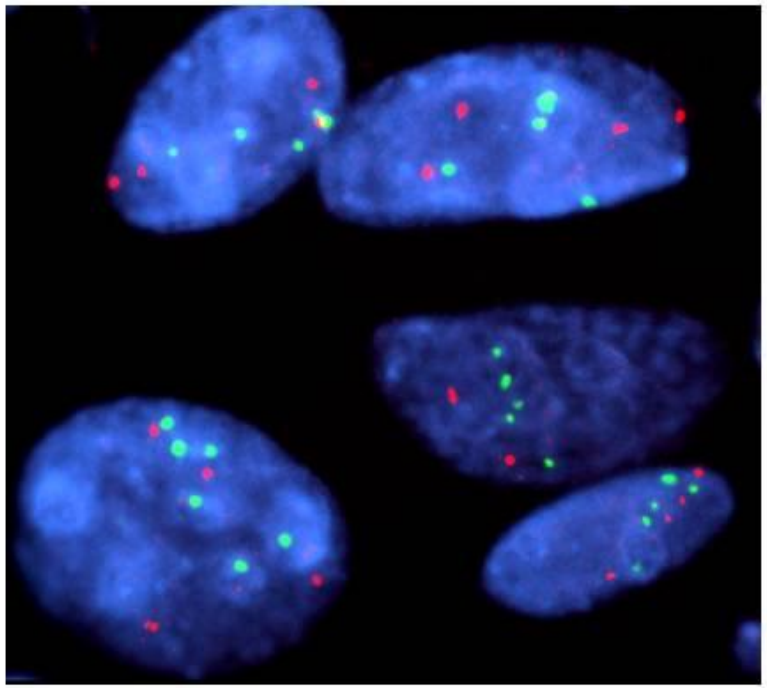
High levels of *MET* amplification drive resistance to EGFR-TKIs

Gefitinib Resistant



MET amplification in HCC827 GR6
Ratio MET/centromere >5

Gefitinib Sensitive



NO MET amplification in HCC827
Ratio MET/centromere <2

Modified from Cappuzzo F et al., Ann Oncol 2008

MET FISH+ not always are *MET* amplified

	N	%
Total analized	435	100
Total *MET FISH+* (mean *MET* GCN ≥5)	48	11.1
Total ratio *MET/centromere* ≥2.2 and <5	13	2.9
Total ratio *MET/centromere* ≥5	3	0.6

Expected efficacy of anti-MET in 3.5% of patients

Cappuzzo F et al., J Clin Oncol 2009

Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial

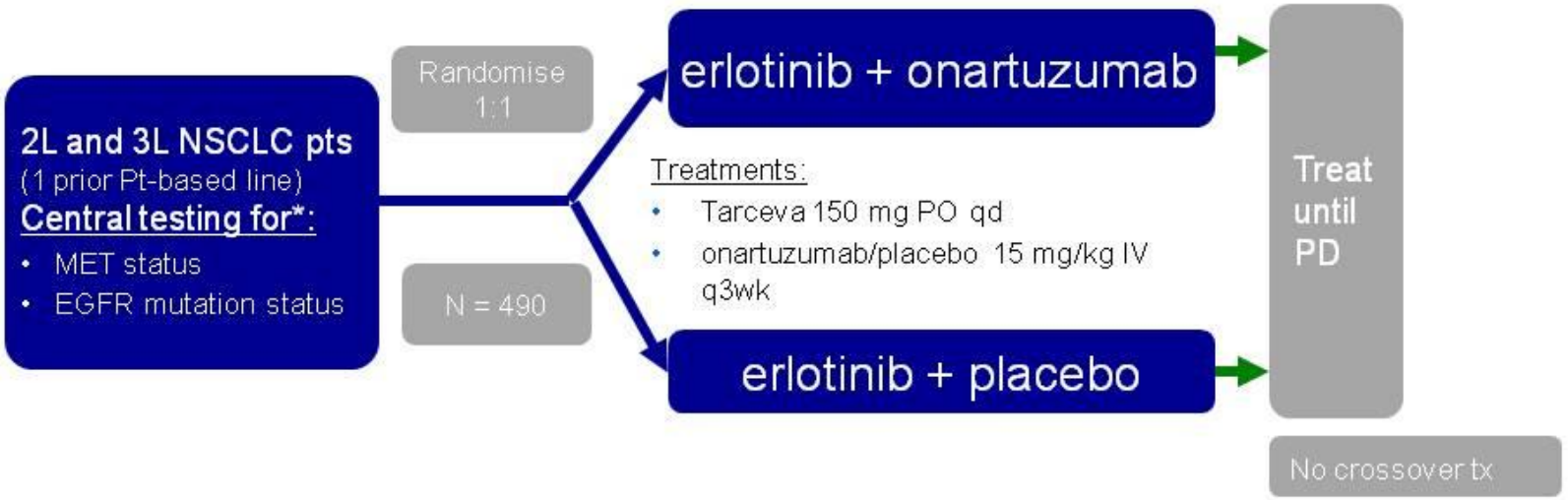
DR Spigel, MJ Edelman, K O'Byrne, L Paz-Ares, DS Shames, W Yu, VE Paton, T Mok

On behalf of the MET Lung Investigators

Sarah Cannon Research Institute, Nashville, TN; University of New Mexico Cancer Center, Albuquerque, NM; Queensland University of Technology, Brisbane, Australia; University Hospital Virgen del Rocio, Seville, Spain; Genentech, South San Francisco, CA; The Chinese University of Hong Kong, Hong Kong, China

Presented By Federico Cappuzzo at 2014 ASCO Annual Meeting

Onartuzumab (MetMAb) Phase III 2L/3L in MET-positive NSCLC



Key eligibility criteria:

- Stage IIIB or IV Met diagnostic positive NSCLC
- 1-2 prior lines of tx
- No prior EGFR inhibitor
- ECOG PS 0 or 1

Stratification criteria:

- EGFR mut status
- MET 2+ or 3+ score
- # of prior lines of tx
- Histology

Primary endpoint:

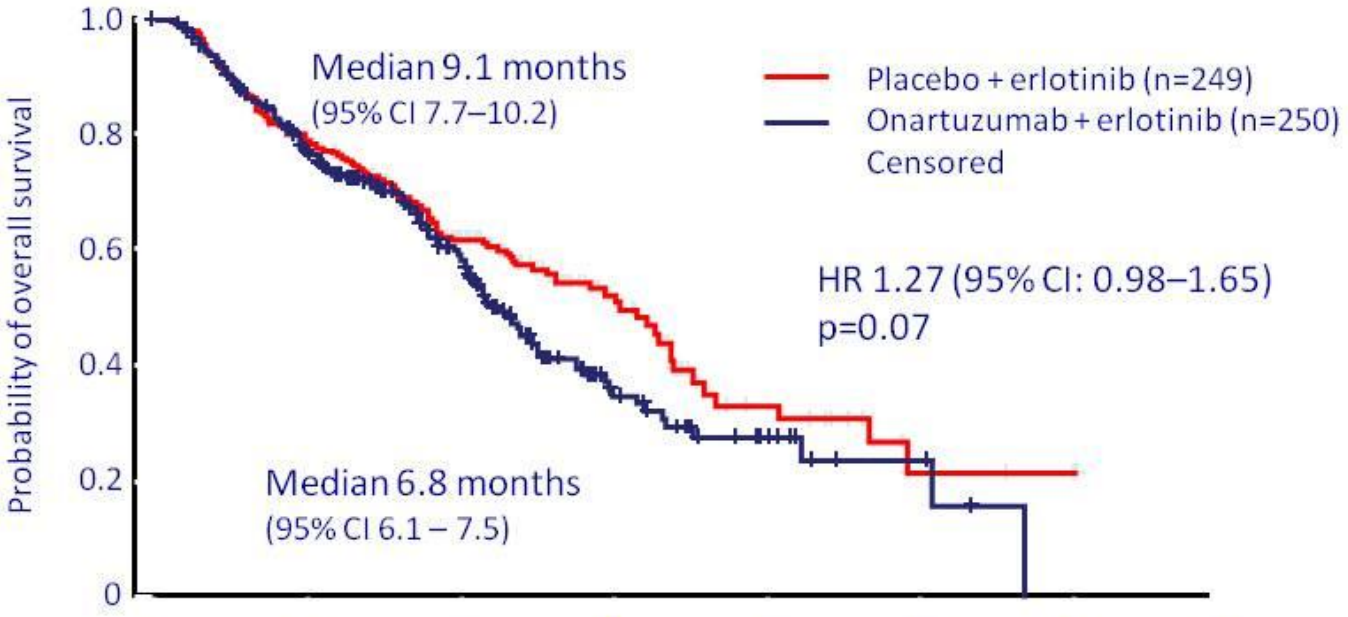
- Overall survival (OS)

Secondary endpoints:

- Progression-free survival (PFS)
- Overall response rate (ORR)
- Quality of life (QoL)
- Safety

*PRE-SCREENING: Patients could submit tumor samples for testing prior to requiring treatment with 2L or 3L therapy

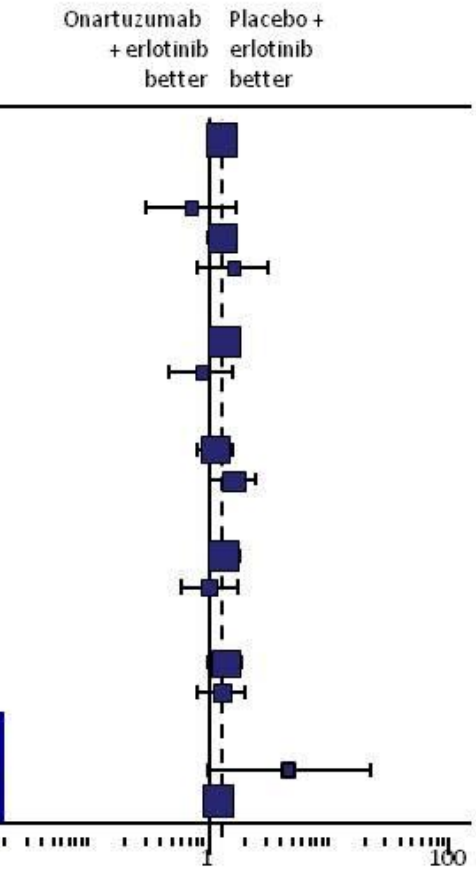
OAM4971g: Overall Survival Results



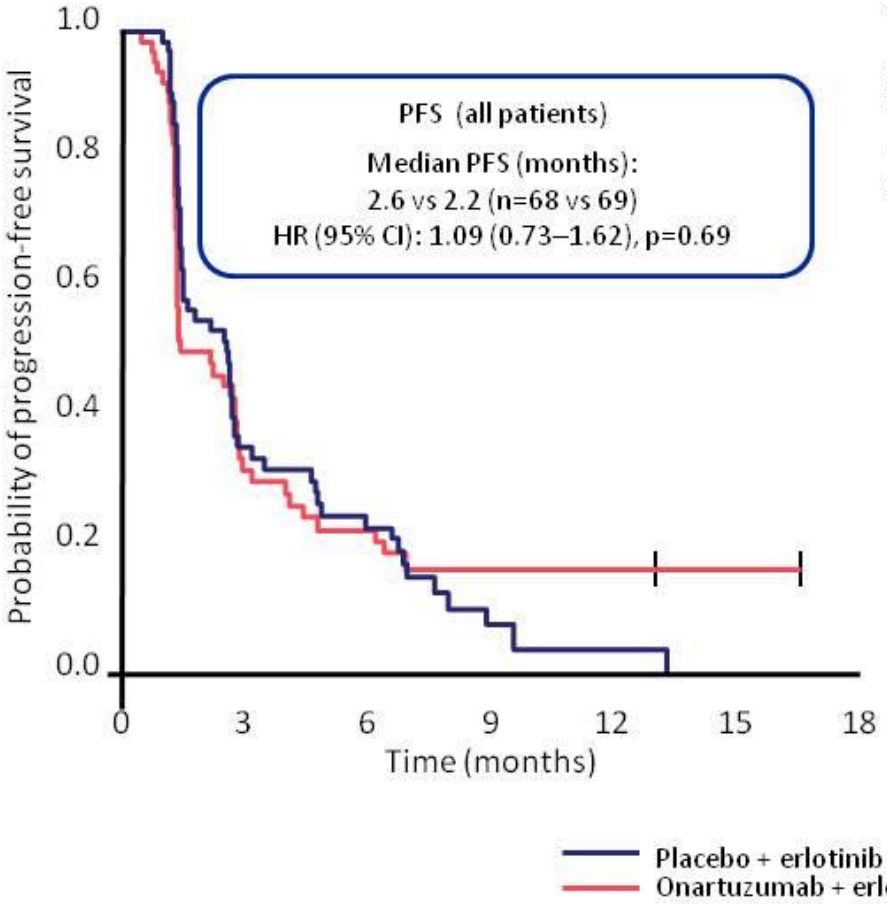
Number of patients at risk							
Placebo + erlotinib	249	183	110	43	14	3	1
Onartuzumab + erlotinib	250	177	100	29	12	4	

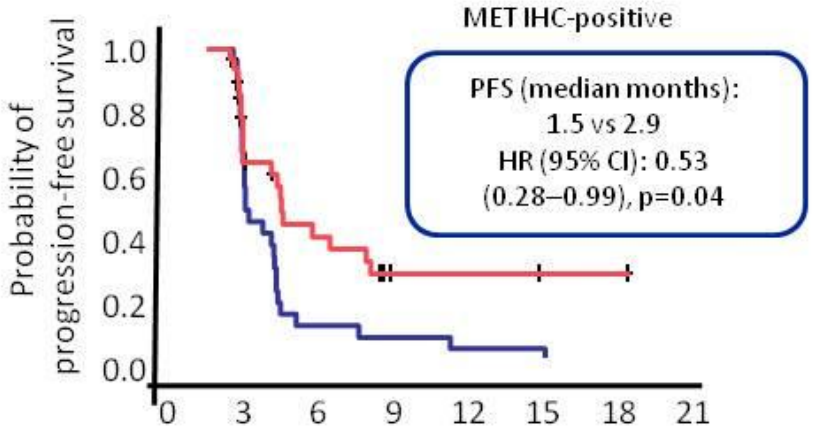
OS subgroup analysis (ITT population)

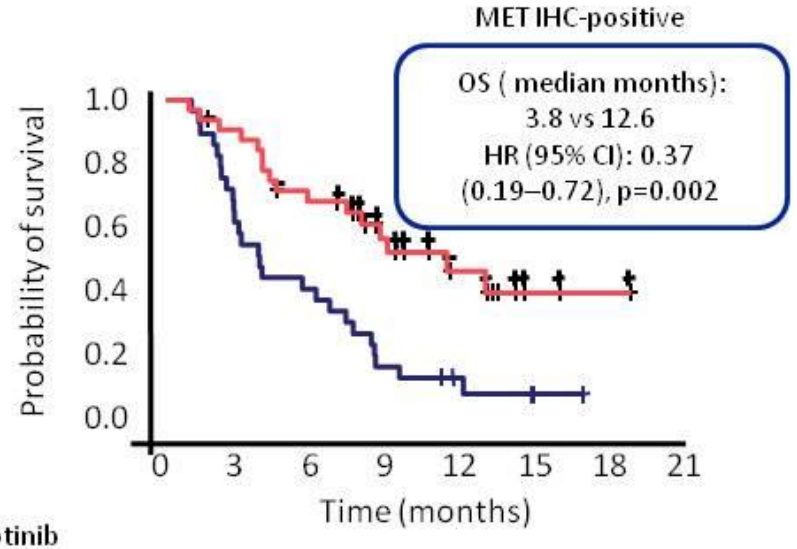
Baseline risk factors	Placebo + erlotinib (n=249) n	Placebo + erlotinib (n=249) Median, months	Onartuzumab + erlotinib (n=250) n	Onartuzumab + erlotinib (n=250) Median, months	Hazard ratio	95% CI
All patients	249	9.1	250	6.8	1.27	(0.98–1.63)
Race						
Asian	37	10.2	35	NE	0.71	(0.30–1.67)
White	180	9.0	182	6.4	1.30	(0.98–1.74)
Other	32	9.4	33	5.6	1.61	(0.82–3.18)
Histology						
Non-squamous	218	9.8	210	6.5	1.34	(1.02–1.77)
Squamous	31	6.4	40	7.2	0.88	(0.47–1.64)
Prior lines of therapy						
1	157	9.0	161	7.1	1.13	(0.82–1.55)
2	92	9.4	89	6.3	1.62	(1.07–2.45)
Met IHC score						
2+	195	9.4	198	6.8	1.35	(1.02–1.80)
3+	54	9.1	52	6.4	1.02	(0.59–1.75)
MET FISH status						
FISH–	150	9.9	165	6.9	1.36	(0.98–1.89)
FISH+	85	9.4	71	6.4	1.28	(0.82–2.01)
***EGFR* mutation**						
Yes	29	NE	28	12.6	4.68	(0.97–22.63)
No	220	7.8	222	6.4	1.19	(0.92–1.54)



MET IHC may predict Onartuzumab sensitivity: Phase II data



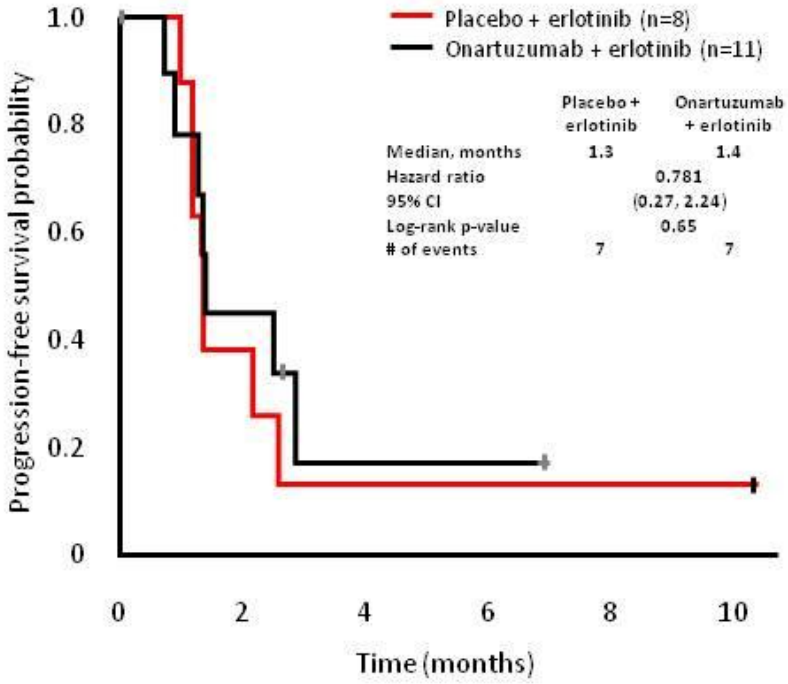




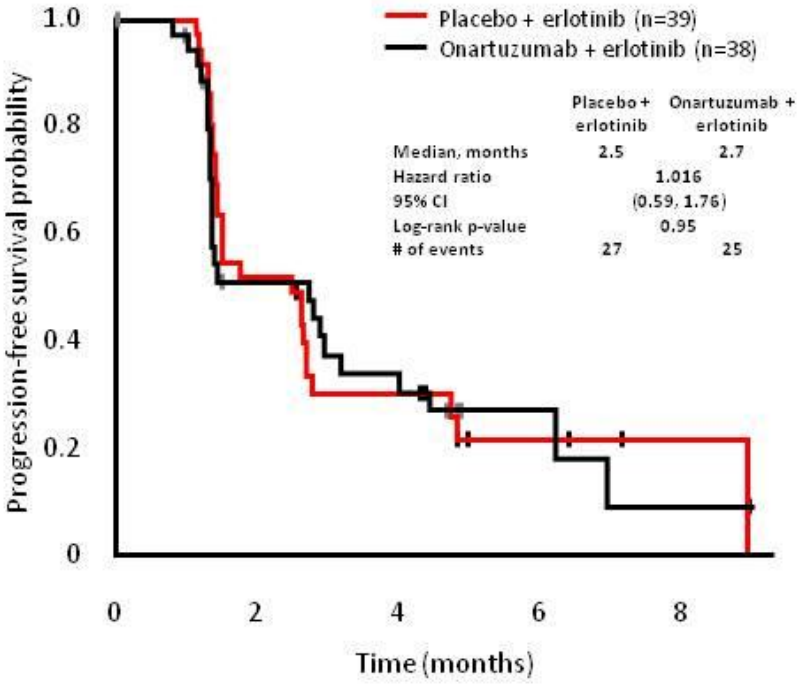
Spiegel DR et al., J Clin Oncol 2013

MET gene copy number may not predict onartuzumab sensitivity: phase II data

MET GCN ≥5 (FISH+ =19)



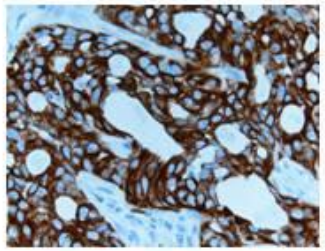
MET GCN<5 (FISH- =77)



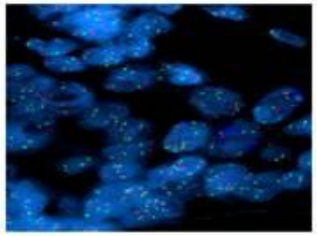
Spiegel DR et al., J Clin Oncol 2013

MET deregulation in lung cancer

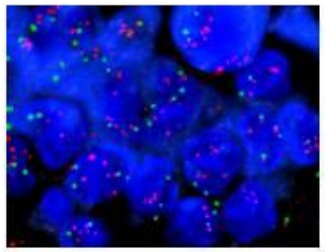
Overexpression (2+/3+) → ≈40%/10%



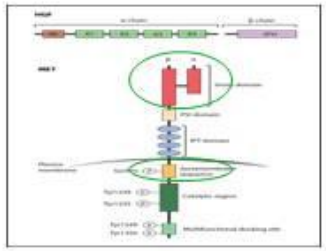
Gene gain (mean ≥5) → ≈10%



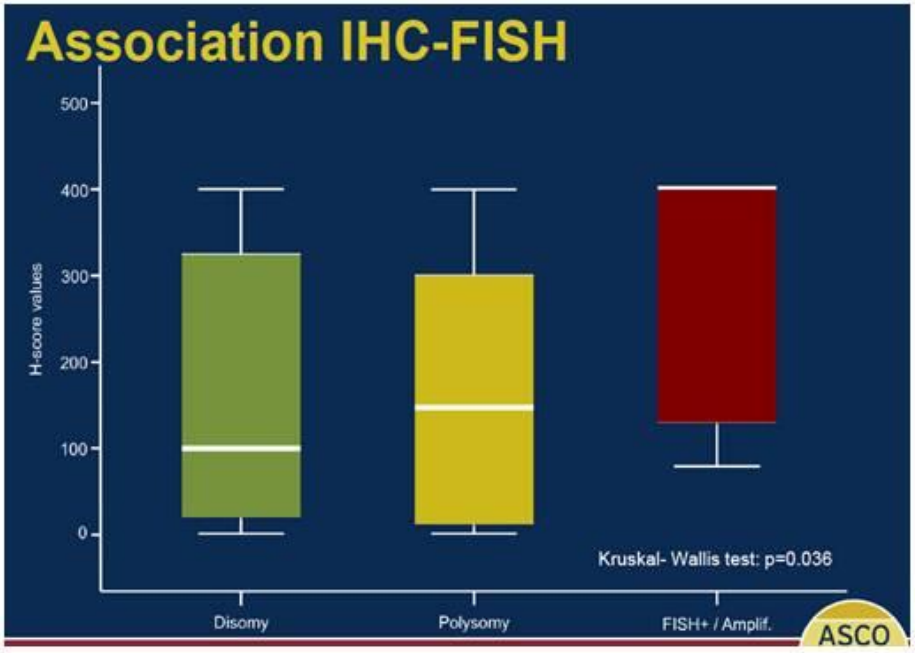
Amplification (ratio ≥2.2) → ≈3-4%

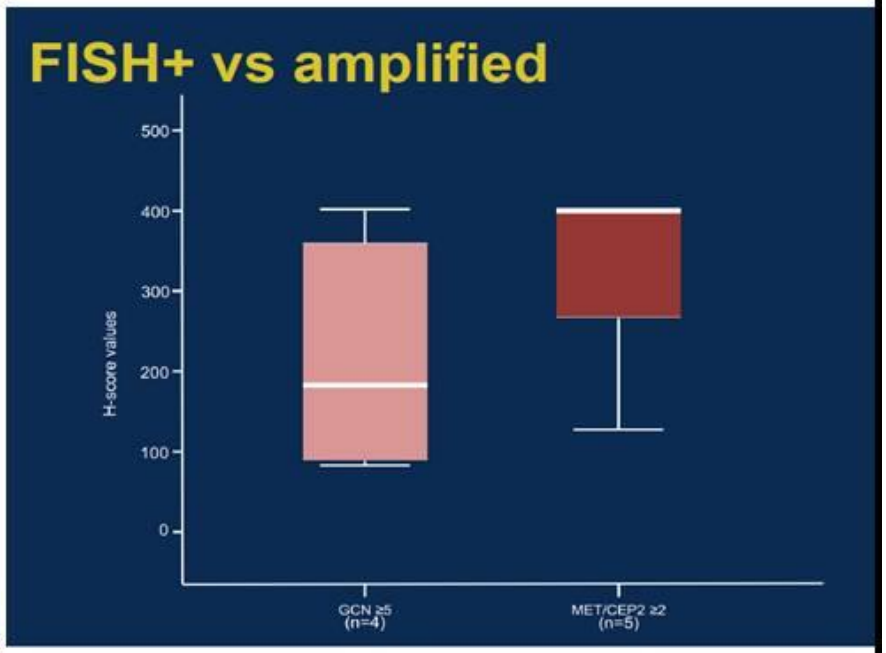


Mutation → ≈3%



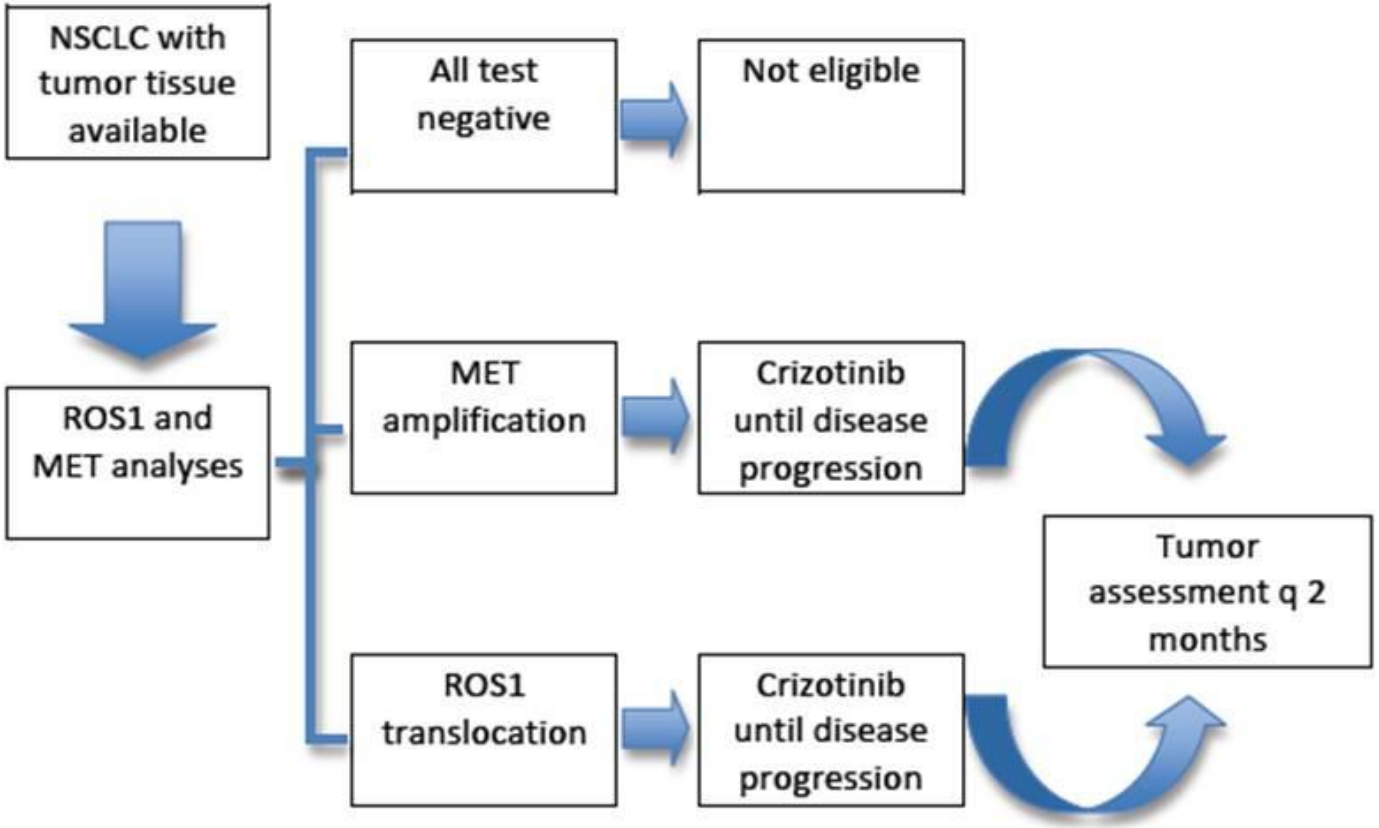
MET expression and amplification





Arriola E et al., ASCO 2014 abstract # 11005

Crizotinib in MET amplified or ROS1 translocated NSCLC: The METROS trial



MET amplification defined as Ratio ≥2 and stratification in ≥2 and <5 versus ≥5

Eudract # 2014-001263-12

Conclusions

- MET remains a relevant target driving tumor growth in approximately 3% of NSCLC with *gene* amplification (ratio ≥2.2)
- Prospective studies need to define the best cut-off (ratio 2.2 versus 5)
- *MET* amplification is detectable in smokers irrespective of histology
- IHC or MET gene copy number are not optimal for detecting patients potentially sensitive to anti-MET strategies
- New studies with anti-MET agents should be conducted ONLY in properly selected patients