Clinical benefits of testing for other oncogenic drivers

Tom Stinchcombe

Duke Thoracic Oncology Program

Case of NSCLC adenocarcinoma with HER2 mutation

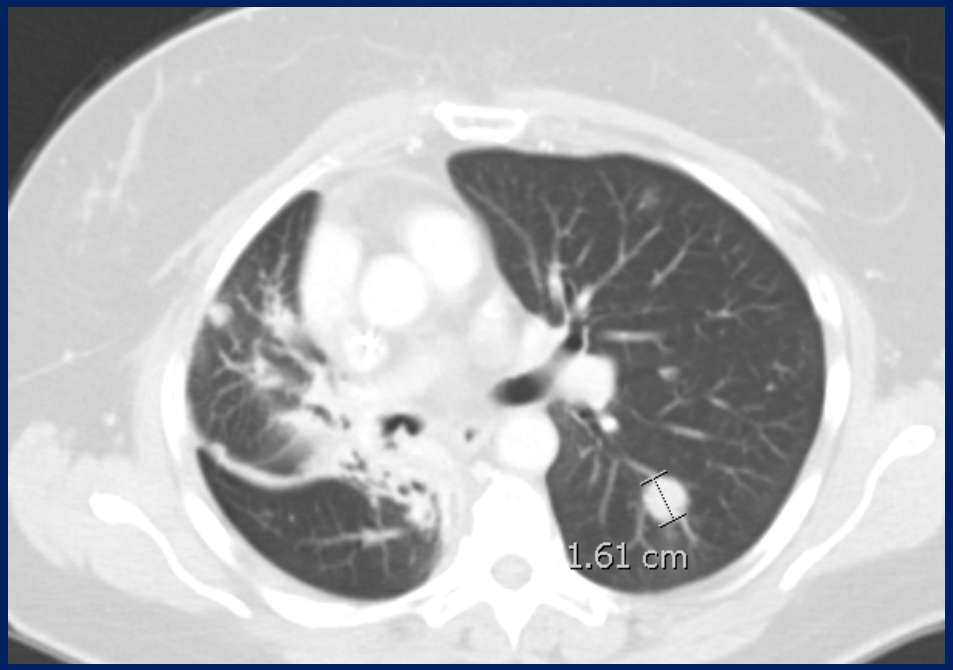
- Patient presented with stage 3 NSCLC (adenocarcinoma) in 12/2013 and was treated with cisplatin and pemetrexed with concurrent thoracic radiation therapy
- Patient reoccurred in contralateral lung and biopsy proven recurrence.
- Molecular testing negative for *EGFR* mutation, *ALK* or *ROS1* rearrangement
- Carboplatin, paclitaxel, and bevacizumab followed by single agent bevacizumab (stopped due to hypertension)

Case of NSCLC adenocarcinoma with HER2 mutation

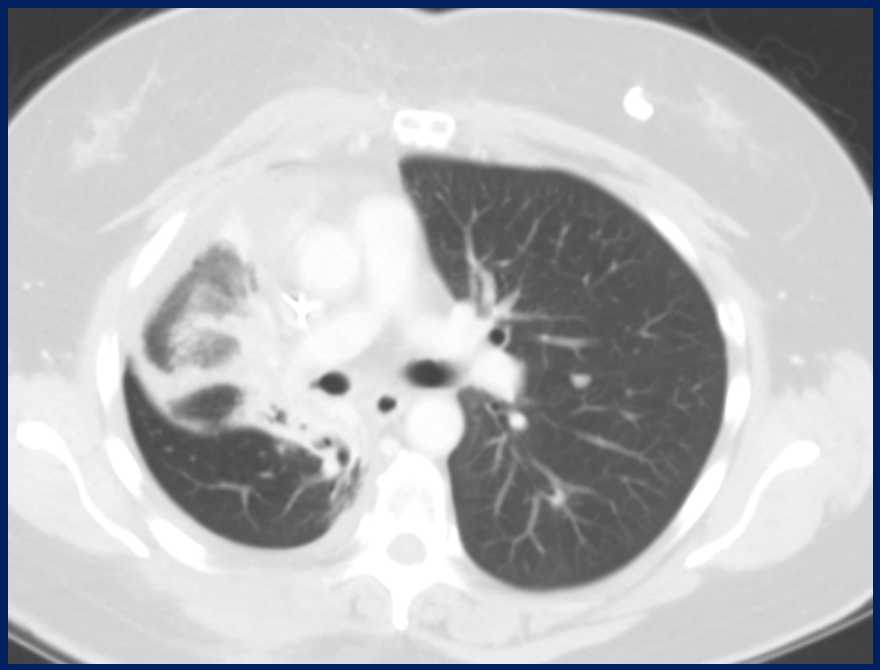
- Sample sent out for more extensive tumor testing
- Testing revealed HER2 exon 20 insertion mutation (G776_V777)
- Patient treated with afatinib for 2 months with progressive disease
- Patient enrolled in clinical trial of T-DM1 and underwent central laboratory testing which revealed HER2 IHC 3+

Partial response

Baseline 6/25/2015



Confirmatory 8/24/2015



Clinical benefits of testing for other oncogenic drivers

Tom Stinchcombe

Duke Thoracic Oncology Program

Disclosures

Consulting Agreements	Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Lilly
Contracted Research	Bristol-Myers Squibb Company, EMD Serono Inc, Genentech BioOncology

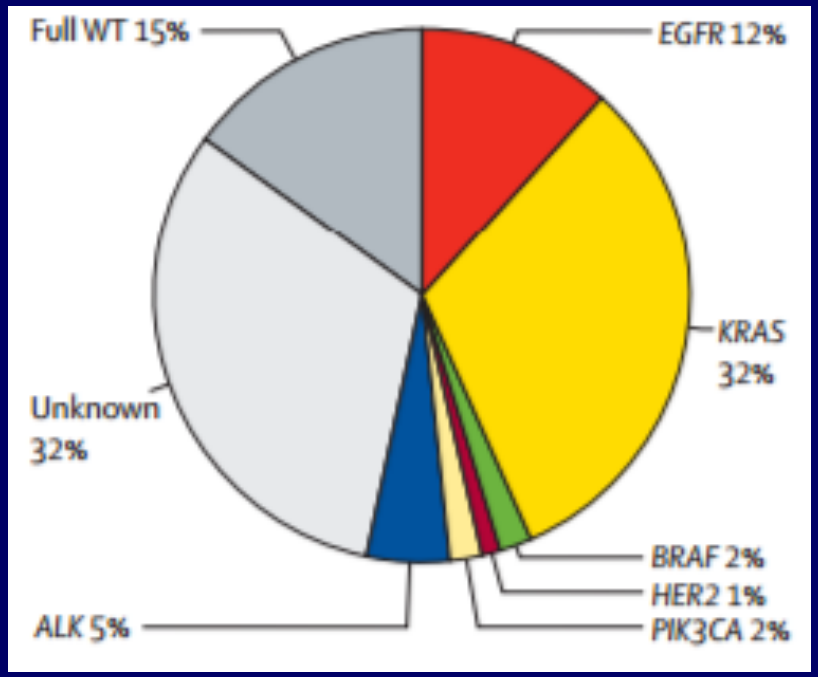
HER2 positive NSCLC

- HER2 positivity has been defined by IHC, FISH, HER2 mutation
- No standard definition of HER2 overexpression
- Discordance between FISH and IHC observed in 35% of cases
- Case reports of activity of T-DM1 and afatinib in *HER2* mutant NSCLC
- Chemotherapy/trastuzumab combinations have demonstrated activity

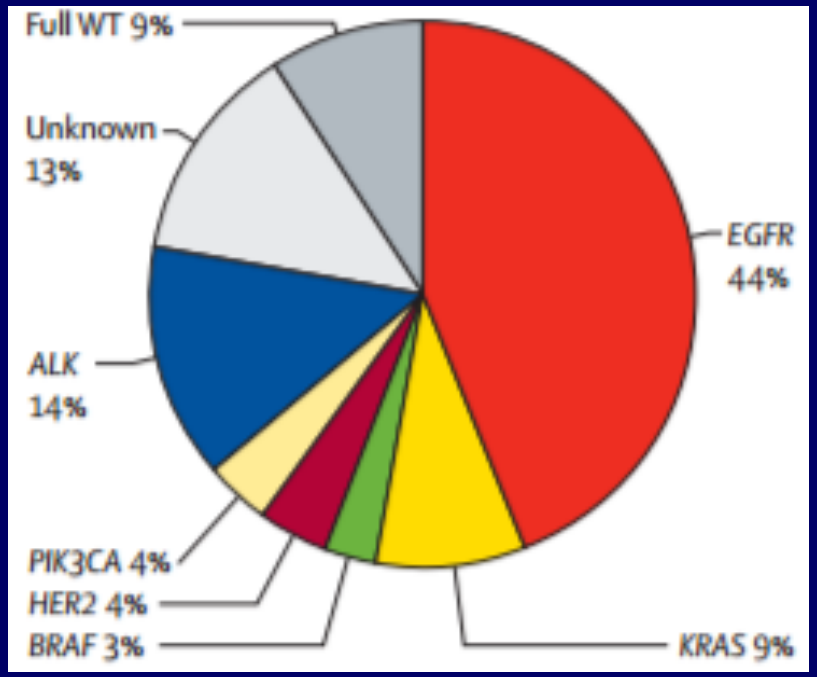
Liu et al. JTO 2010; Varella-Garcia et al. JTO 2009; Tiseo et al. Lung Cancer 2010; Hirsch BJC 2002; Weiler JTO 2015; De Greve et al. Lung Cancer 2012; Mazieres et al. *JCO* 2013.

Rate of the “other” mutations

Adenocarcinoma

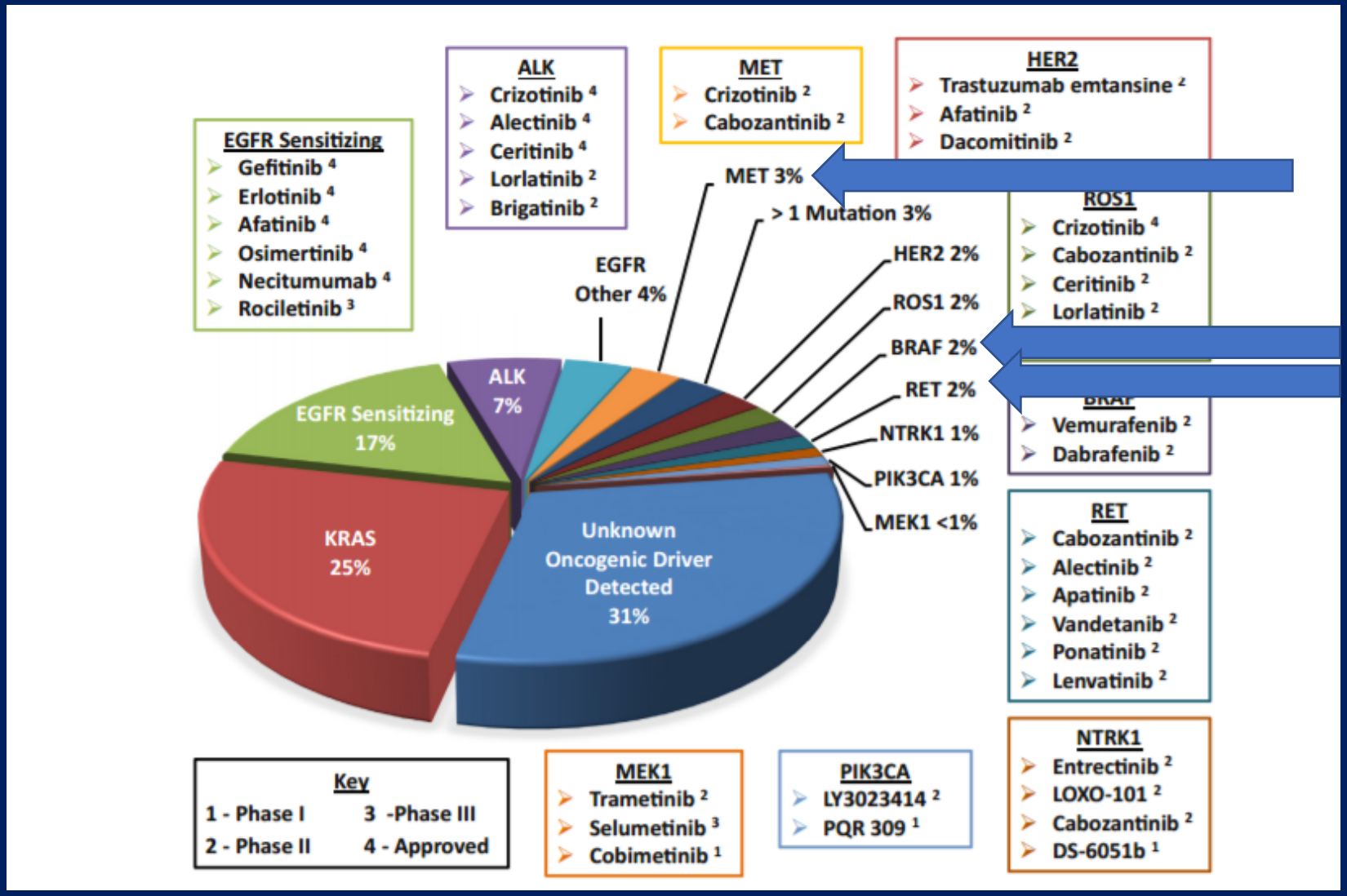


Never-smokers



Barlesi et al. *Lancet* 2017.

Molecular alterations and associated targeted therapies



Tsao et al. *Journal of Thoracic Oncology* 2015.

MET exon 14 alterations

- Introns flanking *MET* exon 14 in pre-mRNA are spliced out resulting in MET mRNA which is translated into functional MET receptor
- *MET* exon 14 encodes the ubiquitin ligase binding site which is used in receptor degradation
- Mutations that disrupt splice sites result in *MET* exon 14 skipping producing a MET receptor that lacks ubiquitin binding site → reduced degradation of MET protein → sustained MET activation
- Next generation sequencing is the preferred testing method
- *MET* exon 14 skipping mutations in 20-30% of pulmonary sarcomatoid carcinoma

Drilon et al. *JTO* 2017; Liu et al. *JCO* 2016 .

Crizotinib in patients with *MET* exon-14 altered

- Crizotinib is a potent MET inhibitor, and was investigated as part of an expansion cohort from a phase 1 trial
- Of 21 patients, 13 were former smokers, 16 with adenocarcinoma histology, 15 female. Response evaluable population (n=18)

Response	Number
Complete response	0
Partial response	8 (44%)
Stable disease	9 (50%)
Unconfirmed CR/PR	5 (28%)
Progressive disease	0
ORR	44% (95% CI, 22-69)

Drilon et al. *ASCO* 2016.

Vandetanib: *RET*-rearranged NSCLC

- RET rearrangements between the RET proto-oncogene and a variety of fusion partners (e.g. KIF5B, CCDC6, NCOA4, or TRIM33) have been recognized as oncogenic alterations
- Vandetanib inhibits RET, EGFR, and VEGFR
- Screened 1,536 patients with *EGFR* mutation-negative disease and 34 patients were RET-positive (2%), and 17 were included in analysis
- ORR: 47% (95% CI, 24 to 71%; n=9)
- Median PFS 4.7 months (95% CI, 2.8 to 8.5)
- Grade 3 or 4 AEs: hypertension 58% (n=11), diarrhea 11% (n=2), rash 16% (n=3), dry skin 5% (n=1), QT prolongation 11% (n=2).
- Dose reduction required in 10 patients (53%)

Yoh et al. *Lancet Respiratory* 2017.

Cabozantinib: *RET*-rearranged NSCLC

- Single arm phase 2 trial of cabozantinib in patients with NSCLC with *RET* rearrangement
- Cabozantinib inhibits RET, ROS1, MET, VEGFR2, AXL, TIE2, and KIT
- ORR 28% (95% CI, 12 to 49%)
- Median PFS 5.5 months (95% CI, 3.8 to 8.4)
- Grade 3 treatment related adverse events: 15% (n=4) increased lipase, 8% (n=2) increased ALT, increased AST, thrombocytopenia, low phosphorus
- 19 patients required 1 dose reduction (73%), 4 patients required 2 dose reductions (15%)

Drilon et al. *Lancet Oncology* 2016.

Take-home points

- For patients who are negative for *EGFR*, *ROS1*, or *ALK* further testing will identify clinically relevant oncogenic drivers
- *MET* exon 14 alteration testing indicated, especially for pulmonary sarcomatoid carcinoma, and crizotinib has demonstrated activity
- Multi-targeted tyrosine kinase inhibitors have shown activity in *RET* rearranged NSCLC but tolerability has been an issue. Adverse events related to “off target” activity

Clinical benefits of testing for other oncogenic drivers

Tom Stinchcombe

Duke Thoracic Oncology Program