Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Management of Mutation-Positive NSCLC (EGFR, ALK, RET, BRAF) — Roy S Herbst, MD, PhD

Select Publications

Drilon A et al. **Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches.** *Clin Cancer Res* 2015;21(16):3631-9.

Drilon AE et al. **Phase II study of cabozantinib for patients with advanced *RET*-rearranged lung cancers.** *Proc ASCO* 2015;**Abstract 8007**.

Felip E et al. **ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8060**.

Gerber DE et al. **ALCHEMIST: A clinical trial platform to bring genomic discovery and molecularly targeted therapies to early-stage lung cancer.** *Proc ASCO* 2015;**Abstract TPS7583**.

Lee CK et al. **Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis.** *J Clin Oncol* 2015;33(17):1958-65.

Ou SHI et al. **Efficacy and safety of the ALK inhibitor alectinib in *ALK*+ non-small-cell lung cancer (NSCLC) patients who have failed prior crizotinib: An open-label, single-arm, global phase 2 study (NP28673).** *Proc ASCO* 2015;**Abstract 8008**.

Paik PK et al. **Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping.** *Cancer Discov* 2015;5(8):842-9.

Planchard D et al. **Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with *BRAF* V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8006**.

Ramalingam SS et al. **AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion cohort.** *Proc ASCO* 2015;**Abstract 8000**.

Sequist LV et al. **Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts).** *Proc ASCO* 2015;**Abstract 8001**.

Soria J-C et al. **Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: Overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8).** *Proc ASCO* 2015;**Abstract 8002**.

Soria JC et al. **Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): A phase 3 randomised trial.** *Lancet Oncol* 2015;16(8):990-8.

Management of Mutation-Positive NSCLC (EGFR, ALK, RET, BRAF)

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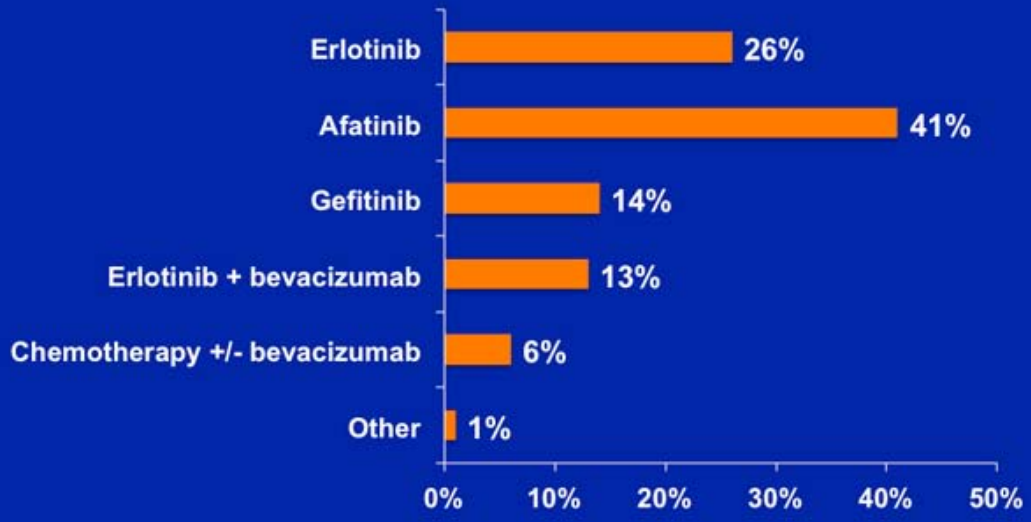
Disclosures

Consulting Agreements	Genentech BioOncology, Lilly, Merck

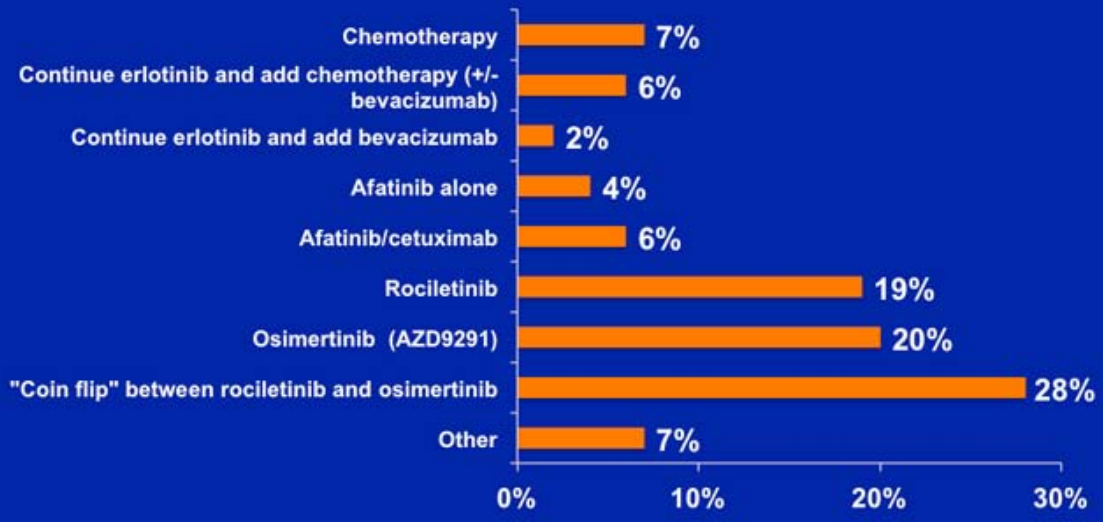
AUDIENCE POLL

Which systemic therapy would you generally recommend for an otherwise healthy patient who has newly diagnosed metastatic adenocarcinoma of the lung and an EGFR del(19) mutation?



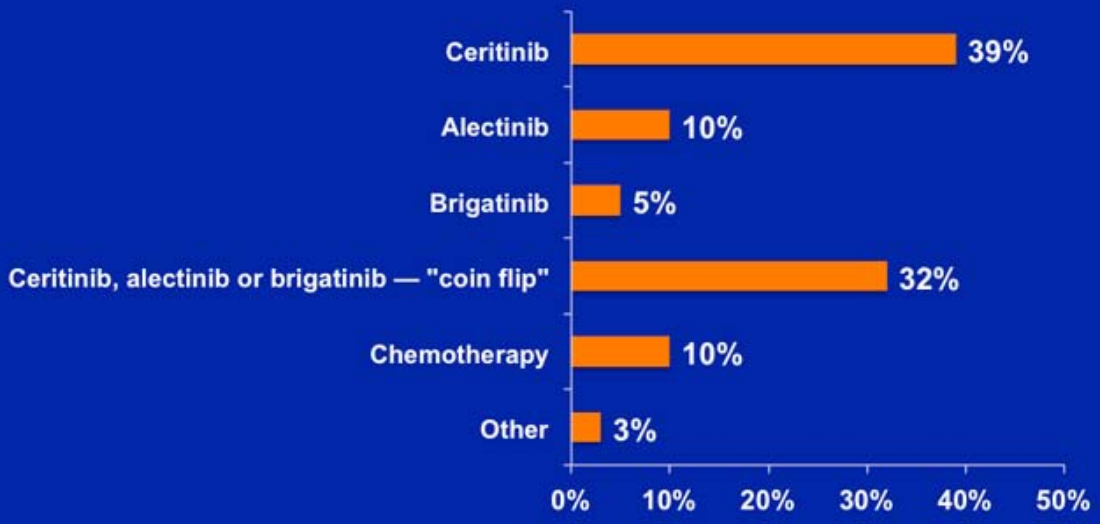
AUDIENCE POLL

A 56-year-old man, a never smoker, with widespread metastatic adenocarcinoma of the lung and an EGFR mutation experiences disease progression on imaging after 11 months on erlotinib. What would be your most likely treatment approach if the patient underwent rebiopsy that revealed a T790M mutation? (Assume osimertinib [AZD9291] and rociletinib are available.)



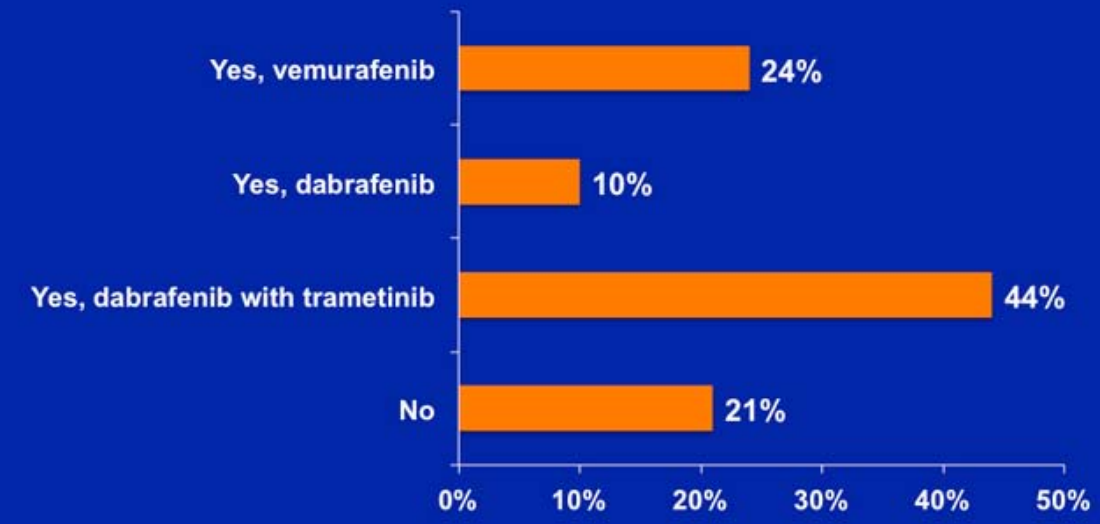
AUDIENCE POLL

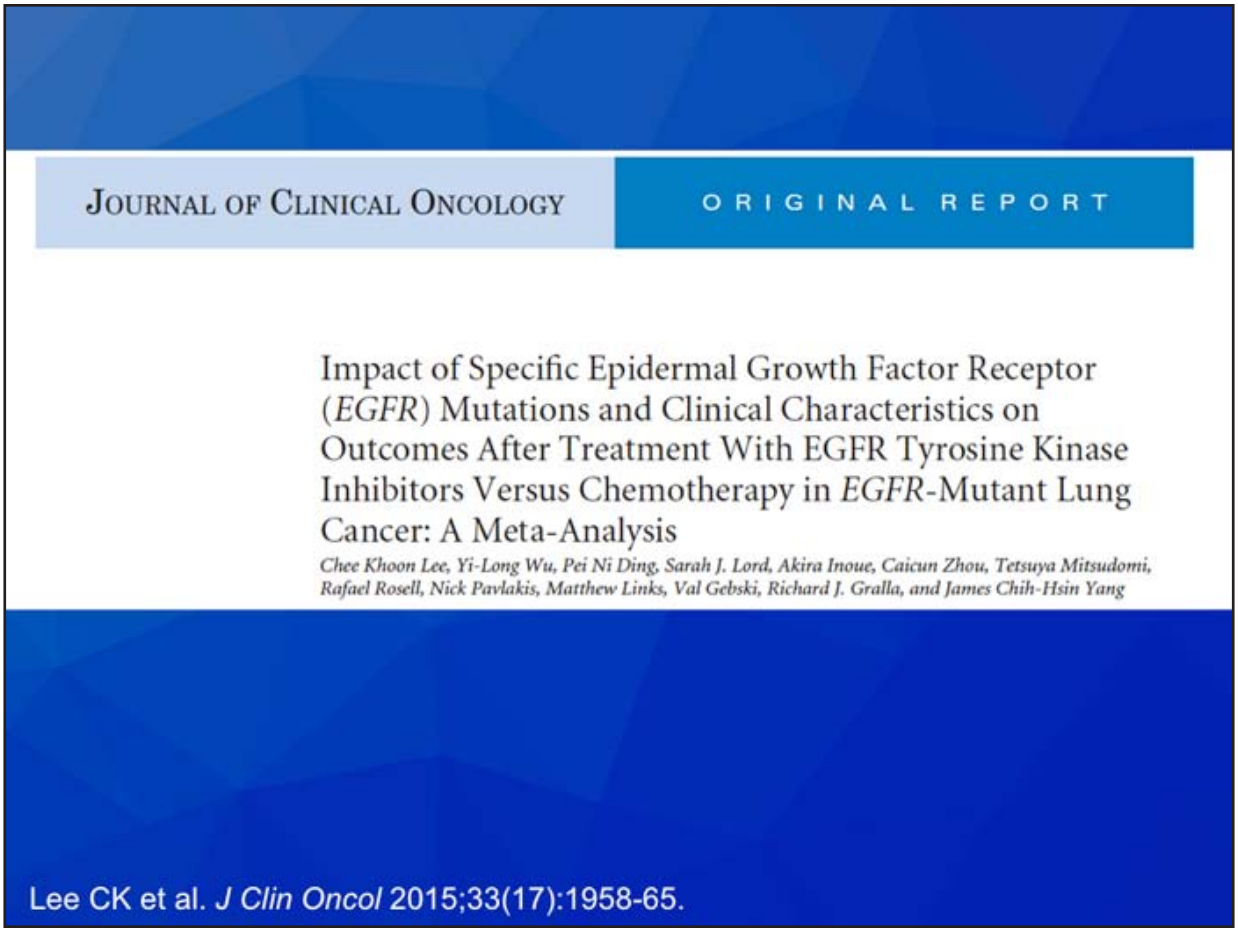
What would be your most likely choice of second-line therapy for a patient with ALK-rearranged metastatic adenocarcinoma of the lung who experiences disease progression on crizotinib (assume all agents are approved and available)?



AUDIENCE POLL

Cost and reimbursement issues aside, would you recommend a BRAF inhibitor, either alone or in combination with a MEK inhibitor, as either first- or later-line treatment for a patient with metastatic nonsquamous cell lung cancer and a BRAF V600E tumor mutation?





Meta-Analysis of PFS Benefit Observed with EGFR TKIs – Subgroup of Patients with Exon 19 Deletion and Exon 21 Substitution EGFR Mutations

Trial	HR	95% CI	HR	95% CI
	Exon 19 deletions		Exon 21 L858R substitution	
ENSURE	0.20	0.12 to 0.33	0.54	0.32 to 0.91
EURTAC	0.27	0.17 to 0.43	0.53	0.29 to 0.97
LUX-Lung 3	0.28	0.18 to 0.44	0.73	0.46 to 1.16
LUX-Lung 6	0.20	0.13 to 0.32	0.32	0.19 to 0.54
NEJ002	0.24	0.15 to 0.38	0.33	0.20 to 0.54
OPTIMAL	0.13	0.07 to 0.24	0.26	0.14 to 0.48
WJTOG 3405	0.42	0.26 to 0.66	0.69	0.44 to 1.07
All	0.24	0.20 to 0.29	0.48	0.39 to 0.58

Lee CK et al. *J Clin Oncol* 2015;33(17):1958-65.

Conclusions

Critical finding(s): Correlation of specific EGFR mutations with outcome

Clinical implication(s): Could help physicians determine prognosis and better predict response to EGFR inhibitors

Research relevance: As new inhibitors are developed would be an opportunity to better personalize therapy

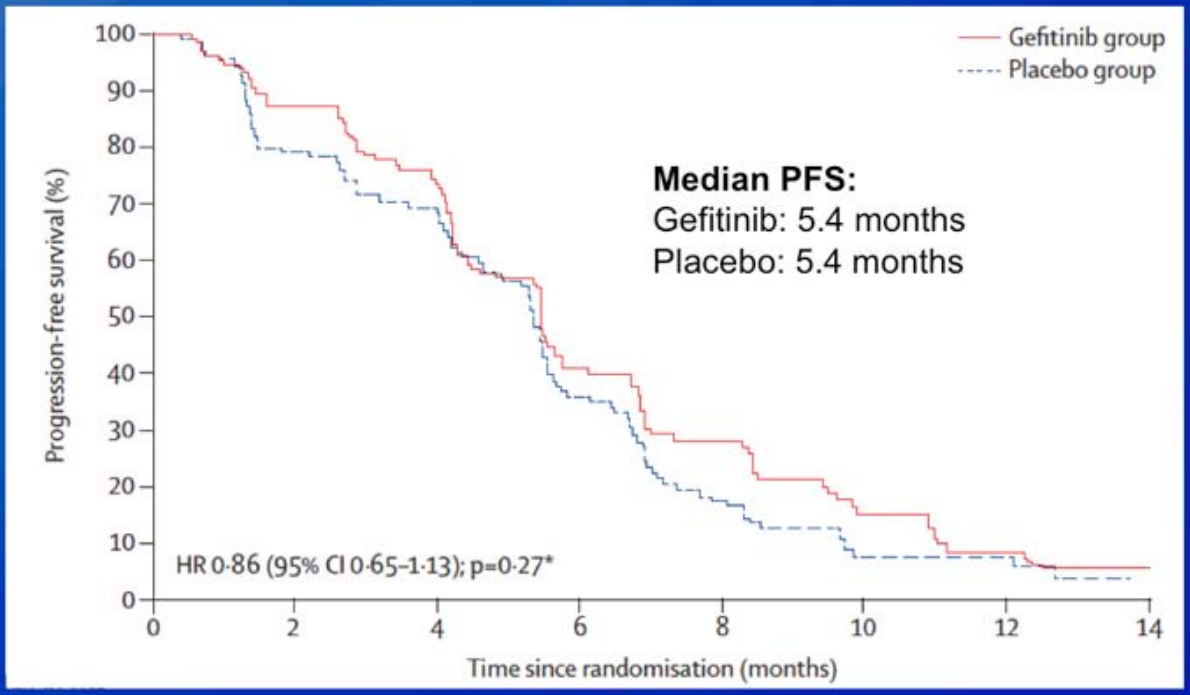
Articles

Gefitinib plus chemotherapy versus placebo plus chemotherapy in *EGFR*-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial

Jean-Charles Soria, Yi-Long Wu, Kazuhiko Nakagawa, Sang-We Kim, Jin-Ji Yang, Myung-Ju Ahn, Jie Wang, James Chih-Hsin Yang, You Lu, Shinji Atagi, Santiago Ponce, Dae Ho Lee, Yunpeng Liu, Kiyotaka Yoh, Jian-Ying Zhou, Xiaojin Shi, Alan Webster, Haiyi Jiang, Tony S K Mok

Soria JC et al. *Lancet Oncol* 2015;16(8):990-8.

IMPRESS: Progression-Free Survival



Soria JC et al. *Lancet Oncol* 2015;16(8):990-8.

Conclusions

Critical finding(s): No benefit to continuing gefitinib after progression versus placebo

Clinical implication(s): No benefit to continuing gefitinib

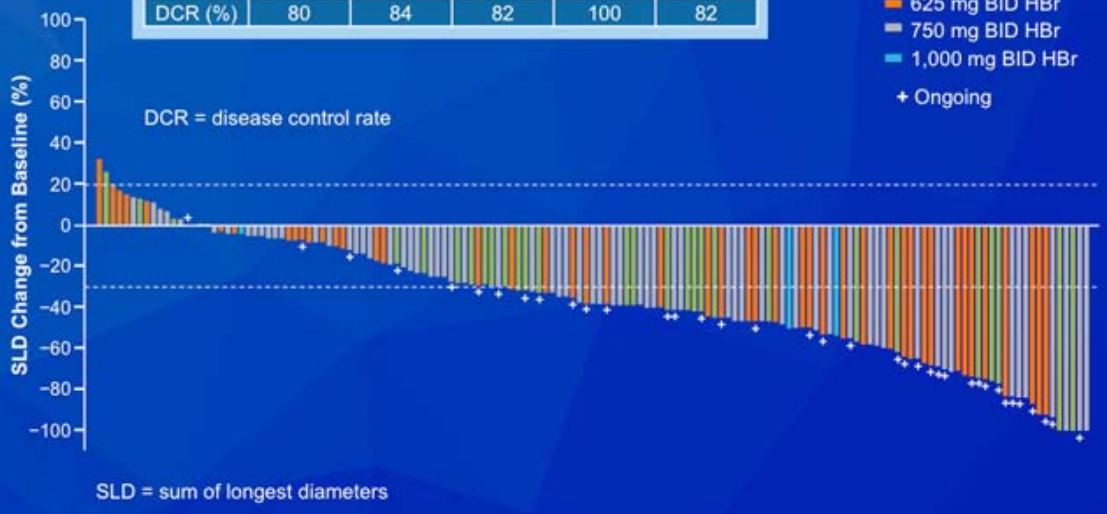
Research relevance: None

Efficacy of Rociletinib (CO-1686) in Plasma-Genotyped T790M-Positive Non-Small Cell Lung Cancer (NSCLC) Patients (pts)

Sequist LV et al.
Proc ASCO 2015;Abstract 8001.

Best Response to Rociletinib in Patients with Plasma T790M Mutation

	500 mg	625 mg	750 mg	1,000 mg	Total
N	30	49	65	3	147
ORR (%)	57	55	49	67	53
DCR (%)	80	84	82	100	82



With permission from Sequist LV et al. *Proc ASCO* 2015;Abstract 8001.

Conclusions

Critical finding(s): Continued evidence for benefit of rociletinib in NSCLC patients with mutations

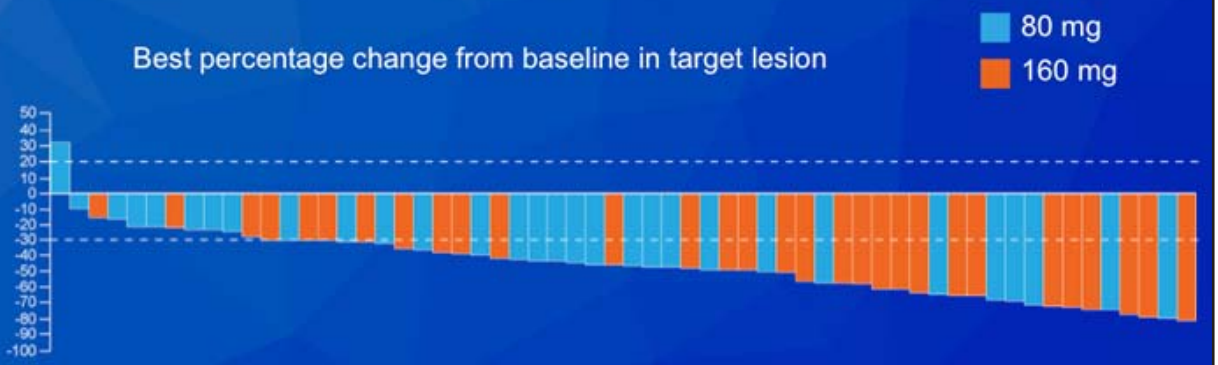
Clinical implication(s): Plasma T790M tests can be used to obtain ORR of 53% and DCR of 82%

Research relevance: Liquid biopsies are applicable

AZD9291, a Mutant-Selective EGFR Inhibitor, as First-Line Treatment for EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC): Results from a Phase 1 Expansion Cohort

Ramalingam SS et al.
Proc ASCO 2015;Abstract 8000.

AURA: Response Summary



- **Objective response rate**:
  - 80 mg (n = 30): 63%
  - 160 mg (n = 30): 83%
  - All patients (n = 60): 73%

Ramalingam SS et al. *Proc ASCO* 2015;Abstract 8000.

Conclusions

Critical finding(s): AZD9291 is effective with ORR of 63% at 80 mg and 83% at 160 mg (total 73%)

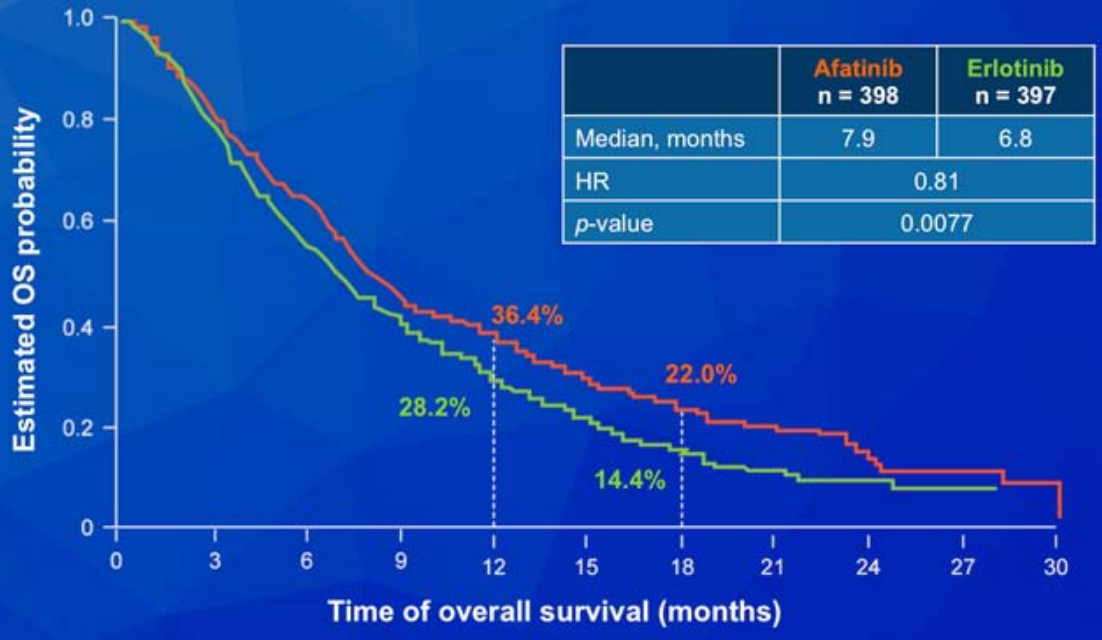
Clinical implication(s): Potential new drug for T790M-resistant, EGFR-mutant NSCLC

Research relevance: New era of third-generation inhibitors

Afatinib versus Erlotinib as Second-Line Therapy of Patients with Advanced Squamous Cell Carcinoma of the Lung following Platinum-Based Chemotherapy: Overall Survival Analysis from LUX-Lung 8 Global Phase III Trial

Soria J-C et al.
Proc ASCO 2015;Abstract 8002.

LUX-Lung 8: Primary Analysis of OS



	Afatinib n = 398	Erlotinib n = 397
Median, months	7.9	6.8
HR	0.81	
p-value	0.0077	

Soria J-C et al. *Proc ASCO* 2015;Abstract 8002.

Conclusions

Critical finding(s): Afatinib was superior to erlotinib for squamous NSCLC (HR = 0.81)

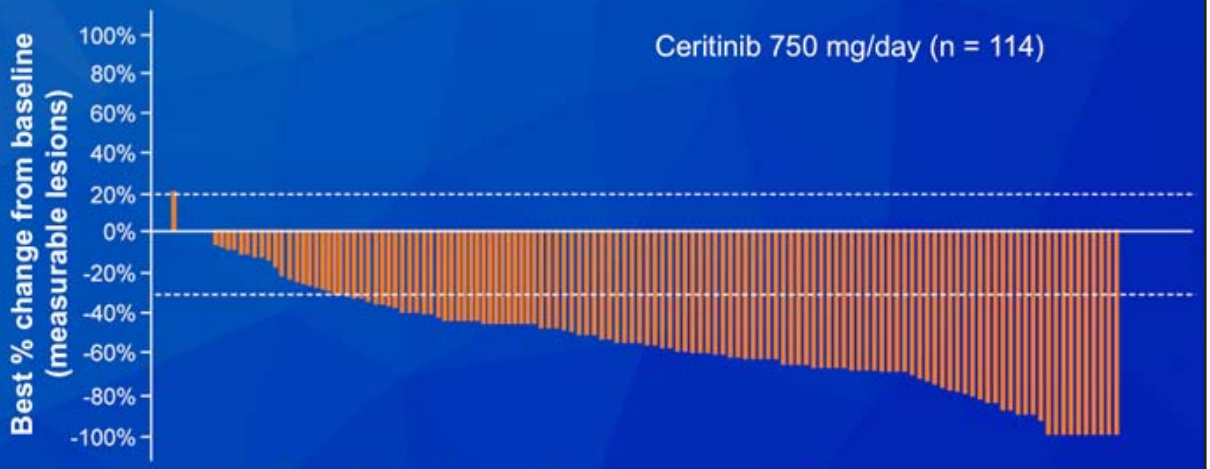
Clinical implication(s): Slight superiority for afatinib in this situation (non-EGFR-mutated patients)

Research relevance: None

ASCEND-3: A Single-Arm, Open-Label, Multicenter Phase II Study of Ceritinib in ALKi-naïve Adult Patients (pts) with ALK-Rearranged (ALK+) Non-Small Cell Lung Cancer (NSCLC)

Felip E et al.
Proc ASCO 2015;Abstract 8060.

Best Percentage Change from Baseline by Investigator Review



Median duration of response = 9.3 mo

Median PFS = 11.1 mo

Felip E et al. *Proc ASCO* 2015;Abstract 8060.

Conclusions

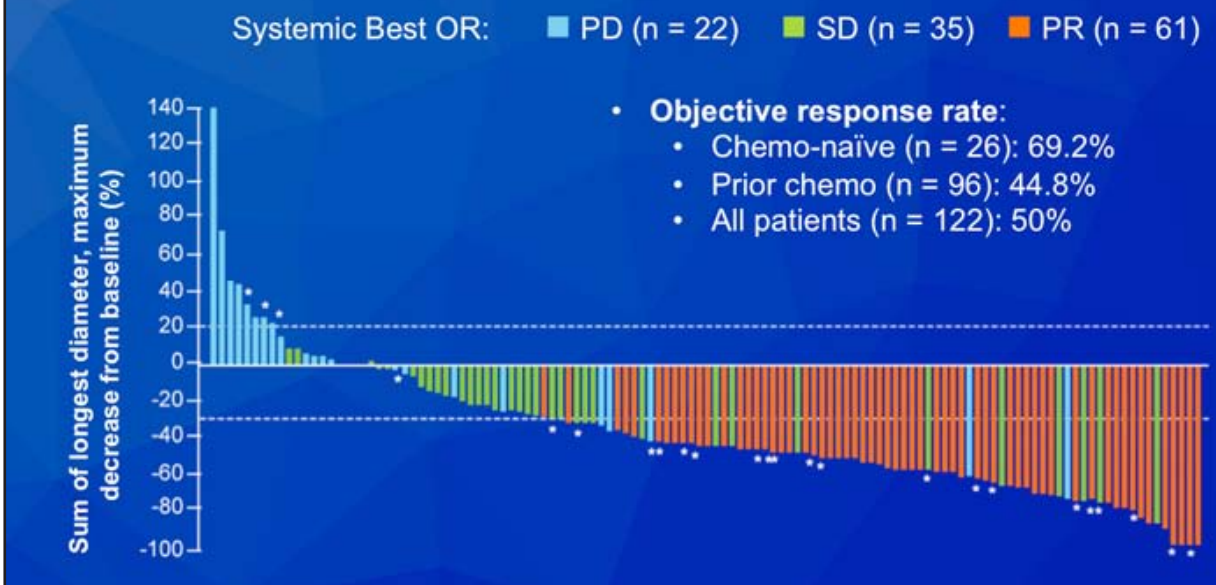
Critical finding(s): Ceritinib is active in this setting; nearly all patients respond; median PFS = 11.1 mo

Clinical implication(s): New-generation agent for ALK-positive disease

Efficacy and Safety of the ALK Inhibitor Alectinib in ALK+ Non-Small-Cell Lung Cancer (NSCLC) Patients who Have Failed Prior Crizotinib: An Open-Label, Single-Arm, Global Phase 2 Study (NP28673)

Ou SHI et al.
Proc ASCO 2015;Abstract 8008.

Activity of Alectinib in Patients with Crizotinib-Resistant ALK+ NSCLC



- **Objective response rate**:
  - Chemo-naïve (n = 26): 69.2%
  - Prior chemo (n = 96): 44.8%
  - All patients (n = 122): 50%

* Chemotherapy-naïve patients

Ou SHI et al. *Proc ASCO* 2015;Abstract 8008.

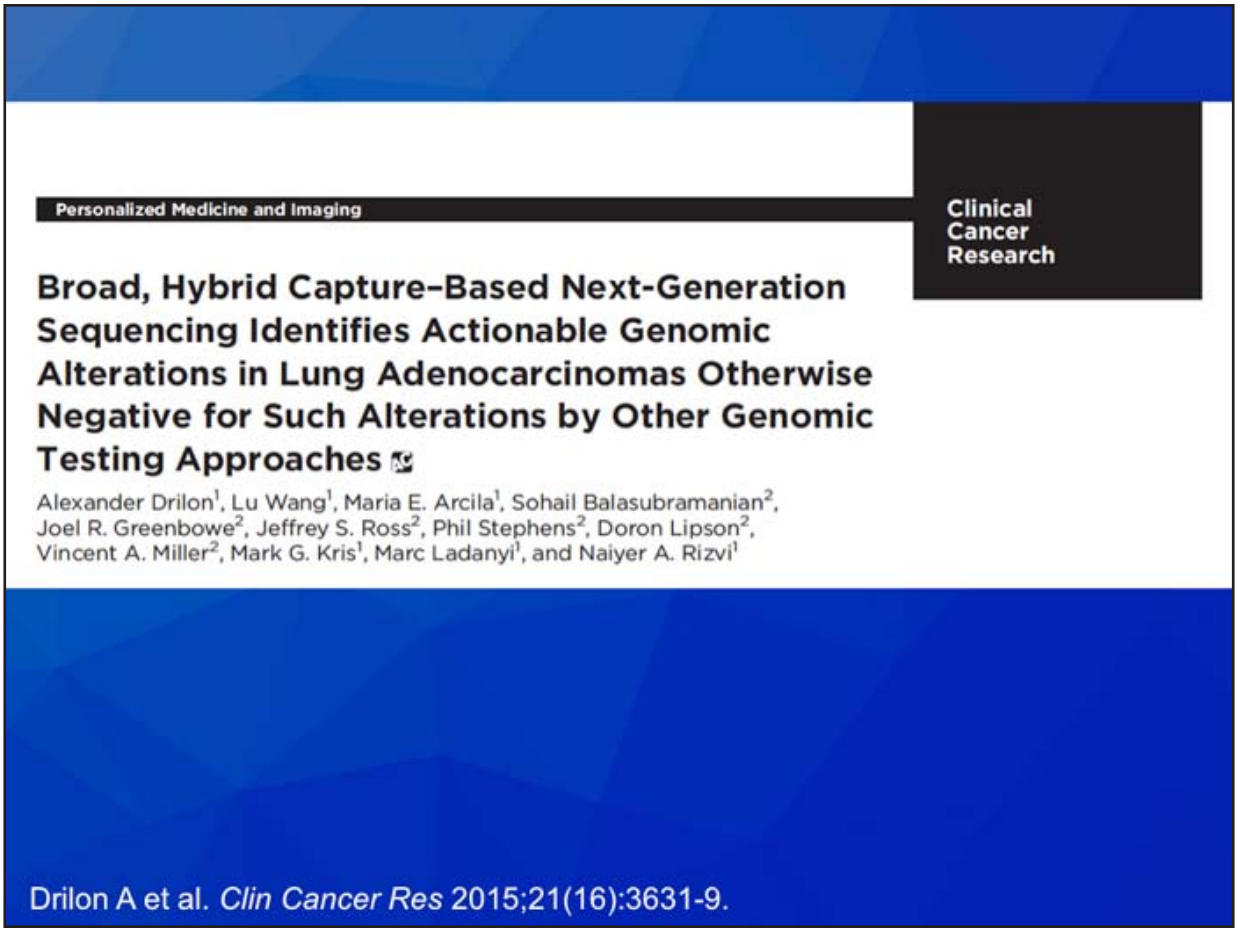
Conclusions

Critical finding(s): Activity of the next-generation ALK inhibitor alectinib in patients with crizotinib-resistant ALK+ NSCLC

ORR 50% for all patients (69.2% chemo-naïve and 44.8% prior chemo)

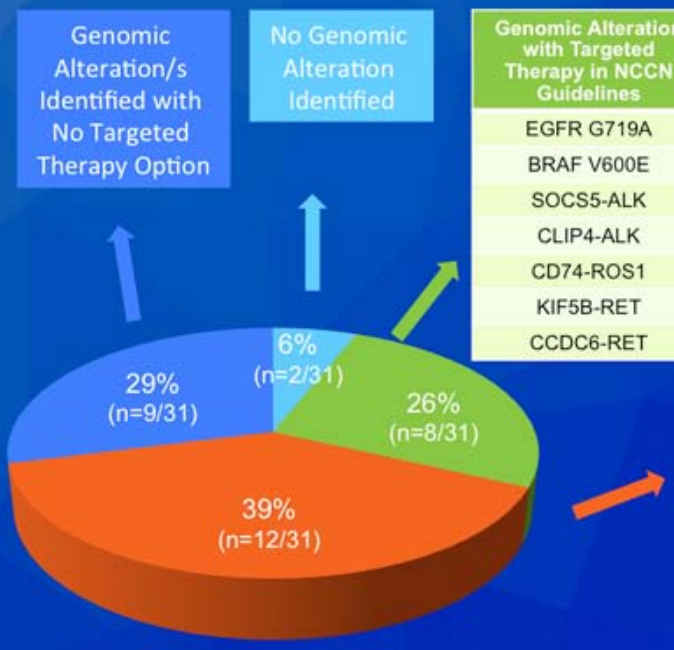
Clinical implication(s): Significant activity of this next-generation agent

Research relevance: Continue to develop new agents to target resistance



Drilon A et al. *Clin Cancer Res* 2015;21(16):3631-9.

NGS in Patients with No Genomic Alterations



Genomic Alteration with Targeted Therapy in NCCN Guidelines
EGFR G719A
BRAF V600E
SOCS5-ALK
CLIP4-ALK
CD74-ROS1
KIF5B-RET
CCDC6-RET

Genomic Alteration with Targeted Agent Available on or off a Clinical Trial	Targeted Therapeutic (Protocol Number) with Potential Activity Available at Institution
CDKN2A Loss	CDK4/6 inhibitor (#10-211)
EGFR L747P	erlotinib, afatinib
EGFR exon 18 del (n=2)	pan-ERBB inhibitor (#13-036)
EGFR exon 20 ins	pan-ERBB inhibitor (#13-036)
ERBB2 L755F	pan-ERBB/mTOR inhibitor (#13-087)
FGFR1 T141R	FGFR inhibitor (#13-131)
KRAS G12C	ERK inhibitor (#13-254)
KRAS Q61H	ERK inhibitor (#13-254)
MDM2 Amp (n=3)	MDM2 inhibitor (#13-171)

Drilon A et al. *Clin Cancer Res* 2015;21(16):3631-9.

Conclusions

Critical finding(s): Next-generation sequencing for lung adenocarcinomas can identify new mutations for potential targeting

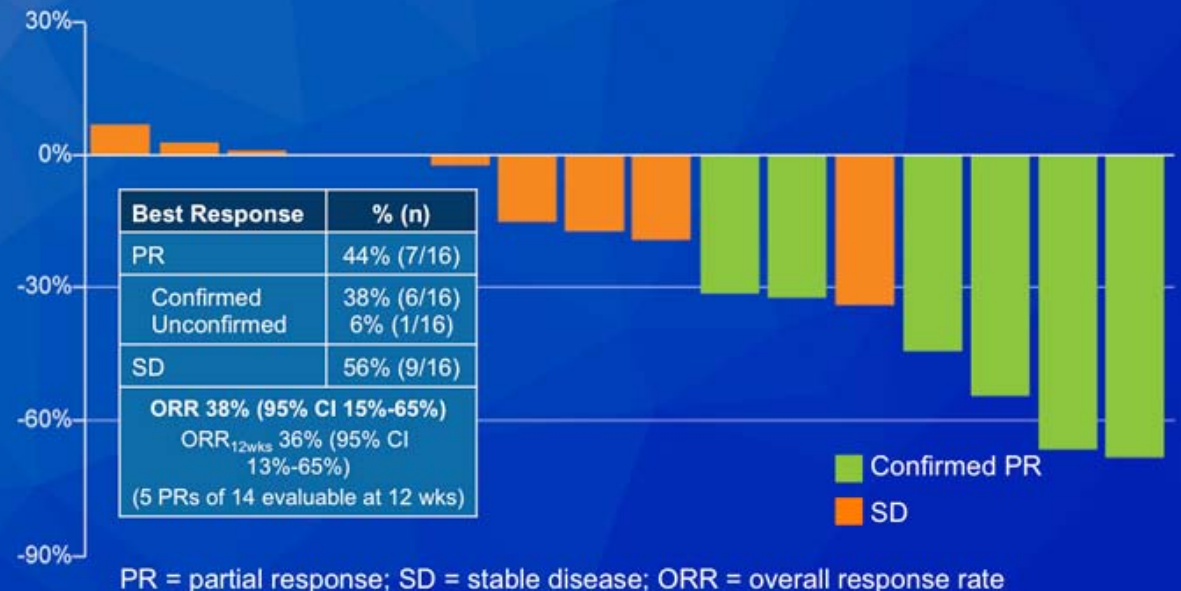
Clinical implication(s): Potential for targeting with new agents

Research relevance: Efficacy needs to be proved in clinical trials

Phase II Study of Cabozantinib for Patients with Advanced RET-Rearranged Lung Cancers

Drilon AE et al.
Proc ASCO 2015;Abstract 8007.

Response to Cabozantinib



PR = partial response; SD = stable disease; ORR = overall response rate

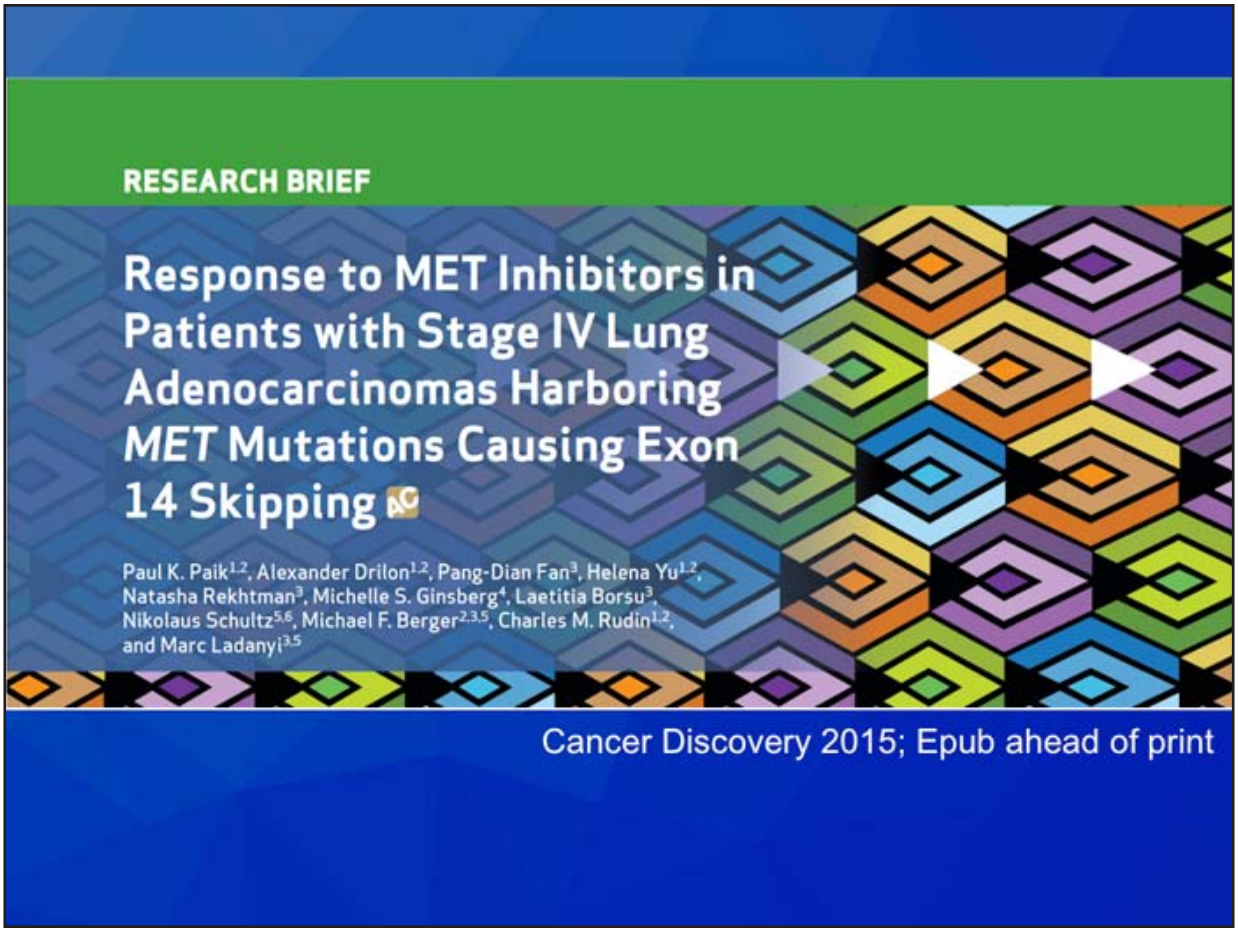
Drilon AE et al. *Proc ASCO* 2015;Abstract 8007.

Conclusions

Critical finding(s): Cabozantinib is clearly active in advanced RET-rearranged lung cancer

Clinical implication(s): Potential treatment for this small subgroup of patients

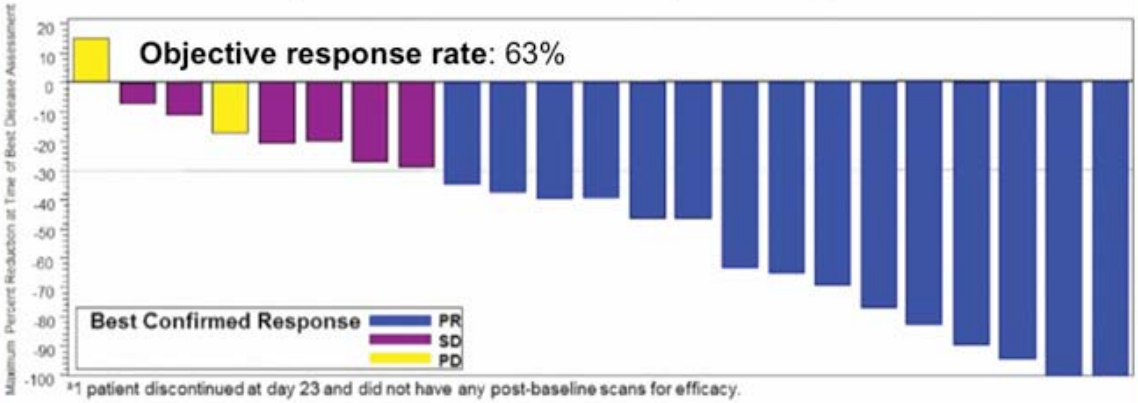
Research relevance: Continue to explore future agents



Interim Results of a Phase II Study of the BRAF Inhibitor (BRAFi) Dabrafenib (D) in Combination with the MEK Inhibitor Trametinib (T) in Patients (pts) with BRAF V600E Mutated (mut) Metastatic Non-Small Cell Lung Cancer (NSCLC)

Planchard D et al.
Proc ASCO 2015;Abstract 8006.

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 24[a])



[a]1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

- The median duration of response was not reached

Planchard D et al. *Proc ASCO* 2015;Abstract 8006.

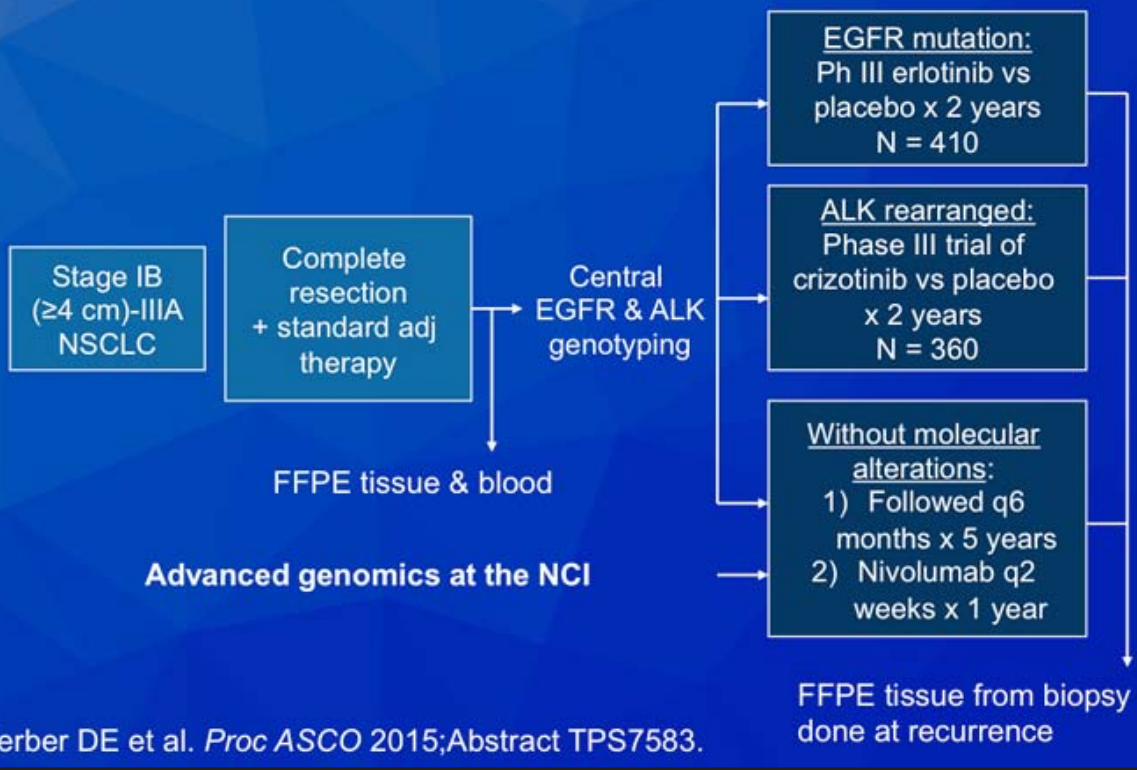
Conclusions

Critical finding(s): In patients with V600E, dabrafenib plus trametinib is highly active

Clinical implication(s): 63% response rate

Research relevance: More such combos are needed

ALCHEMIST: National Trial for Molecular Characterization of Early-Stage Nonsquamous NSCLC



Gerber DE et al. *Proc ASCO* 2015;Abstract TPS7583.