Personalized Therapy for Advanced NSCLC in the New Millenium: An American's Perspective on Precision Medicine

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Langer Disclosures: Past 12 months

- Grant/Research Support:
  - Genentech, OSI (Astellas), Merck, GlaxoSmithKline, Nektar, Advantagene, Clovix; Ariad; Inovio, Threshold, AZ, Celgene, MGA
- DSMC:
  - Lilly, Amgen, Synta, Agennix, SWOG, Peregrine, Incyte, AbbVie
- Scientific Advisor:
  - Bristol Myers Squibb, Pfizer, Lilly, Astra Zeneca, Novartis, Genentech, Abbott, Celgene, Boehringer-Ingelheim, Hospira, Clovis, Merck

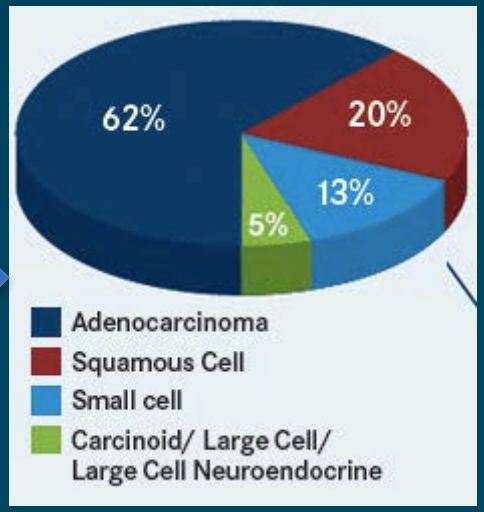
Case 1

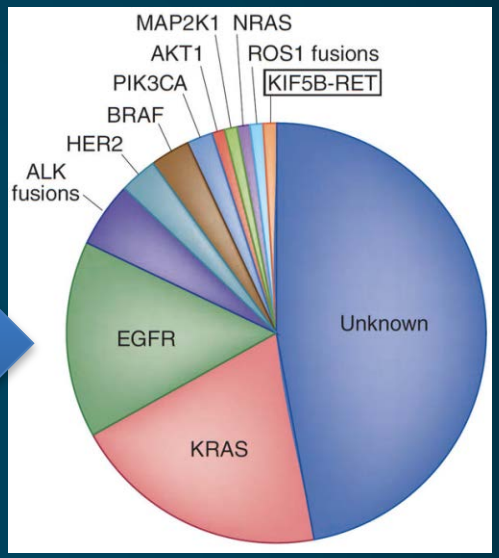
- 49 yo Asian-American Female never smoker presents with hemoptysis and DOE. CXR reveals multiple pulmonary nodules
- CT confirms a 6 cm L hilar mass as well as multiple 3-5 cm lesions in both lungs and a small L pleural effusion. CT A/P also shows multiple space-occupying lesions in the liver, spleen and kidneys.
- Bx of the liver returns (+) for adenoca
- What is the chance this patient will have an EGFR mutation?
  1. 85-90%
  2. 60-65%
  3. 30-35%
  4. 10-15%

Molecular Determinants of Therapy for Advanced NSCLC

Metastatic lung cancer in evolution

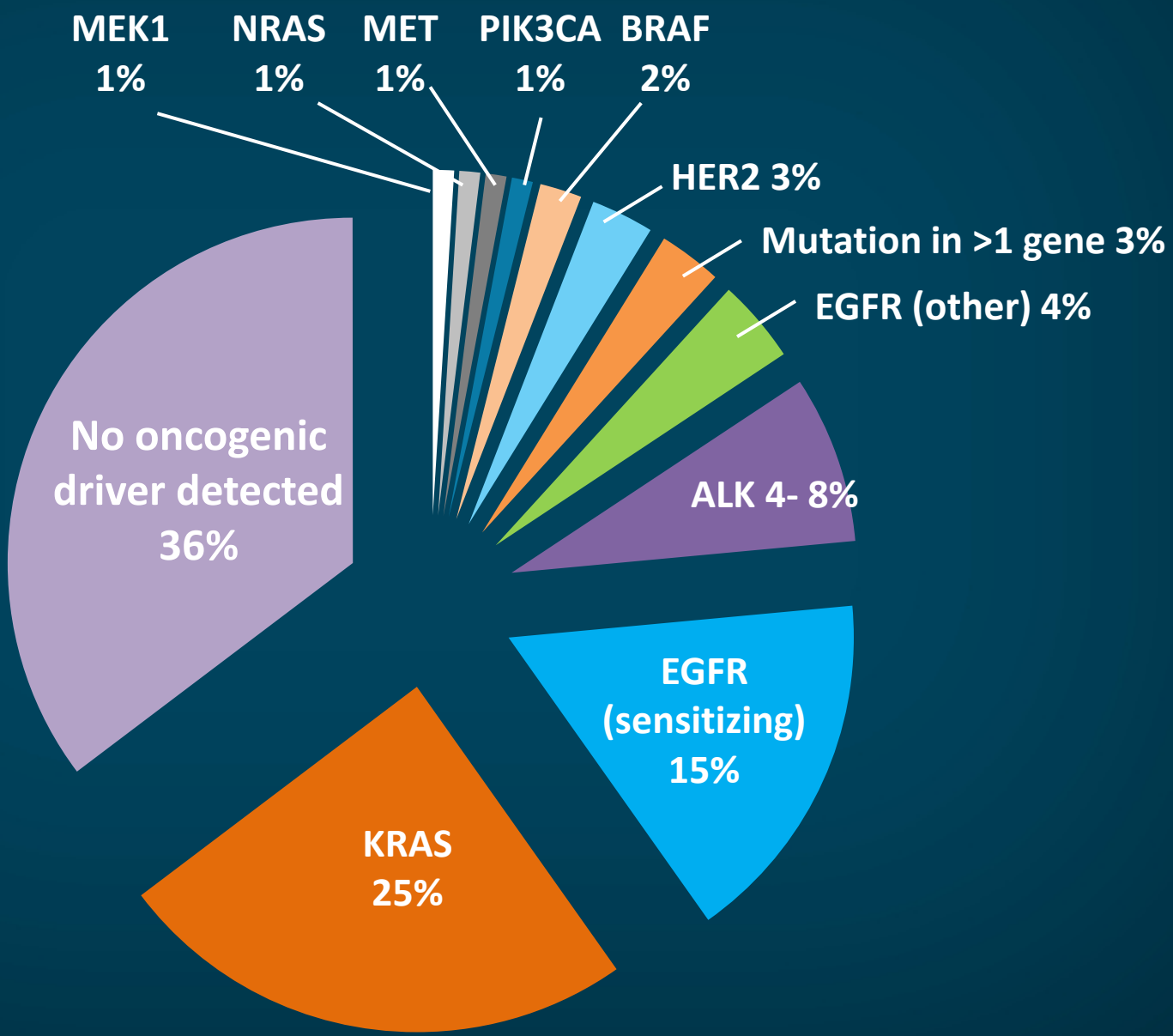
LUNG CANCER





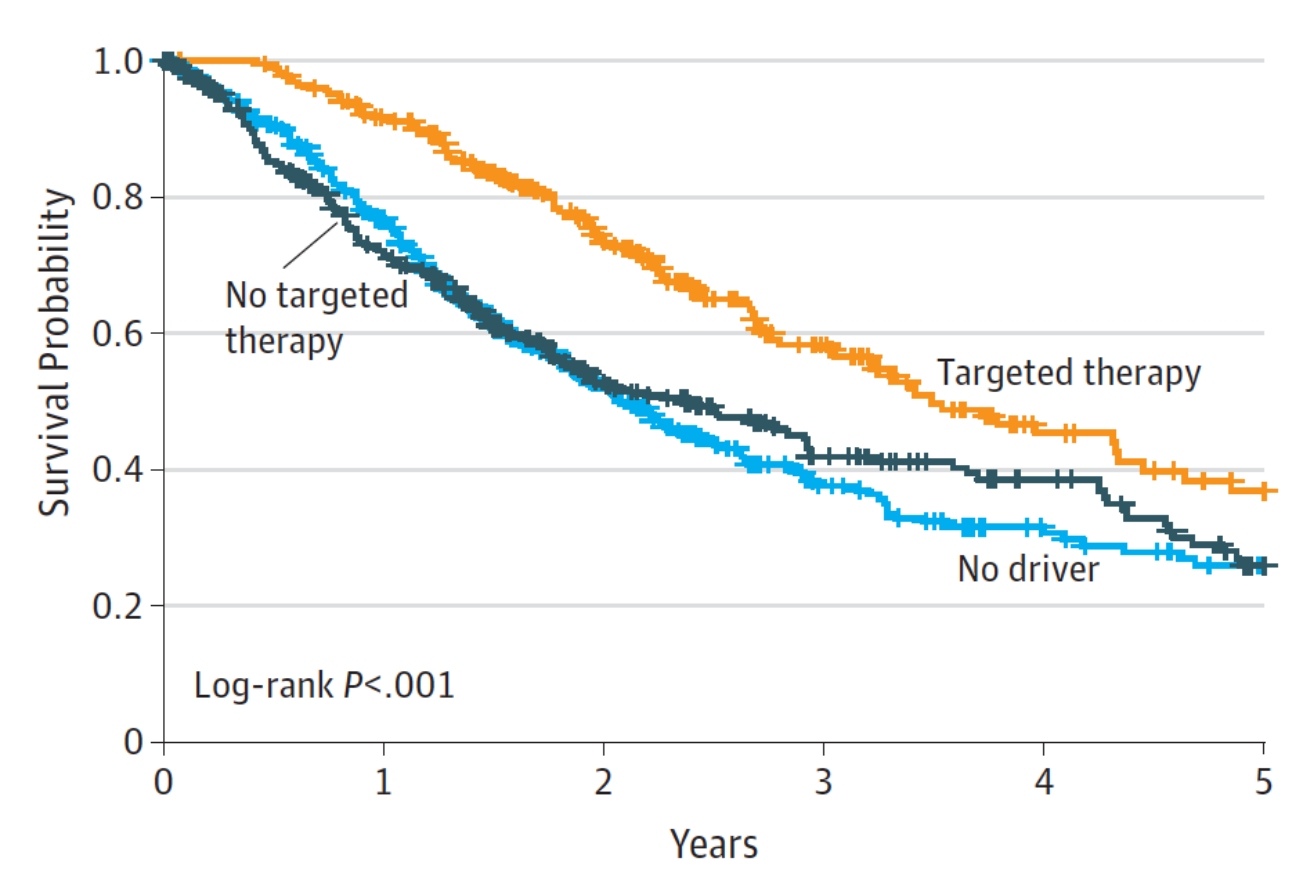
Lung Cancer Mutation Consortium

Incidence of Driver Mutations



Kris MG et al. *JAMA*. 2014;311:1998-2006.

Use of targeted therapies in a targeted age

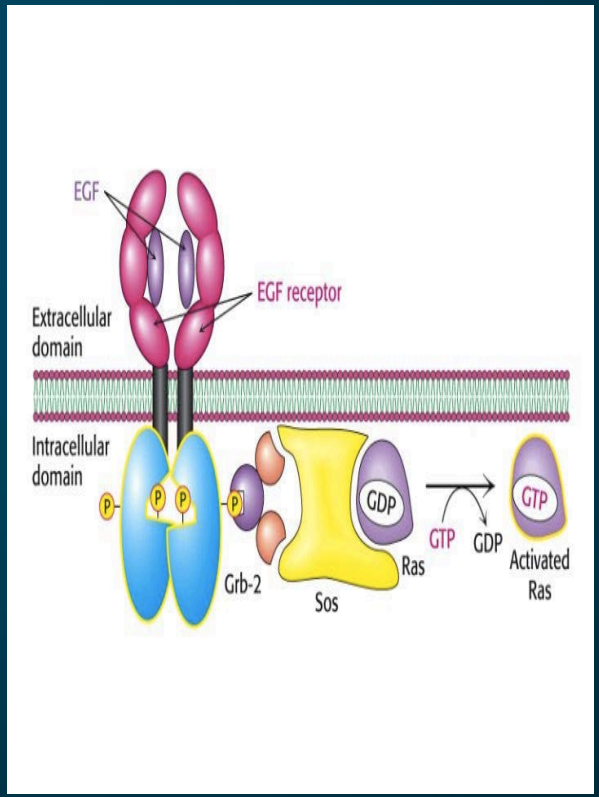


Genotype/Therapy	No	Median OS	95% CI
Oncologic driver + targeted therapy	264	3.49 years	3.02-4.33
Oncologic driver + no targeted therapy	313	2.38 years	1.81-2.93
No Oncogenic driver	361	2.08 years	1.84-2.46

Kris et al JAMA 2014

Epidermal Growth Factor Receptor

- Mutations most common “actionable” driver
  - 10-15% of Caucasians
  - 30-35% East Asians
- Strongly associated with epidemiology
  - Female
  - Never or light smokers (PY matters!)
- Overall prognosis better c/w wt
- Distribution
  - Exon 19 deletion ~ 45-50%
  - L858R mutations ~ 40-45%
  - Exon 20 mutations ~ 5-10%
    - Associated with Tx resistance to TKIs



Randomized Studies of First-Line EGFR TKI in Patients with EGFR Mutations

Author	Study	Agent	N (EGFR mut+)	RR	Median PFS (mos.)	OS (mos.)
Mok et al[1]	IPASS	Gef	261	71.2% vs 47.3	9.8 vs 6.4	21.6 vs 21.9
Lee et al[2]	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al[3]	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al[4]	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al[5]	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al[6]	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al[7]	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 v. 28.2
Wu et al[8]	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

1727

Cross-over to an EGFR TKI in the control group nullifies any chance of an OS benefit.

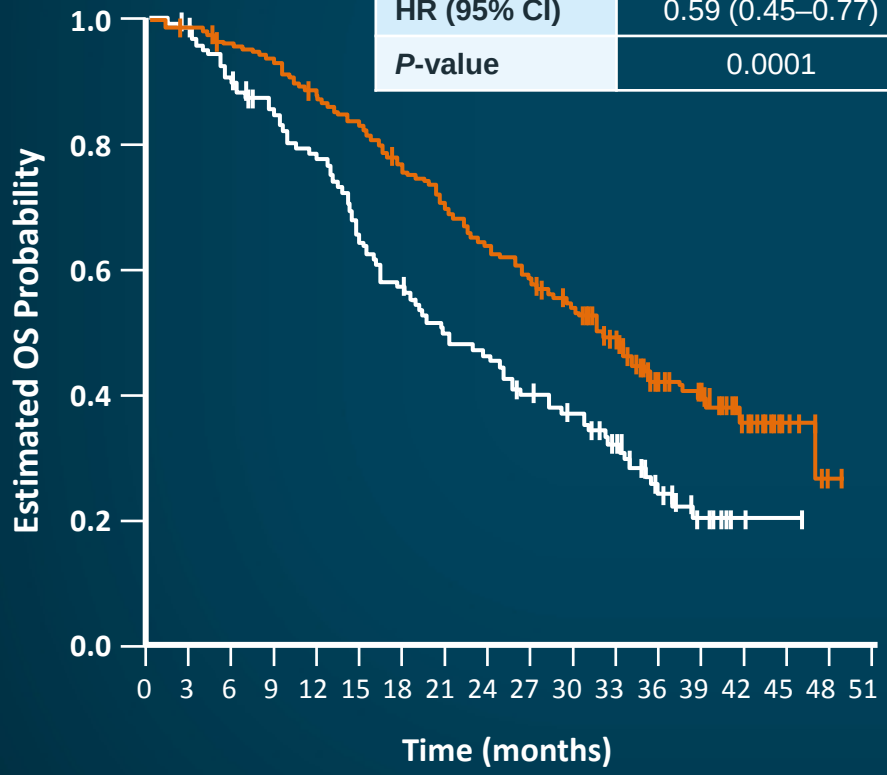
TKI = tyrosine kinase inhibitor; RR = response rate.

1. Mok TS et al. *N Engl J Med.* 2009;361:947-957. 2. Lee JS et al. WCLC meeting, 2009: PRS.4. 3. Mitsudomi T et al. *Lancet Oncol.* 2010;11:121-128. 4. Maemondo M et al. *N Engl J Med.* 2010:362:2380-2388. 5. Zhou C et al. *Ann Oncol.* 2010;21(suppl 8):LBA13. 6. Rosell R et al. *J Clin Oncol.* 2011;29 (suppl):abstract 7503. 7. Yang JC-H et al. *J Clin Oncol.* 2012;30(suppl):abstract LBA7500. 8. Wu YL et al. *J Clin Oncol.* 2013;31(suppl):abstract 8016.

LUX-Lung 3 and 6 Pooled Analysis

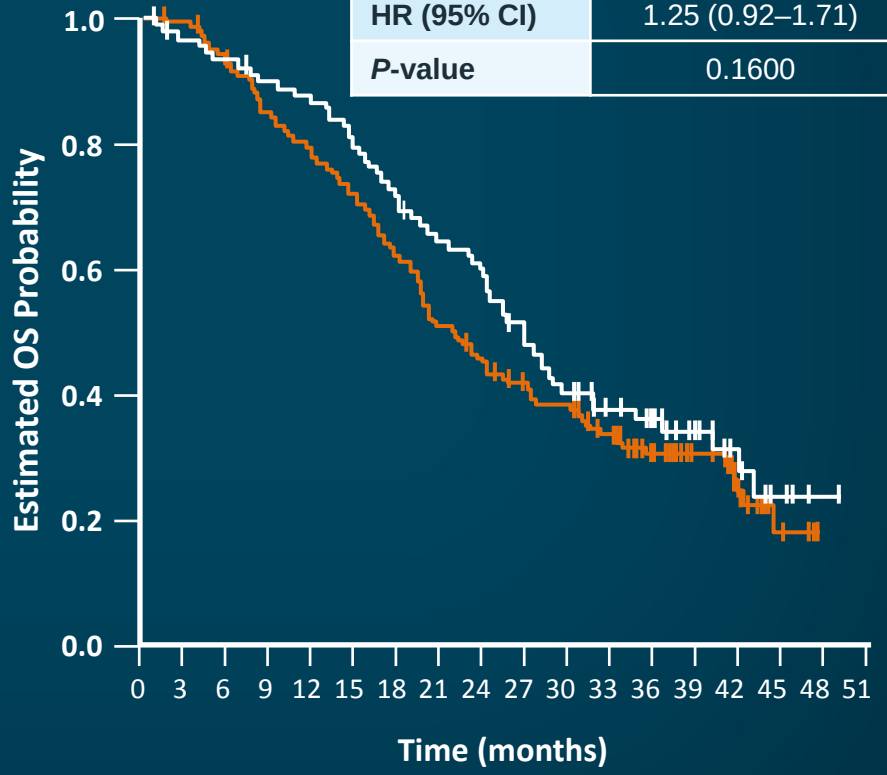
Overall Survival of Del19 vs L858R Patients

DEL19	Afatinib n = 236	Chemo n = 119
Median (mos.)	31.7	20.7
HR (95% CI)	0.59 (0.45–0.77)	
P-value	0.0001	



Number of patients																		
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R	Afatinib n = 183	Chemo n = 93
Median (mos.)	22.1	26.9
HR (95% CI)	1.25 (0.92–1.71)	
P-value	0.1600	



Number of patients																		
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

Yang JC-H et al. *J Clin Oncol*. 2014;32(suppl 15): abstract 8004.

Study design

Chemotherapy-naïve
Stage IIIB/IV or
postoperative recurrence
Non-squamous NSCLC
Activating *EGFR* mutations*
Exon 19 deletion
Exon 21 L858R
Age ≥20 years
PS 0–1
No brain metastasis

*T790M excluded

R

1:1

EB combination
Erlotinib 150mg qd +
bevacizumab 15mg/kg q3w
(*n* = 75)

→ PD

E monotherapy
Erlotinib 150mg qd
(*n* = 75)

→ PD

Stratification factors:
sex, smoking status,
clinical stage,
EGFR mutation type

Primary endpoint:
PFS (RECIST v1.1, independent review)

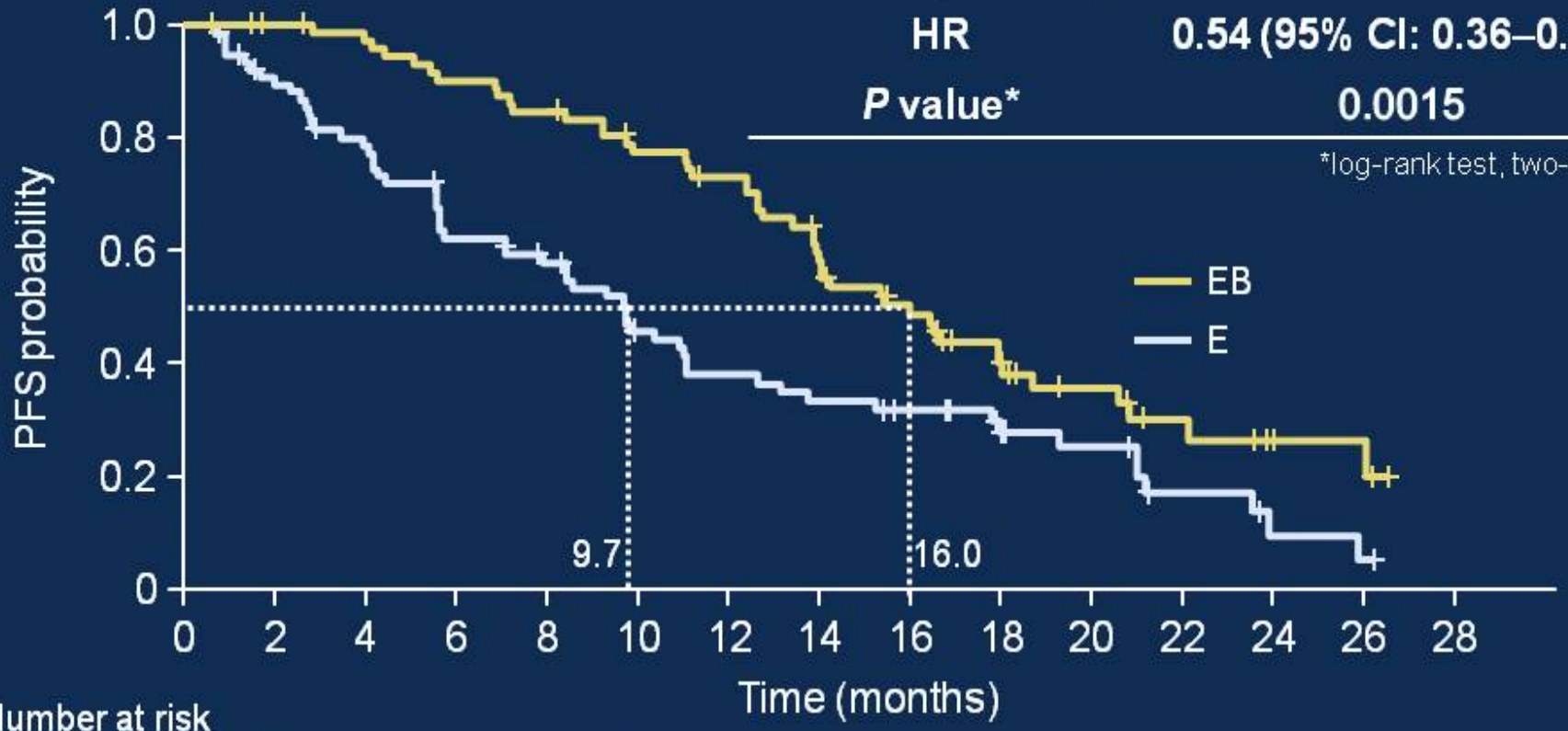
Secondary endpoints:
OS, tumor response, QoL, safety

Exploratory endpoint:
biomarker assessment

Primary endpoint: PFS by independent review

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided



Number at risk

EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

Presented by: Terufumi Kato

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Terufumi Kato at 2014 ASCO Annual Meeting

Acquired Resistance to EGFR Inhibition

- Mechanisms of acquired resistance
  - Secondary mutations in exon 20 (T790M) in ~60%
    - Associated with better prognosis than other mechanisms of resistance
  - Amplification of HER2: 8–12%
  - Activation of Met pathway: 4–8%
  - Conversion to small cell lung cancer: <5%
- Tissue biopsy at the time of progression is now "gold standard."
  - Increasing use of "liquid biopsy" to detect ctfDNA
  - T790 (+) acquired resistance: osimertinib (agent of choice)
  - T790 (–) acquired resistance:
    - afatinib/C225 or chemotherapy (default);
    - No proven role for continuing EGFR TKI beyond PD along with subsequent chemo

Sequist LV et al. *Sci Transl Med.* 2011;3:75ra26. Pao W et al. *PLoS Med.* 2005;2:e73.

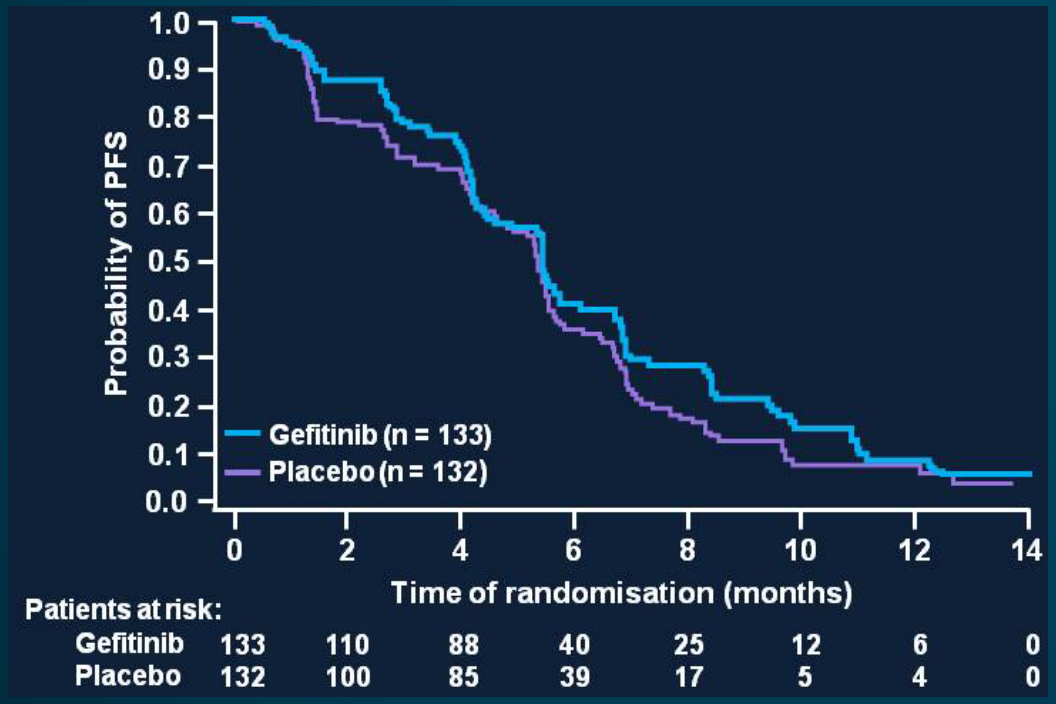
Ongoing EGFR TKI: IMPRESS Trial

Activating *EGFR* mutation
Resp to EGFR TKI >4 mo
No prior chemotherapy
N = 250

RANDOMIZE

- Cisplatin/pemetrexed
- Cisplatin/pemetrexed + ongoing gefitinib

Primary endpoint: PFS



	Gefitinib (n = 133)	Placebo (n = 132)
Median PFS, mos.	5.4	5.4
Events, n (%)	98 (73.7)	107 (81.1)
HR (95% CI) = 0.86 (0.65–1.13), *P*=0.273		

Median OS = 14.8 mos. (G) vs 17.2 mos. (P)
HR = 1.62, *P*=0.029 but 33% of events

Soria JC et al. *Lancet Oncol.* 2015;16:990-998.

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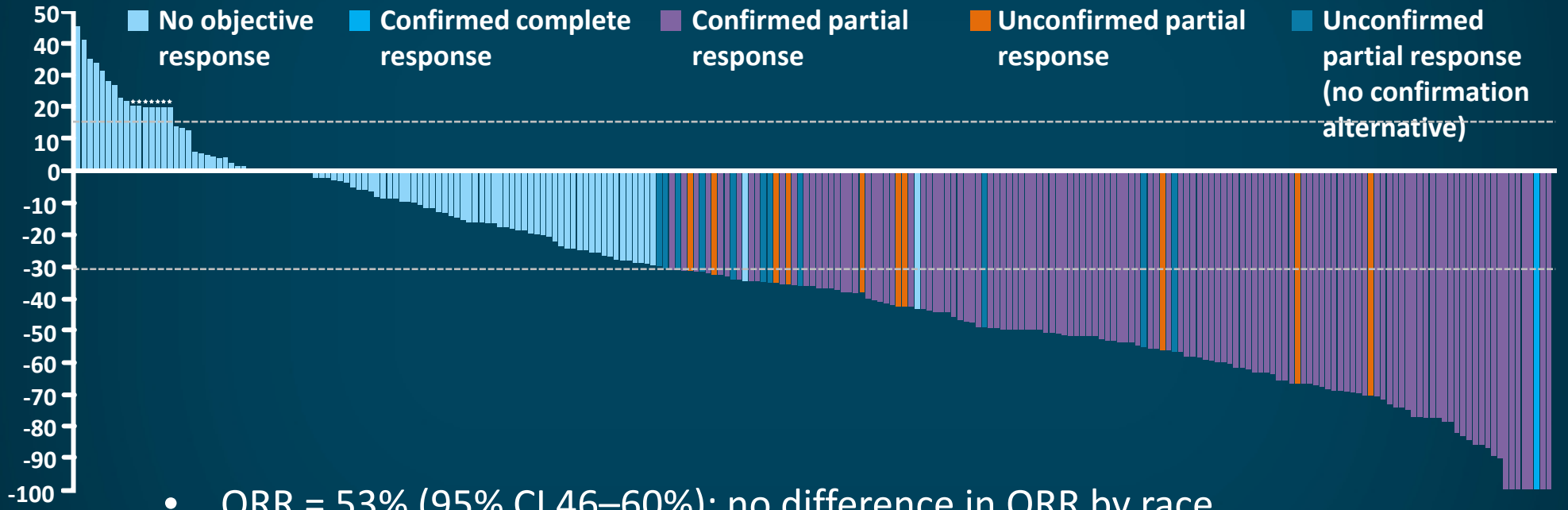
  - T790 (–) acquired resistance:
    - afatinib/C225 or chemotherapy (default);
    - No proven role for continuing EGFR TKI beyond PD along with subsequent chemo
- Continuation of original targeted therapy if disease progression is slow or "smoldering"
- Judicious use of local therapy for isolated areas of progression

Sequist LV et al. *Sci Transl Med.* 2011;3:75ra26. Pao W et al. *PLoS Med.* 2005;2:e73.

AZD9291: Response Rate* in Overall Population

T790 Acquired Resistance

Best percentage change from baseline in target lesion: all evaluable patients, escalation, and expansion (N = 205)



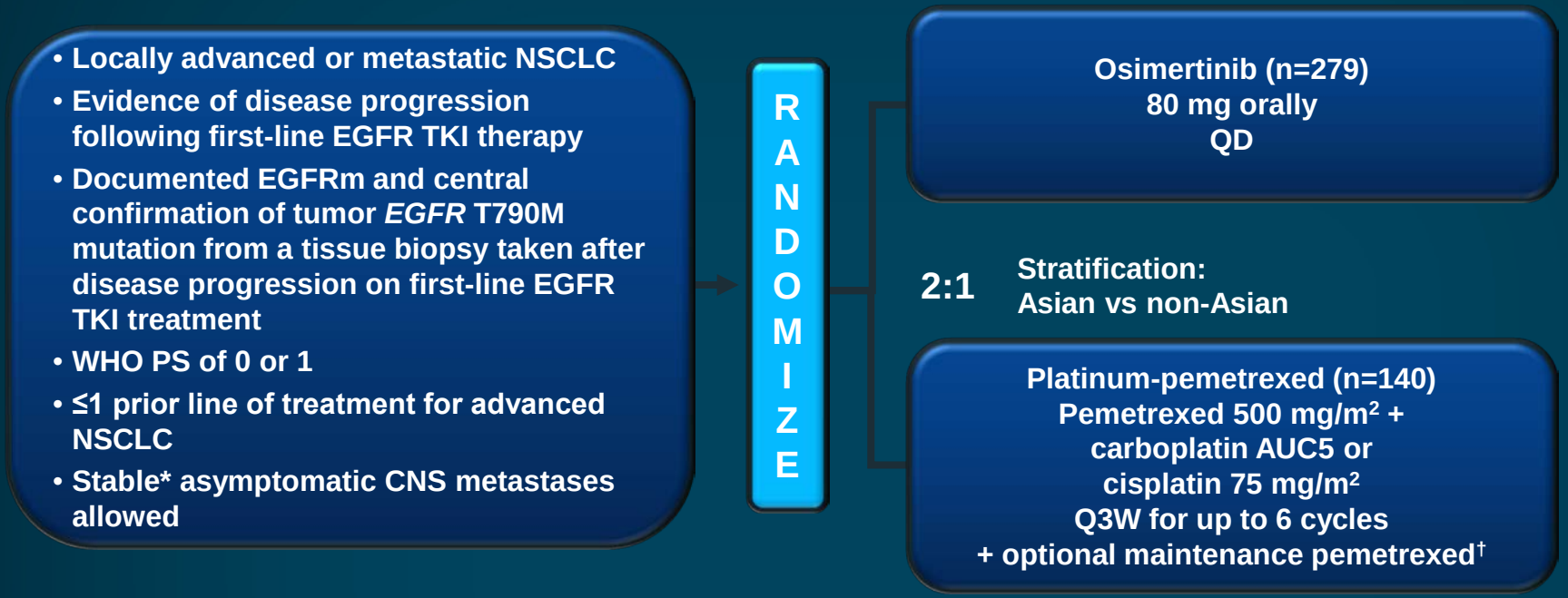
- ORR = 53% (95% CI 46–60%); no difference in ORR by race
- Overall disease control rate (CR+PR+SD) = 83% (95% CI 78–88%)
- PFS ~ 9.3 mos with 40% inc of rash and 47% inc of diarrhea, mostly gr 1/2

***Includes confirmed responses and responses awaiting confirmation.**

Population = all dosed patients with a baseline RECIST assessment and an evaluable response (CR, PR, SD, or PD).

Jänne PA et al. *New Engl J Med.* 2015;372:1689-1699.

AURA 3: Phase III Trial of Osimertinib vs Platinum-Pemetrexed in *EGFR* T790M-Positive NSCLC – Study Design

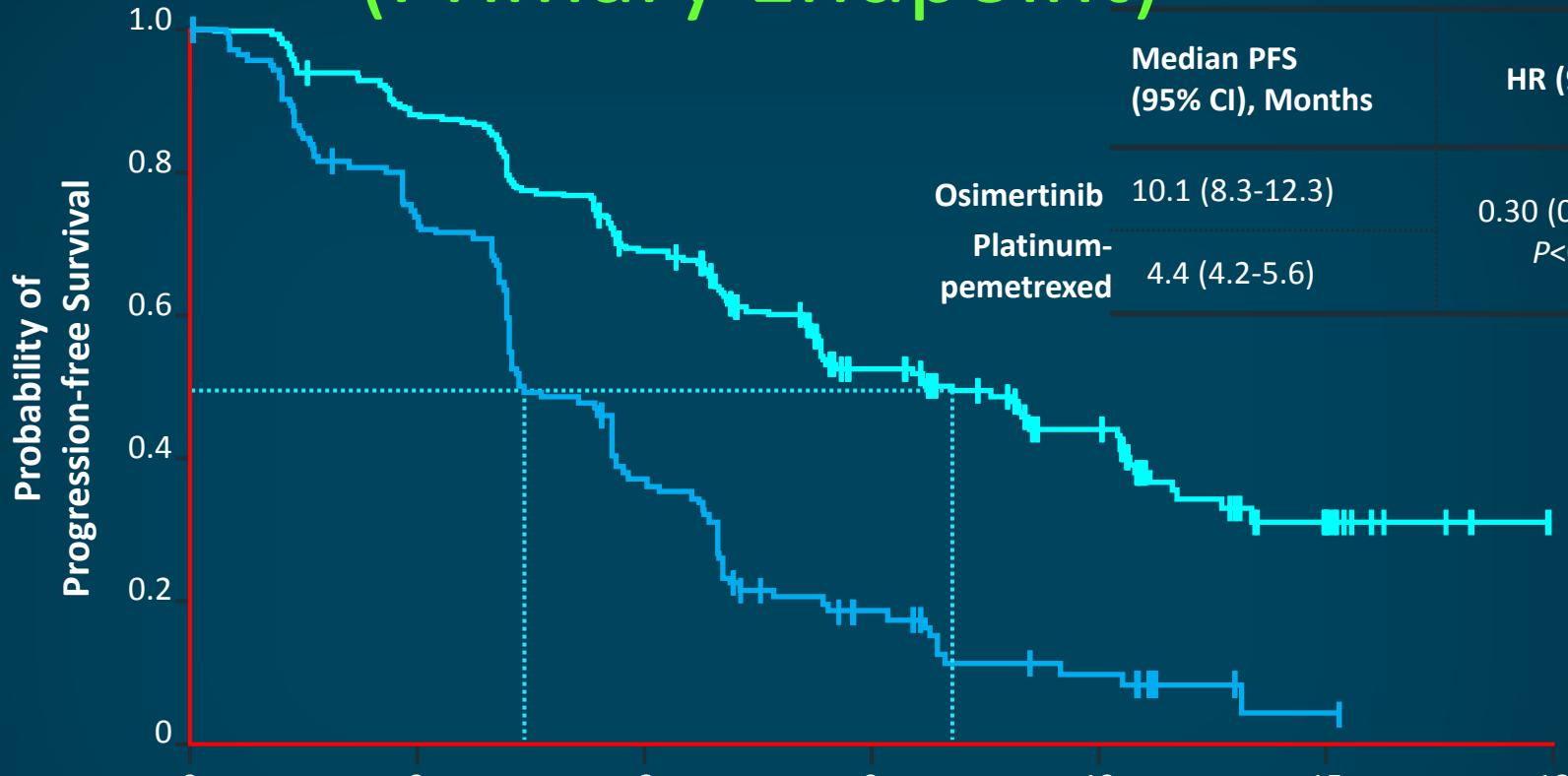


Primary endpoints: PFS by investigator assessment (RECISTv1.1)
Secondary endpoints: OS, ORR, DOR, DCR, tumor shrinkage, BICF-assessed PFS, PROs, safety, and tolerability

- RECISTv1.1 assessments performed every 6 weeks until objective disease progression; patients could receive study treatment beyond RECISTv1.1 defined progression as long as they experienced clinical benefit
- With 221 events of progression or death, the study would have 80% power to reject the null hypothesis of no significant difference in duration of PFS between the two treatment groups, assuming a treatment effect HR of 0.67 at 5% two-sided significance

*Defined as not requiring corticosteroids for 4 weeks prior to study treatment.
†For patients whose disease had not progressed after 4 cycles of platinum-pemetrexed.
Papadimitrakopoulou, et al. Presented at: WCLC. 2016 (abstr PL03.03).

AURA 3: PFS by Investigator Assessment (Primary Endpoint)



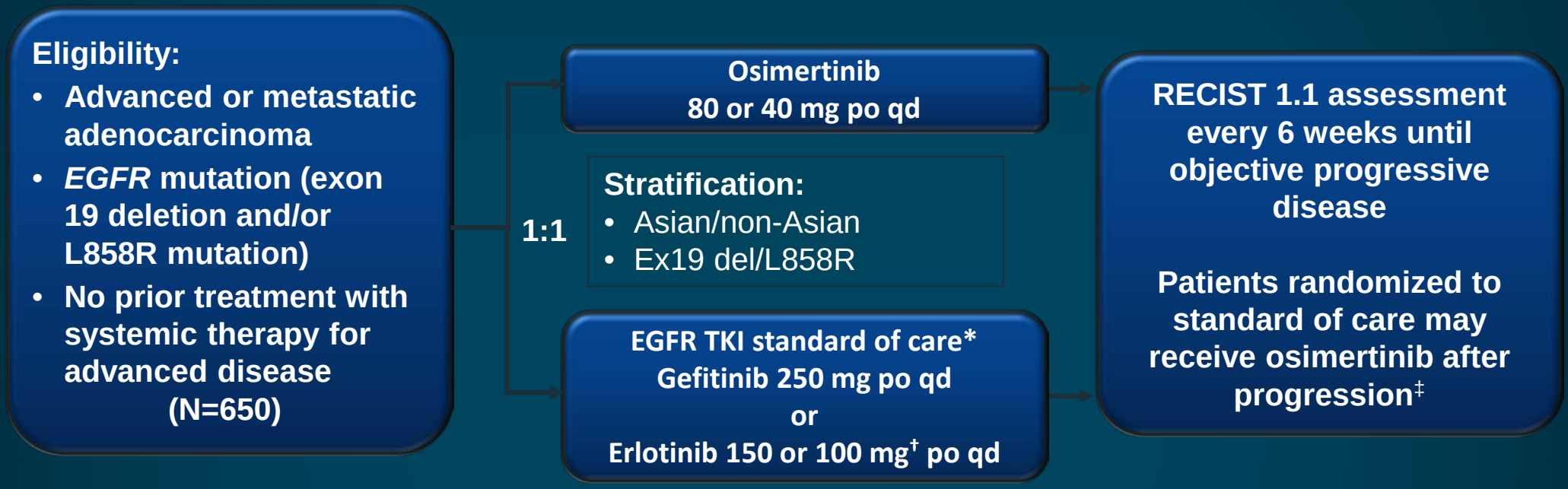
	Median PFS (95% CI), Months	HR (95% CI)
Osimertinib	10.1 (8.3-12.3)	0.30 (0.23-0.41) *P*<0.001
Platinum-pemetrexed	4.4 (4.2-5.6)	

Patients at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), *p*<0.001; median PFS 11.0 vs 4.2 months

Population: intent-to-treat.
Progression-free survival defined as time from randomization until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data.
Papadimitrakopoulou, et al. Presented at: WCLC. 2016 (abstr PL03.03).

FLAURA: Randomized, Phase III Trial of Osimertinib vs Gefitinib or Erlotinib in First-line *EGFR* Mutation–Positive NSCLC – Study Design



Primary endpoint: PFS

Secondary endpoints: ORR, PFS by T790M status, OS, PRO, HRQOL, DOR, DCR

Start date: December 2014.
Estimated primary completion date: May 2017.
*Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation. †100 mg only if dose reduction is required, per physician guidance. ‡Patients randomized to the standard of care treatment arm may receive open-label treatment with osimertinib on central confirmation of both objective disease progression and T790M-positive tumor.
Ramalingam S, et al. Presented at: ASCO. 2015 (abstr 8000). https://www.clinicaltrials.gov/ct2/show/NCT02296125. Accessed 07/26/16.

Case 1 (cont'd)

- 49 yo Asian-American Female never smoker presents with hemoptysis and DOE. CXR reveals multiple pulmonary nodules
- CT confirms a 6 cm L hilar mass as well as multiple 3-5 cm lesions in both lungs and a small L pleural effusion. CT A/P also shows multiple space-occupying lesions in the liver, spleen and kidneys.
- Bx of the liver returns (+) for adenoca
- What is the chance this patient will have an EGFR mutation?

1. 85-90%
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Case 1 (cont'd)

- EGFR mutation was detected in exon 19.
- Afatinib was started, with excellent PR lasting roughly 12 mos, at which point she developed recurrent DOE and streak hemoptysis.
- Scans, which had shown near cCR, demonstrated PD in liver and lung.
- Bx of the largest liver lesion confirmed T790, prompting switch to osimertinib.
- She enjoyed another response lasting ~ 8 mos, at which point her disease has "roared back."
- What do you do at this point?

1. Paclitaxel/Carboplatin/Bevacizumab
2. Pemetrexed/Carboplatin/Bevacizumab
3. Pemetrexed/Carboplatin
4. Resumption of 1st generation TKI
5. PD1 inhibitor

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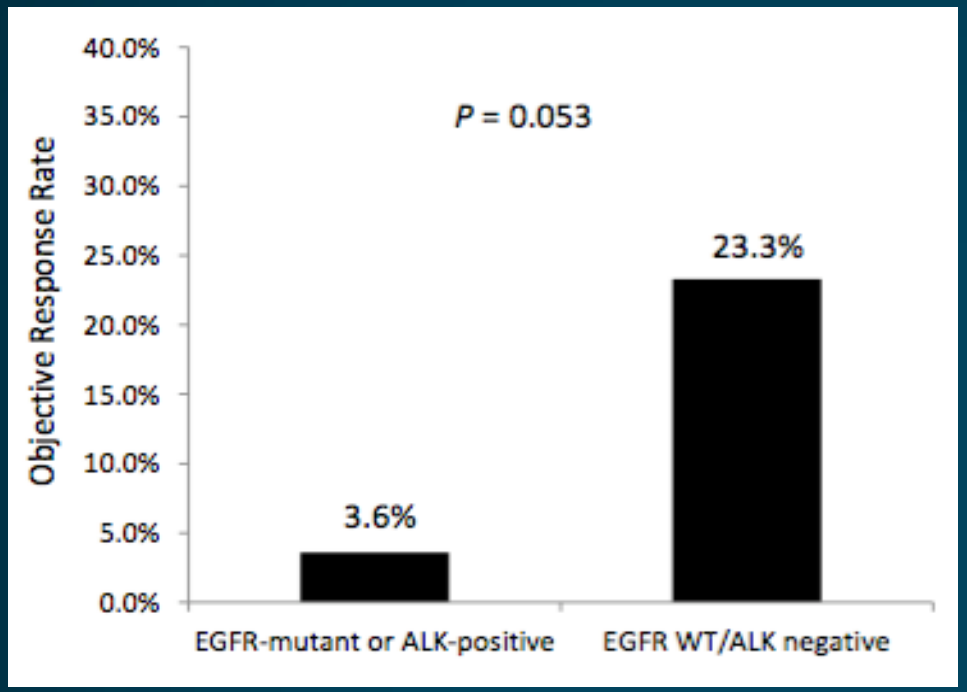
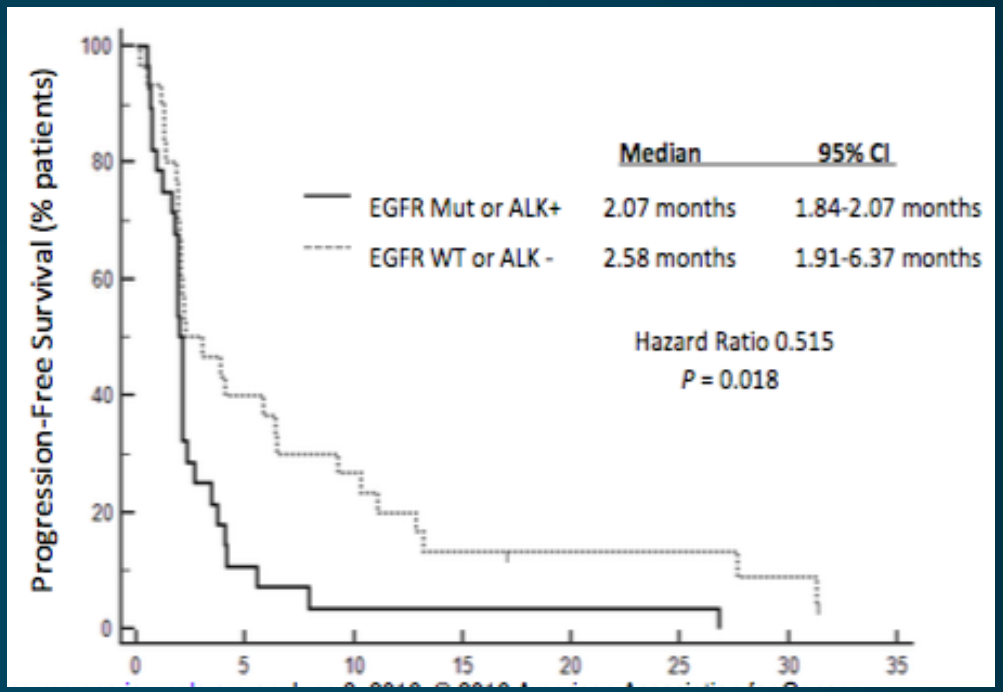
Could immunotherapy help?





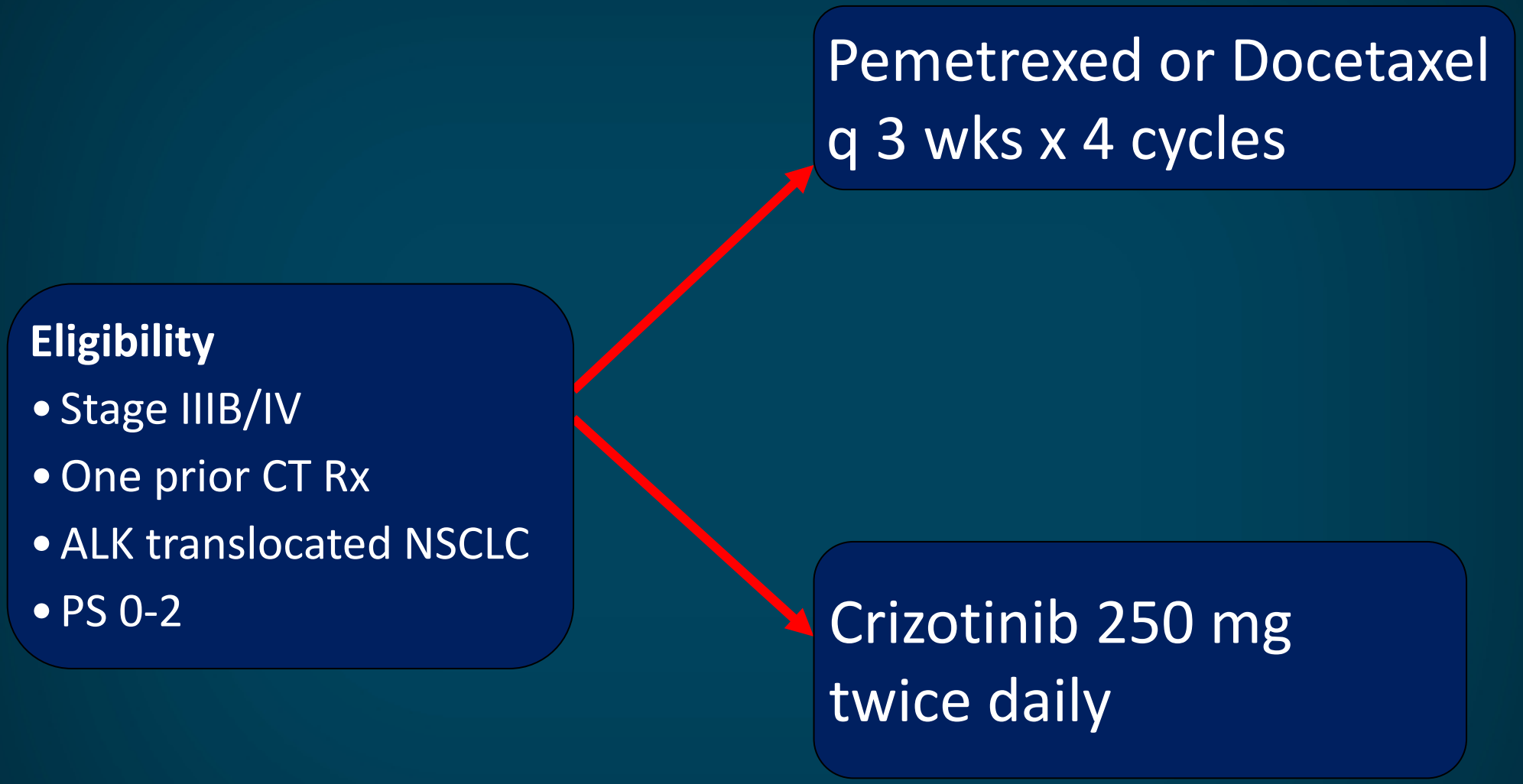
- Retrospective analysis of 28 EGFR/ALK NSCLC compared to 30 wild type
- ORR and PFS of immunotherapy is significantly worse in EGFR/ALK NSCLC

Gainor et al CCR 2016

ALK and ROS1 Translocations

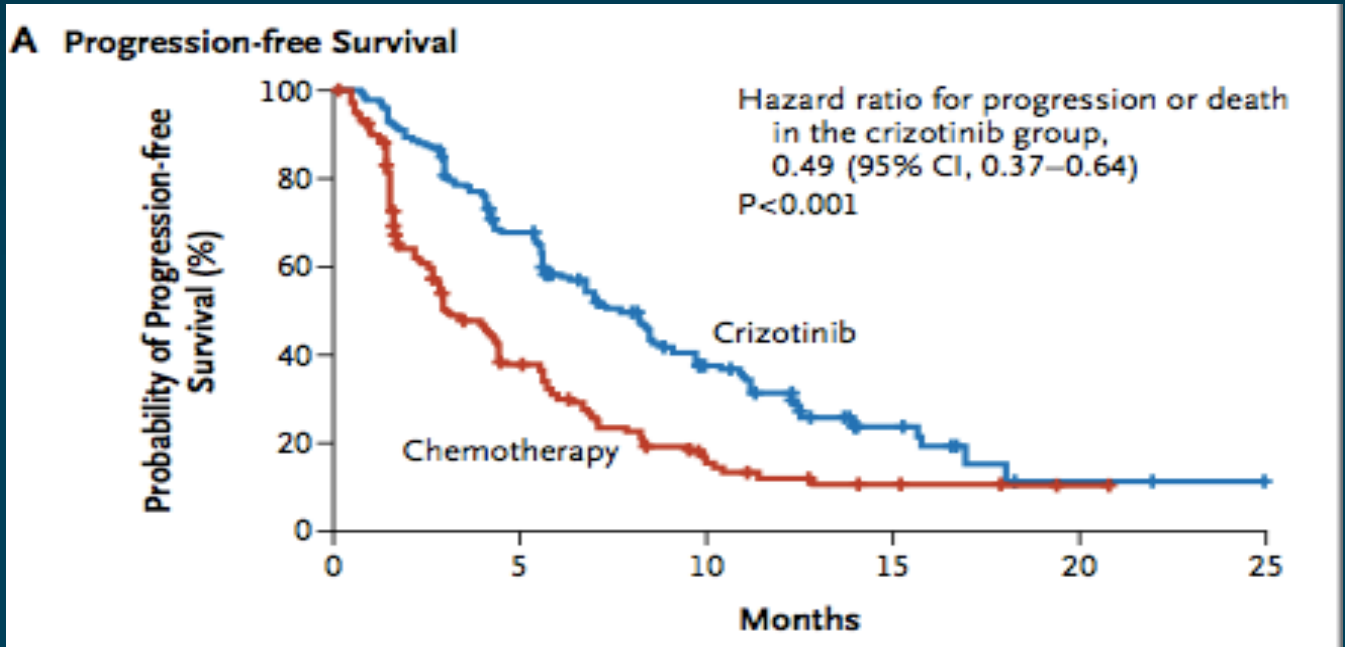
- ALK translocation seen 3-7% of all NSCLC
  - Younger patients
  - Never/light smokers
  - Signet ring cell adenocarcinoma
- ROS1 translocation seen 1-3% of all NSCLC
  - Young patients
  - Never/light smokers
  - Adenocarcinoma
- Significant homology in binding domains
- Diagnosed by break apart FISH in $\geq$ 15% of cells
  - Be alert when reading next gen sequencing
    - ALK Mutation is NOT ALK translocation
    - IHC is a screen; it dose not automatically equate FISH positivity

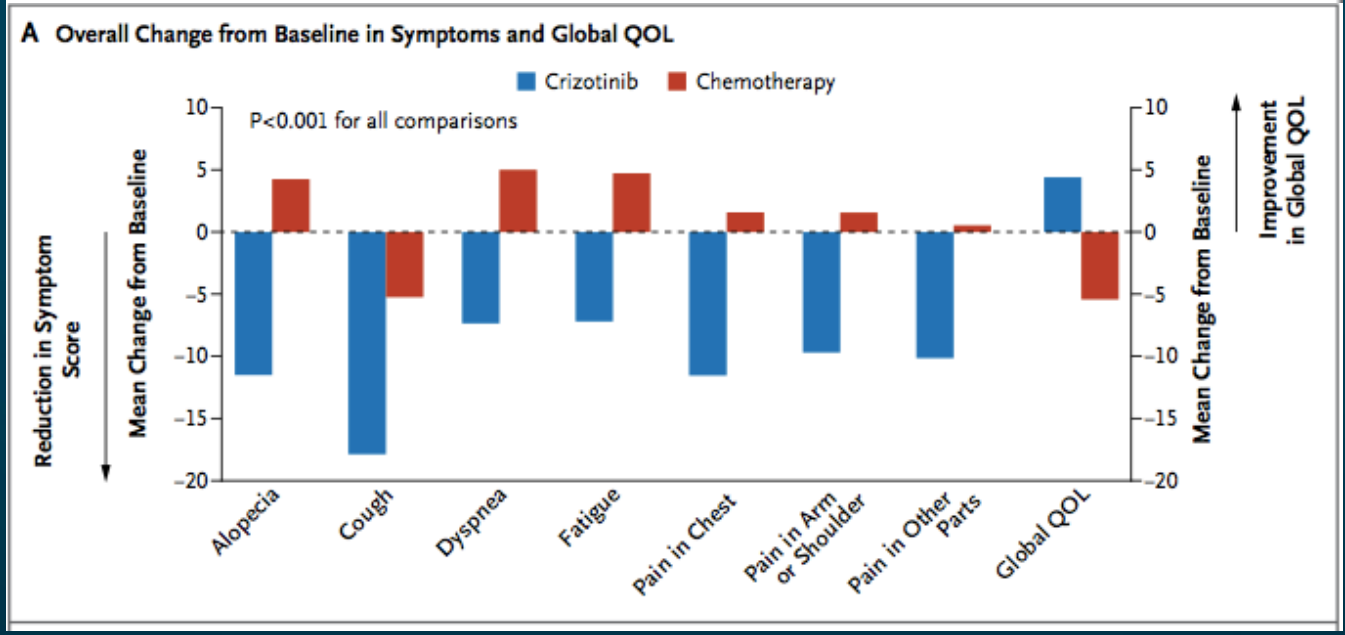
Phase III Study Crizotinib vs Chemotherapy



Shaw et al NEJM 2013

Crizotinib vs chemotherapy results

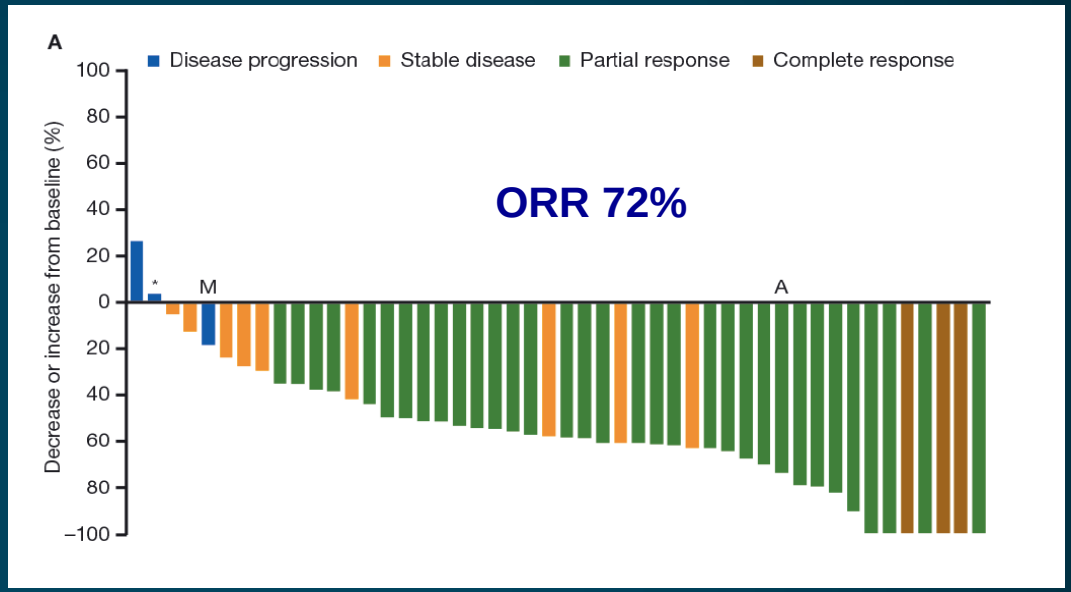




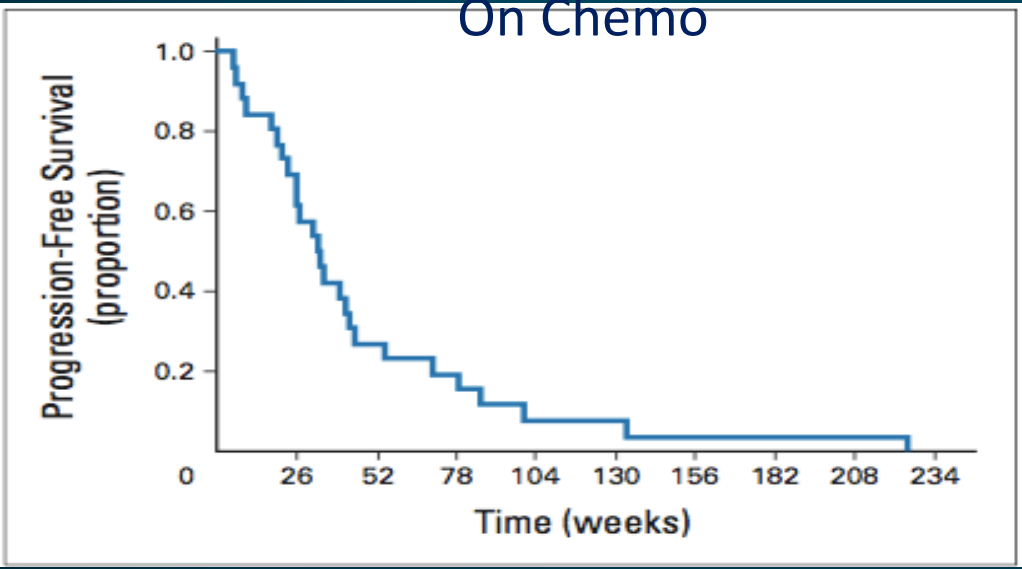
Shaw et al NEJM 2013

Crizotinib in ROS1 translocated NSCLC

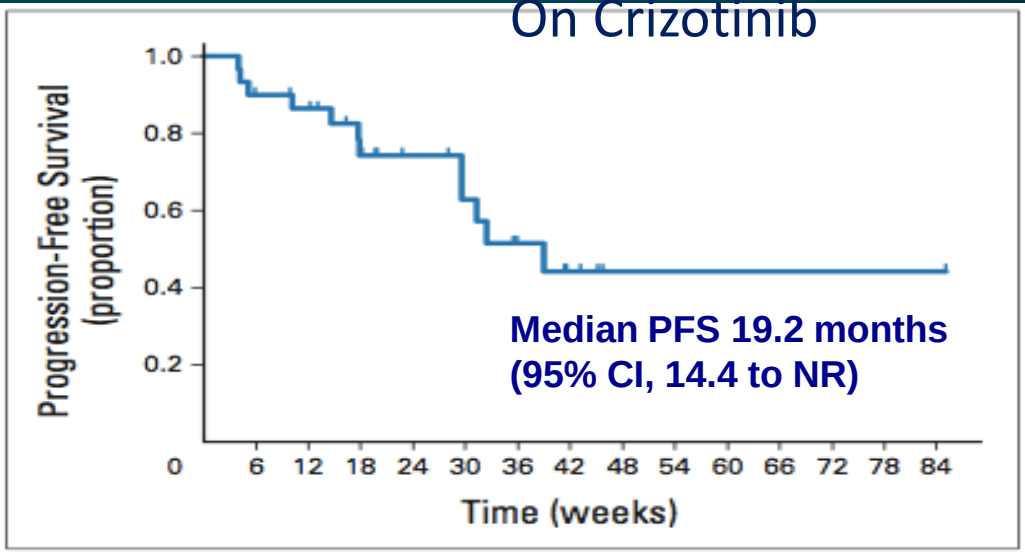
- No RCTs evaluating crizotinib in ROS1 because the incidence is very rare
- Frequent limitation we encounter with precision medicine in low incidence “drivers.”



On Chemo



On Crizotinib



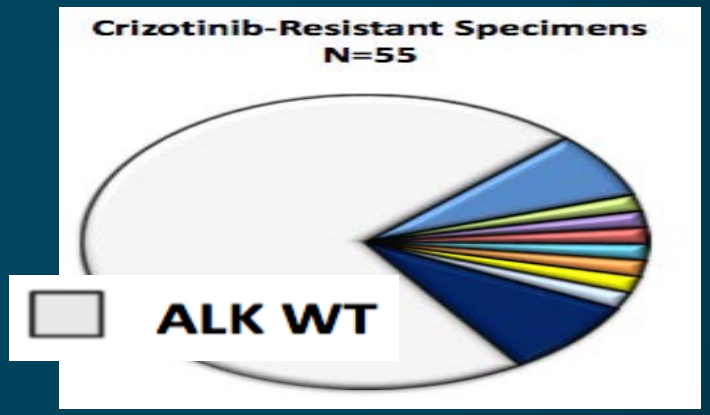
Mazieres et al JCO 2015

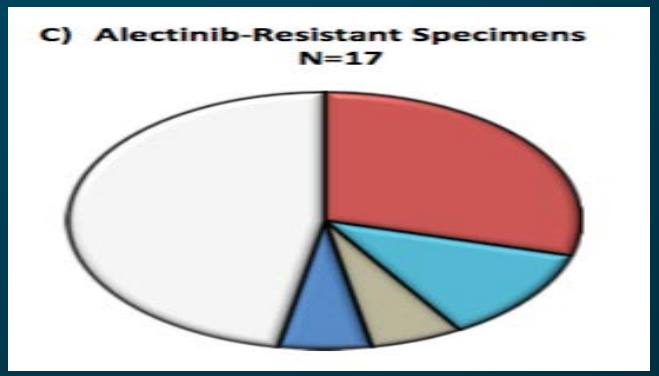
Shaw et al. NEJM 371(21): 1963-71, 2014

Resistance to ALK TKI therapy

- ALK Resistance is more complex
  - Dependent upon TKI used
  - ALK mutations are not as common a resistance mechanism c/w T790 in pts with EGFR mutations

ALK Resistance Mutations[a]	Crizotinib (N=55)	Ceritinib (N=24)	Alectinib (N=17)	Brigatinib (N=7)
1151Tins	2%	0%	0%	0%
C1156Y	2%	8%	0%	0%
I1171T/N/S	2%	4%	12%	0%
F1174L/C	0%	17%	0%	0%
V1180L	0%	4%	6%	0%
L1196M	7%	8%	6%	0%
G1202R	2%	21%	29%	43%
G1202del	0%	8%	0%	0%
D1203N	0%	4%	0%	14%
S1206Y/C	2%	0%	0%	14%
E1210K	2%	0%	0%	29%
G1269A	4%	0%	0%	0%
ALK Mutations[b]	**20%**	**54%**	**53%**	**71%**





Gainor et al Cancer Discovery 2016

Subsequent ALK Therapy Choices)

Cellular ALK Phosphorylation Mean IC50 (nM)					
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4-ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

Gainor et al Cancer Discovery 2016

Second Generation ALK inhibitors

	Ceritinib[1] N= 163	Alectinib[2] N=138	Brigatinib[3] N = 110
Design/ Assessment	Phase I/II Investigator/BIRC	Phase 2 BIRC	Phase 2 Investigator
PS 2	12%	9%	8%
Brain Mets	60%	61%	67%
Previous Rx	56% (≥ 3 prior)	80% (≥ 2 prior)	74% (≥ 2 prior)
ORR	56% (49-64)	50% (41 – 59)	54% (43-65)
CNS Response	36%* N = 28	57% N = 35	67% N = 12
Median PFS	6.9 m (5.6 – 8.7)	8.9 (5.6-11.3)	12.9 (11.1- NR)

* Retrospective Assessment

1. Kim,Lancet Oncol,2016
2. Ou, JCO 2016
3. Kim, ASCO 2016

J-ALEX

Primary Endpoint: PFS by IRF (ITT Population)

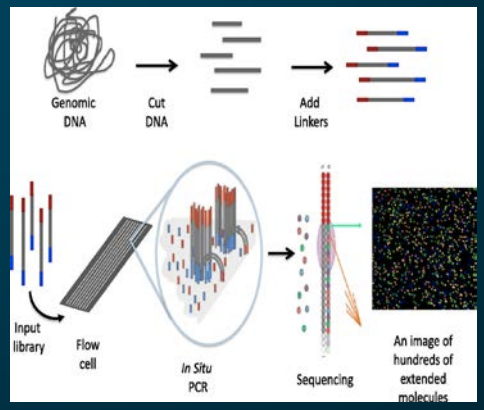
	Alectinib (N=103)	Crizotinib (N=104)
Events, n (%)	25 (24.3%)	58 (55.8%)
Median, mo [95% CI]	NR [20.3 - NR]	10.2 [8.2 - 12.0]
P-value	<0.0001	
HR [99.6826% CI]	**0.34 [0.17 - 0.71]**	

What about other molecular targets?

- Current standard of care is to perform EGFR, ALK and ROS1 analyses
- This ignores 10% of patients with other potentially actionable mutations or molecular aberrations
  - Other more obscure EGFR mutations
  - CMET mutations (and amplification)
  - BRAF V600
  - NTRK
  - HER2 (exon 20)
  - Others
- Can we do better for these patients??
- Potential role for NGS

Principles of molecular management

- All adenocarcinomas regardless of smoking hx
- All never smokers or minimal remote smokers regardless of histology should be tested
  - Do not exclude based upon risk factors
  - EGFR, ALK, ROS1 certainly, but add others
- Next generation sequencing alters the paradigm
  - Massive parallel sequencing
  - Identify multiple mutations, with limited samples
  - Can gauge tumor mutation burden (TMB)
  - Liability: Tx delays; complex bioinformatics
- Need to be careful about panels used
  - Not all capture translocations

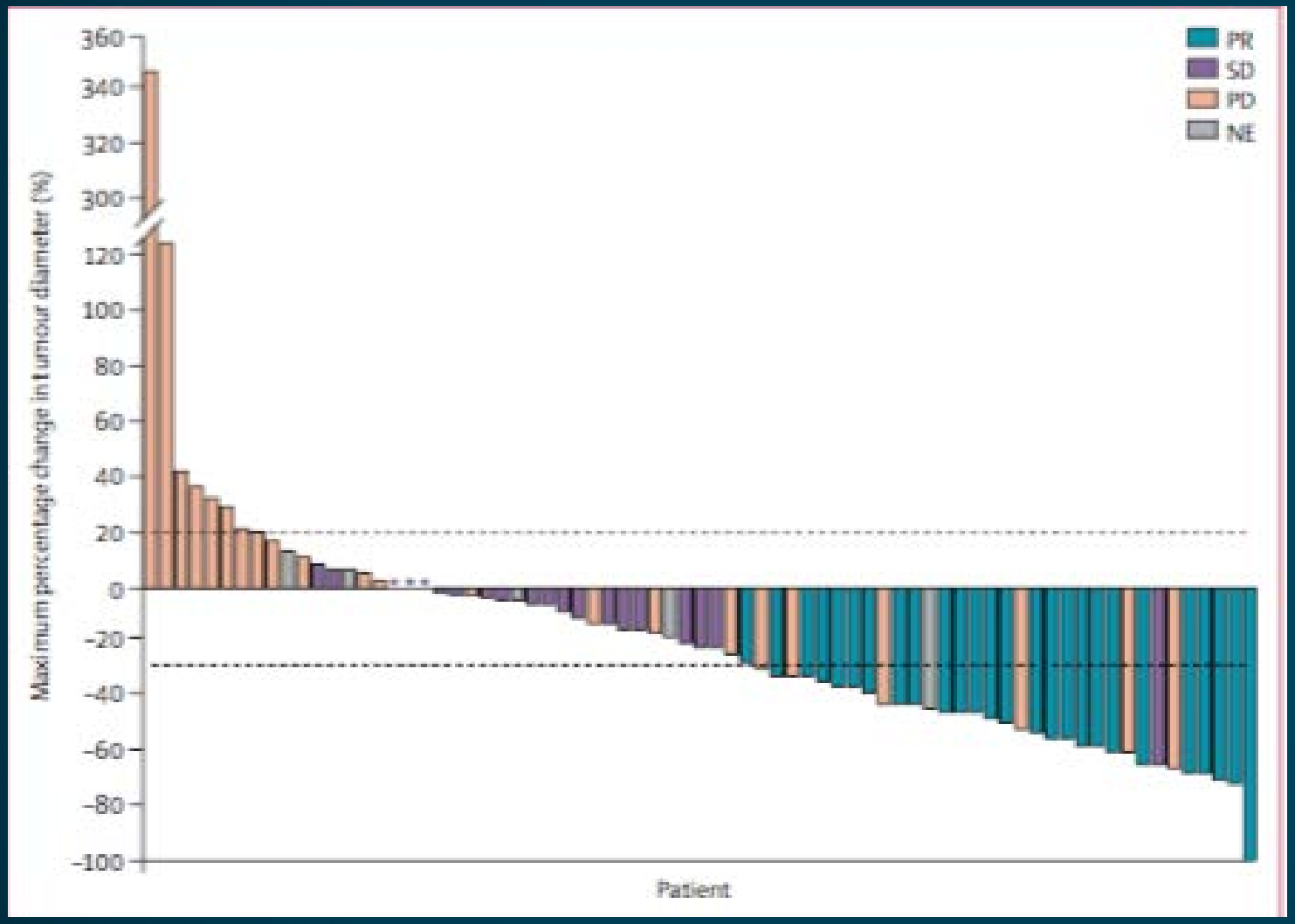


BRAF Mutations in NSCLC

- 1-3% lung cancers
- 56.8% occur in V600E (activating mutation) compared to 80% in melanoma
- Poorer prognosis:
  - decreased PFS and OS
  - Higher likelihood of former/current smokers
- Dabrafenib in melanoma:
  - 53% ORR; 8.8 months PFS
- Dabrafenib/Trametinib in melanoma
  - 69% ORR; 11 months PFS

Long et al Lancet 2015
Marchetti et al JCO 2011

Dabrafenib in BRAF V600E NSCLC



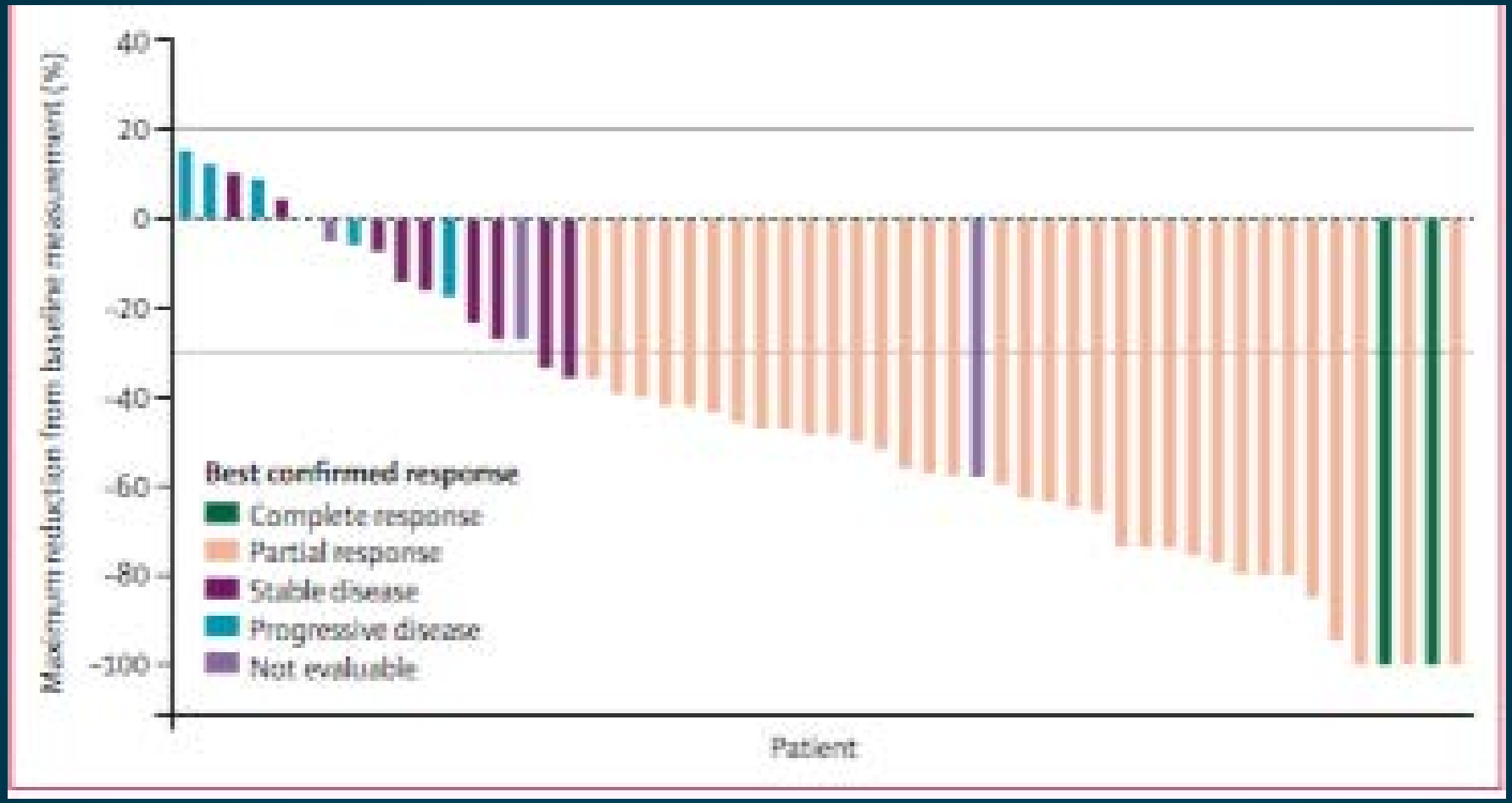
ORR: 33% (1 CR)
PFS: 5.5 months
DOR: 9.9 months

Toxicities:

- Skin Cancers 17%
- Gr 3 Fatigue 5%
- Fevers 11%

Planchard et al Lancet Oncology 2016

Dabrafenib/Trametinib in BRAF V600E NSCLC



- ORR: 63.2% (2 CR)
- DOR: 9 months
- PFS: 8.6 months

- Gr >3 AE 49%
- Anorexia 30% (Gr1-2)

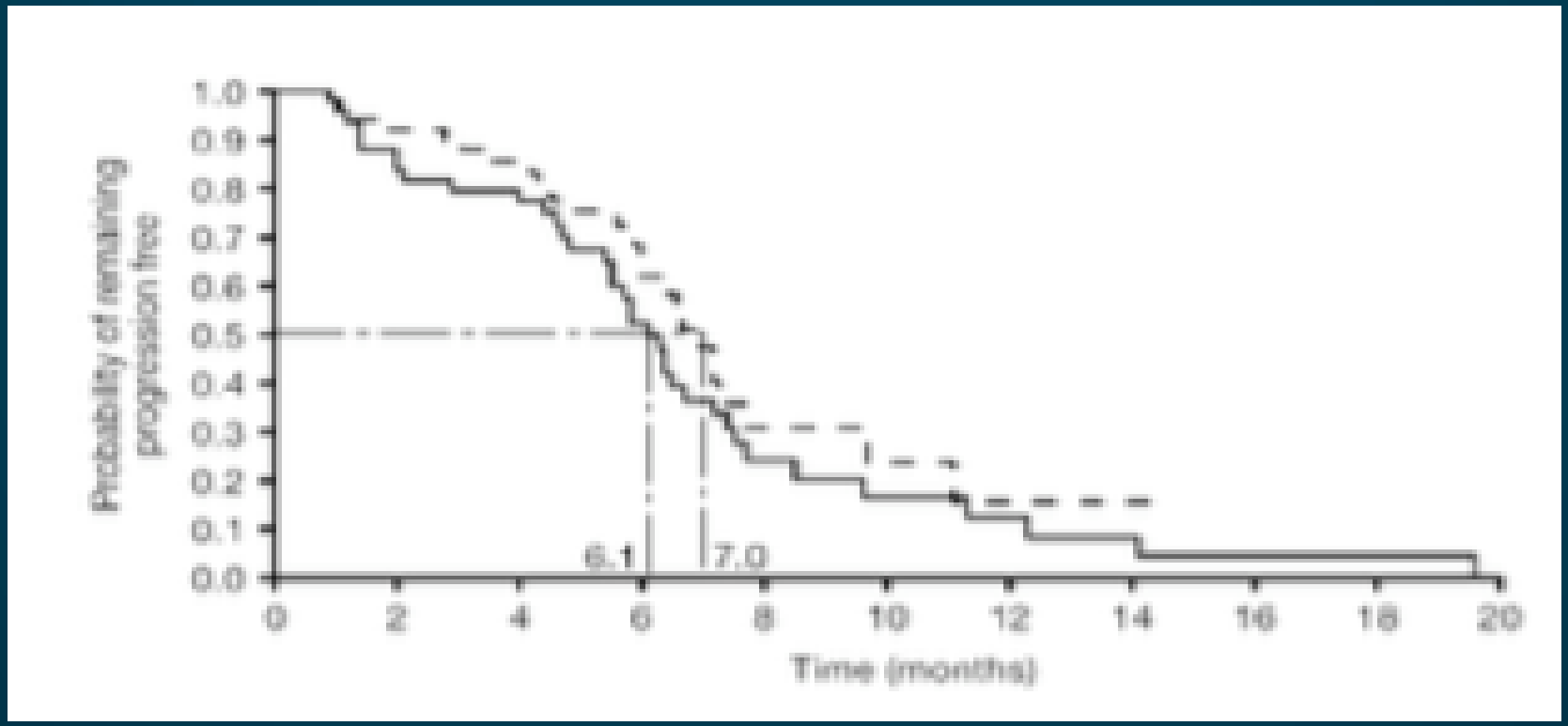
Planchard et al Lancet Oncology 2016

HER2 Driven NSCLC

- HER2 can be both amplified and mutated in NSCLC
  - Overexpression 59% NSCLC
    - 2-3+ up to 30%
  - Mutation rate: 1.7% of adenocarcinomas
    - Mostly Exon 20 In-frame insertions
- HER2 directed therapies are central in the treatment of HER2 amplified breast cancer
  - Trastuzumab
  - Ado-trastuzumab emtansine
  - Lapatinib
  - Pertuzumab
  - Afatinib

Trastuzumab + Chemotherapy in NSCLC

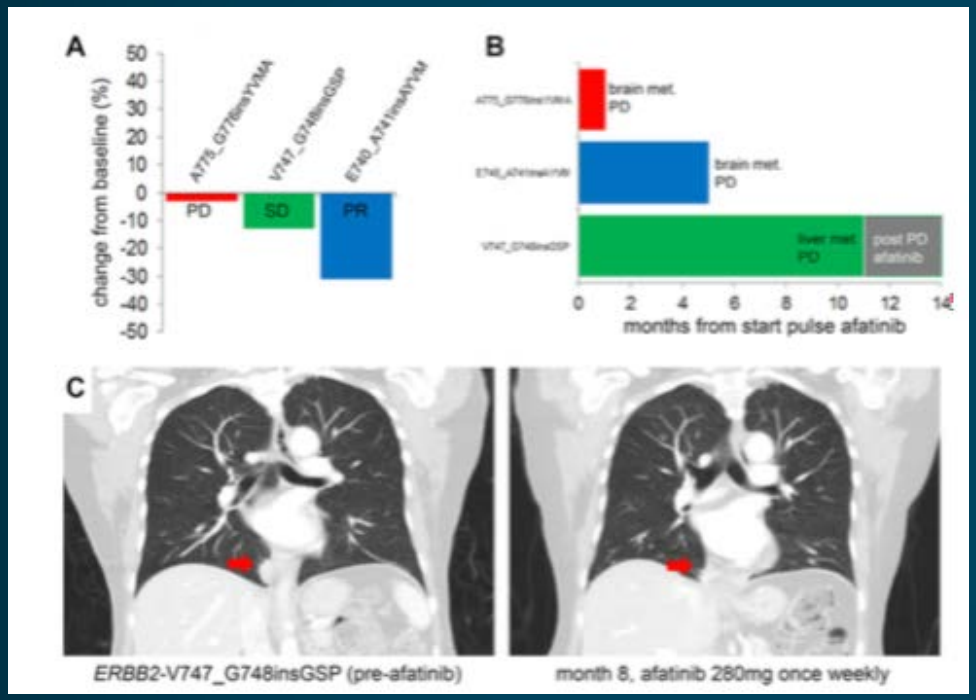
- Randomized Phase II of HER2 Positive NSCLC
  - Cisplatin and Gemcitabine with or without Trastuzumab



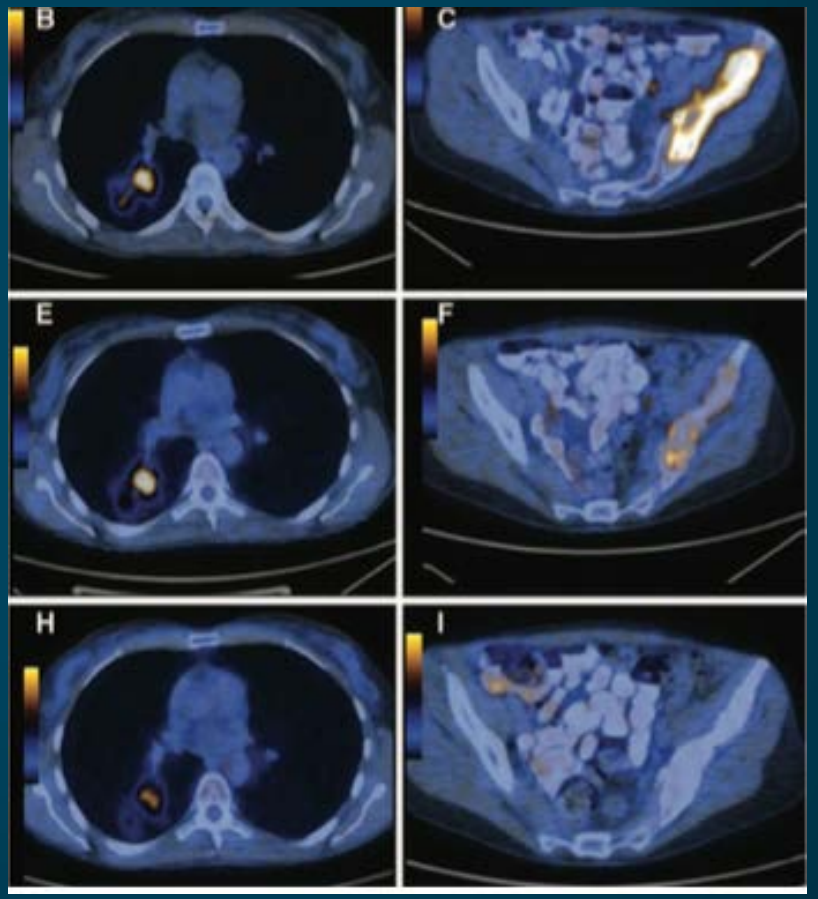
Gatzemeier et al Annals of Oncology 2004

Novel HER2 Targeting Approaches

Pulse Afatinib for HER2 Mutation



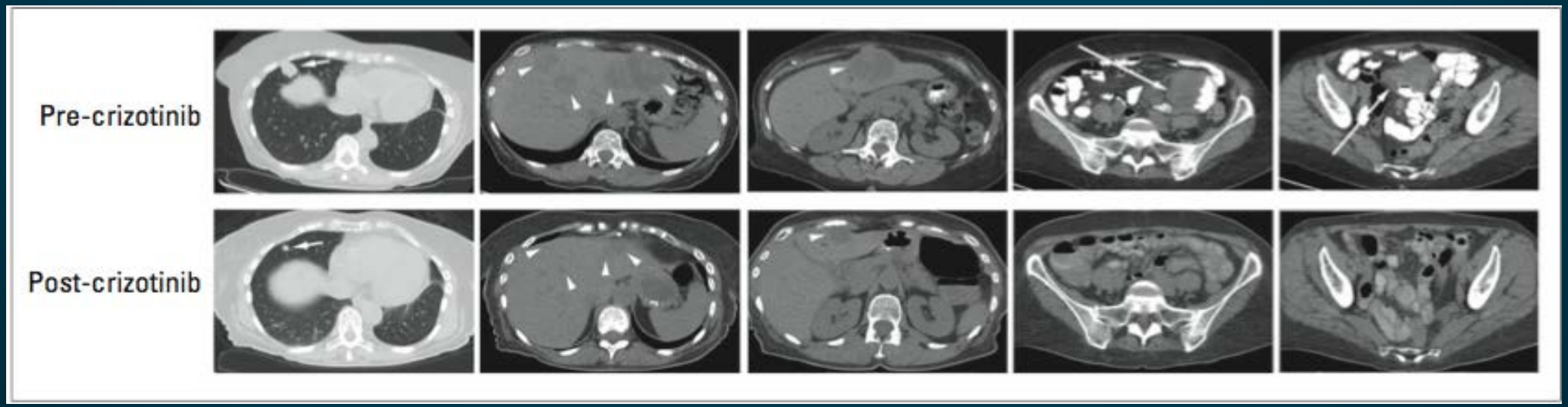
T-DM1 for HER2 Mutation and Amplification



Costa et al JTO 2016
Weiler et al JTO 2015

MET mutation in NSCLC

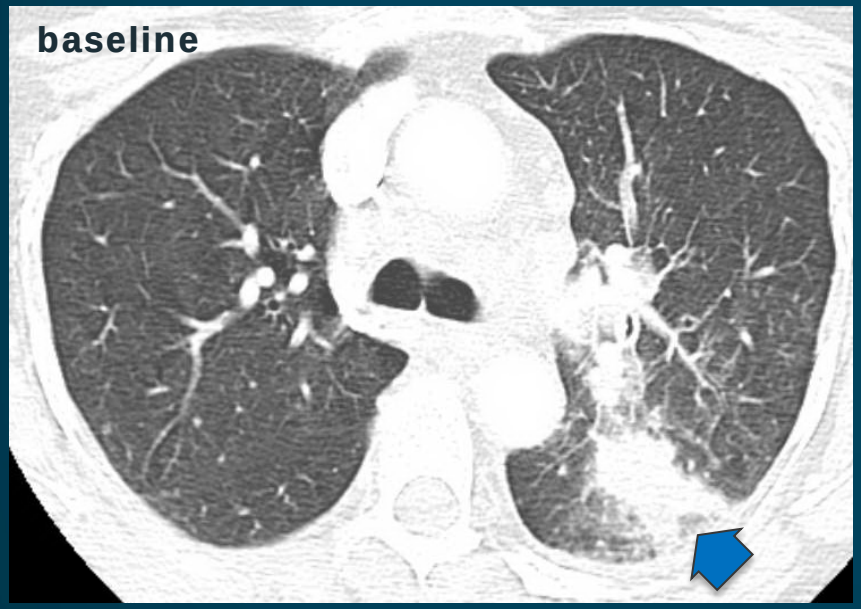
- MET mutation is rare in “typical” NSCLC (~2-3%)
- Recent data shows up to 22% of sarcomatoid NSCLC has MET exon 14 mutation
- Sarcomatoid lung cancer has a very poor prognosis
  - Highly resistant to chemotherapy
  - Unclear if we should be adopt NSCLC or sarcoma style regimens
  - Sensitive to crizotinib

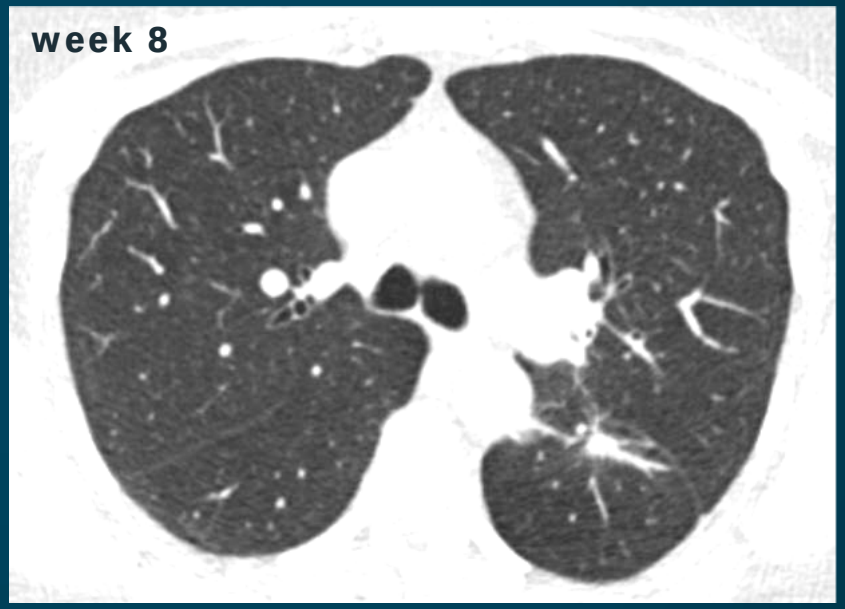


Liu et al JCO 2015

Antitumor Activity of Crizotinib in MET mt (+) NSCLC

- 54 year-old female with *MET* exon 14-altered lung adenocarcinoma
  - metastatic disease involving lung and lymph nodes, treatment-naive
  - confirmed partial response with crizotinib (-48%), ongoing at 5+ months*



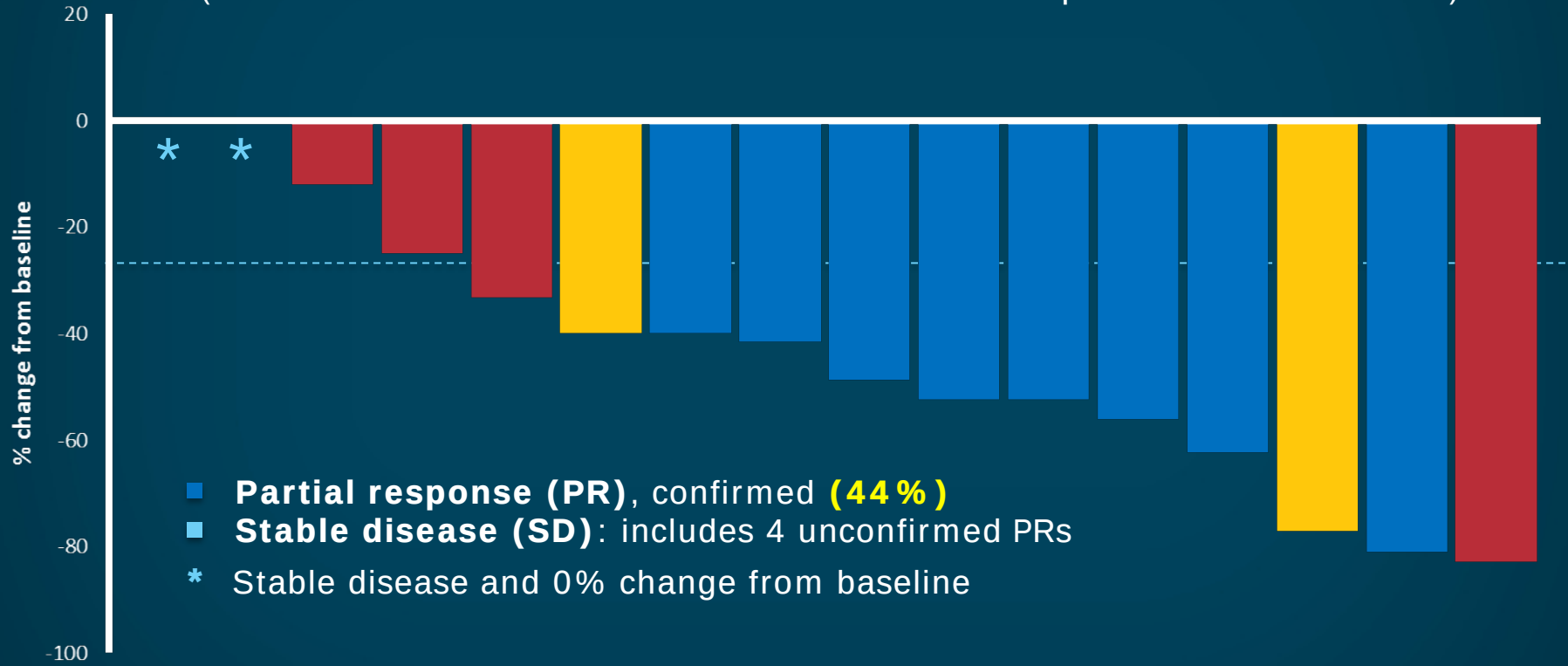


*response duration as of May 2016, Images courtesy of Ross Camidge, University of Colorado Cancer Center

Presented by: **Alexander Drilon MD**

Antitumor Activity of Crizotinib in MET mt (+) NSCLC

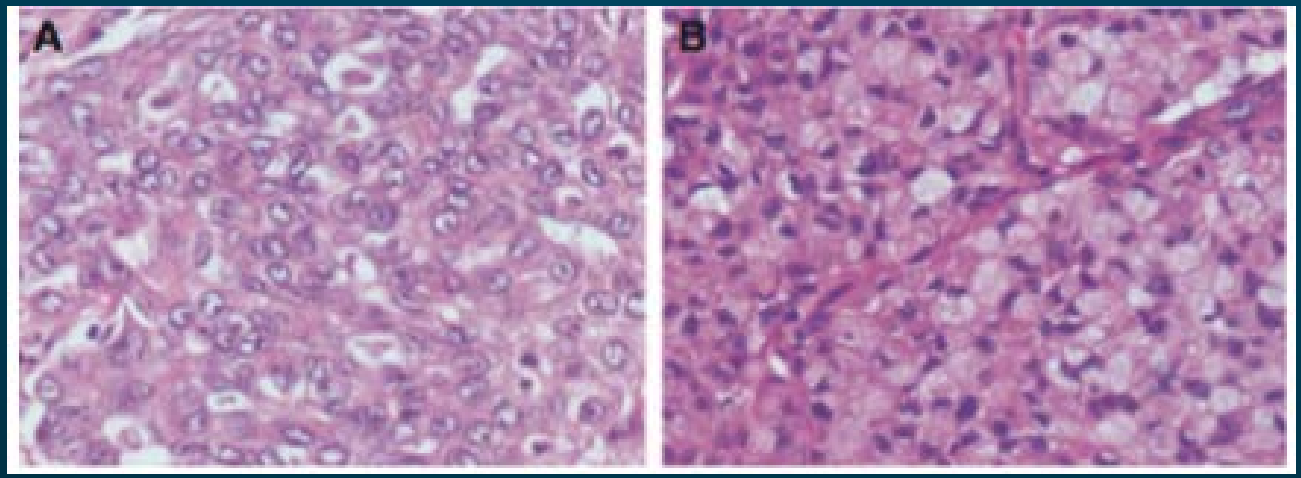
Maximum Response to Crizotinib in Patients with *MET* Exon 14-Altered Lung Cancers
(n=16 with measurable disease at baseline and ≥1 response assessment scan)



Presented by: **Alexander Drilon MD**
ASCO 2016

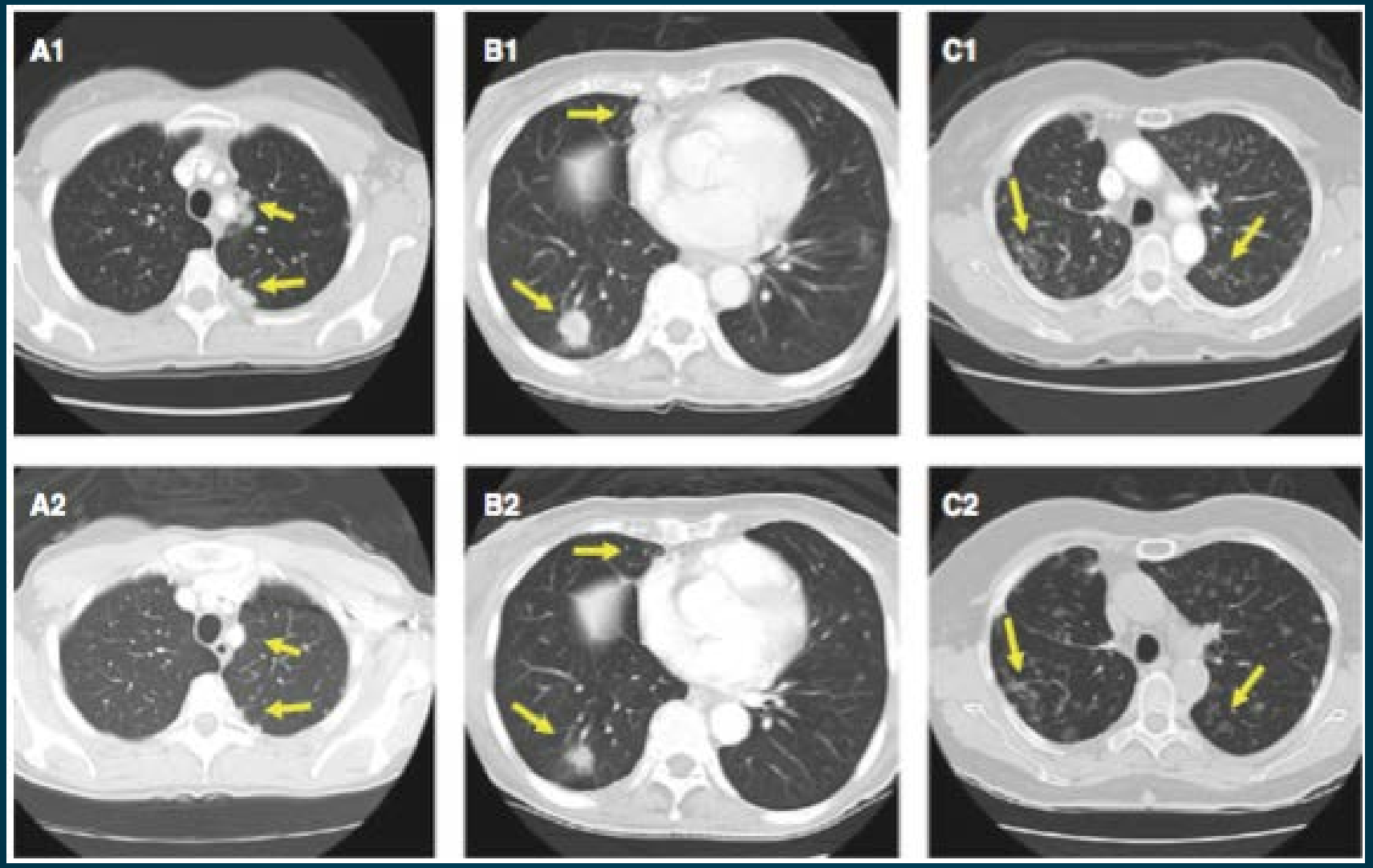
RET Translocation in NSCLC

- Mutations are associated with MTC
- Fusions present in papillary thyroid cancer and NSCLC
- Present in 1.7% of adenocarcinomas
  - Younger, never smokers, more poorly differentiated
- KIF5B is most common partner
  - CCDC6 and NCOA4 can also partner
- Solid and signet ring cell histologies most common



Wang et al JCO 2012

Cabozantinib in RET Rearranged NSCLC



Drilon et al Cancer Discovery 2013

RET Inhibitors—Efficacy Summary

Agent	RET testing	n	ORR (%)	PFS (months)	OS (months)
Cabozantinib (Drilon, ASCO 2015)	FISH/NGS	Stage I, 16	38	7	10
Cabozantinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	13	31	3.6	4.9
Vandetanib (Sato, ASCO 2016)	FISH/RT-PCR	19/17	47/53	4.7	47% 1-year
Vandetanib (Lee, ASCO 2016)	FISH confirmed	18	17	4.5	11.6
Vandetanib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	11	18	2.9	10.2
Sunitinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	9	22	2.2	6.8
Any RET inhibitor (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	41	23	2.9	6.8

Are there alternatives to being tissue-centric?

- Repeated assessments are increasingly critical for these tumors
  - Biopsies are not popular with patients or providers
    - Risk of adverse events
    - Painful
    - Scheduling can be complex
    - Tissue accessibility is an issue
- Tissue biopsies are considered the “gold standard” but should they be?
  - At diagnosis, tumors with targetable mutations are quite homogenous
  - Resistance, when it occurs, is often heterogeneous
    - T790M rarely develops in brain metastases
    - Oligoprogression is a real issue

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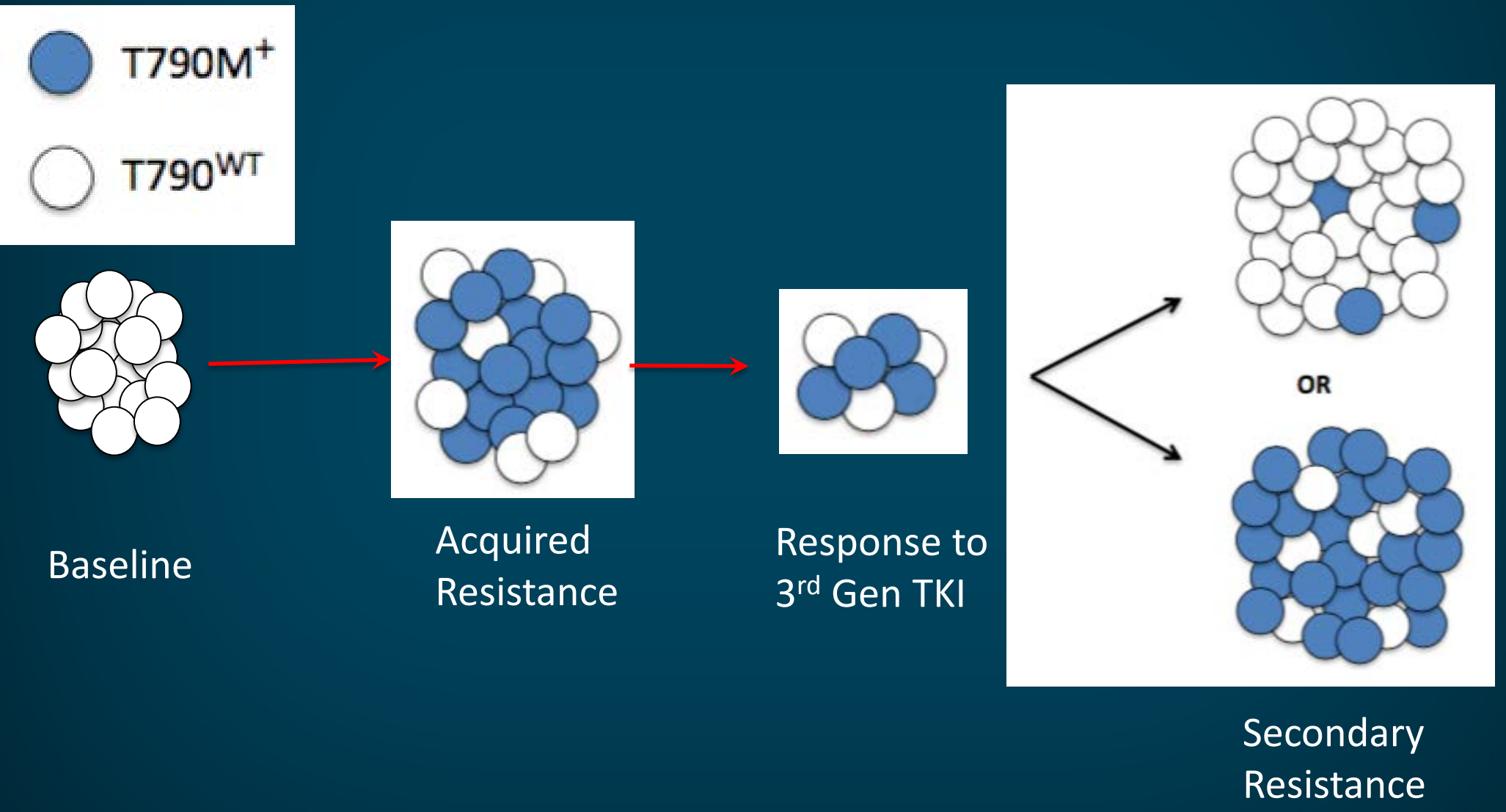
    - T790M rarely develops in brain metastases
    - Oligoprogression is a real issue
- **Can “Liquid Bx” substitute?**

Resistance Heterogeneity in EGFR (+) NSCLC

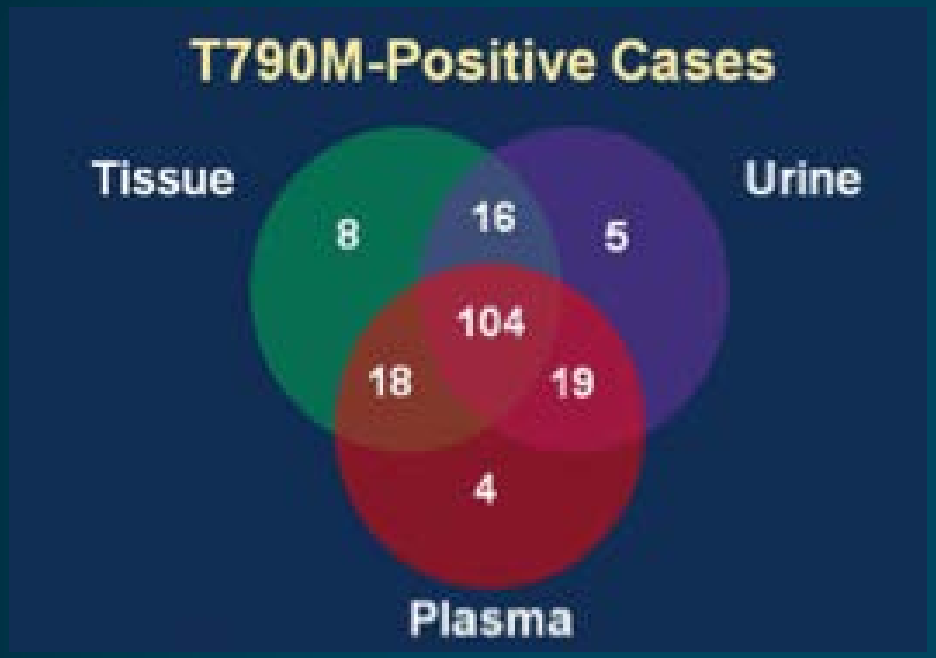


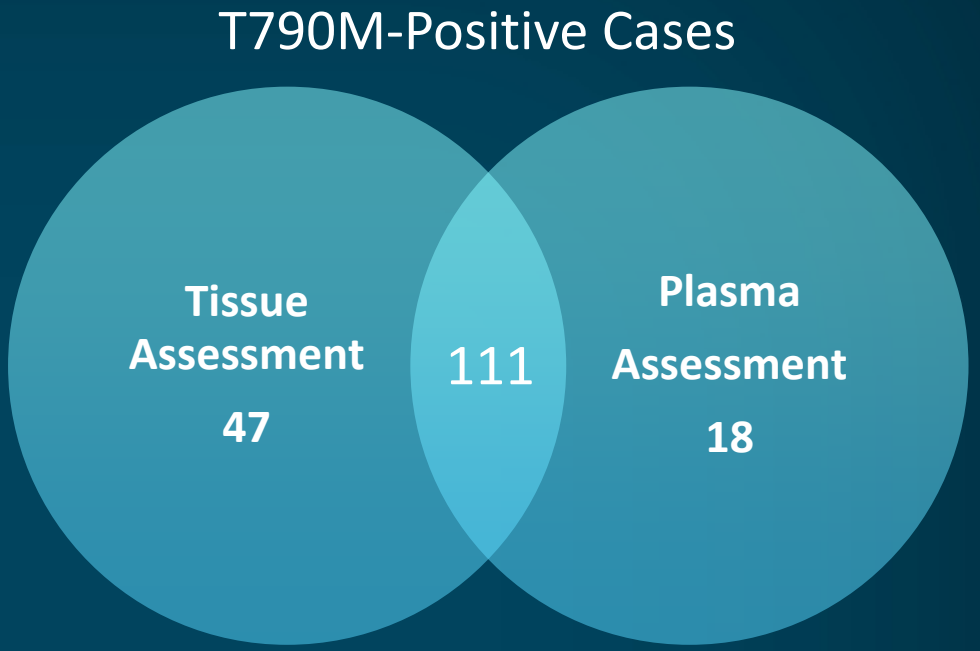
Piotrowska et al Cancer Discovery 2015

Plasma and Urine Testing

- Cell-free DNA can be detected in both plasma and urine
- Given rapid tumor growth and cellular turnover c/w normal tissue, the bulk of this is likely tumor related
- Multiple commercial and academic laboratories have developed so-called “liquid biopsies”
- Theoretically appealing
  - Minimally invasive; turn-around is faster c/w bx
  - Potential for serial testing
  - Can compensate for “tumor heterogeneity”
- Panels can be targeted or contain comprehensive NGS

Sensitivity of Testing for T790M



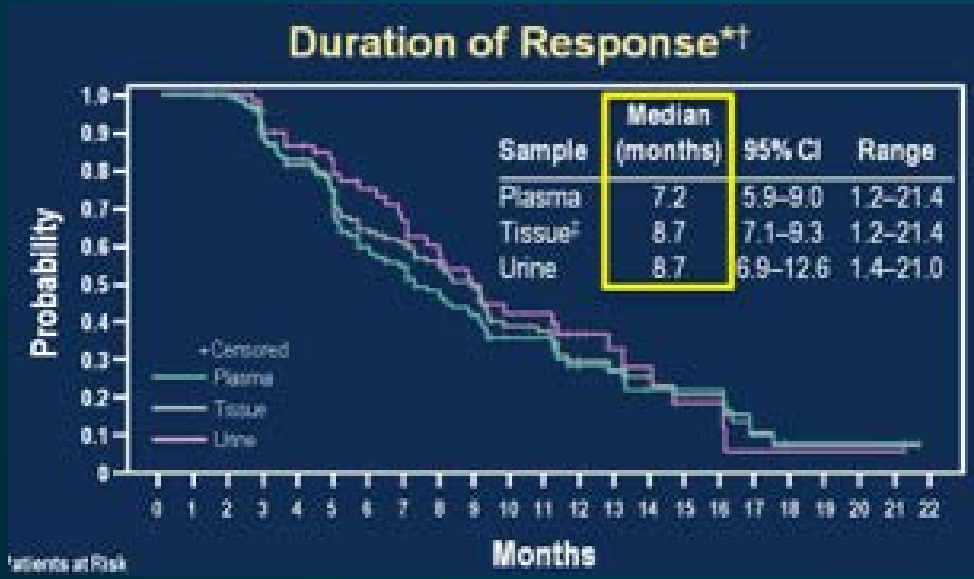


- The majority of patients who are positive are positive by all methods
  - Plasma "sensitivity" ranges from 70.3%-80.9%
  - Urine Sensitivity 81%
  - Specificity generally higher
- Higher rates in patients with distant metastases

Wakelee et al ASCO 2016
Oxnard et al JCO 2016

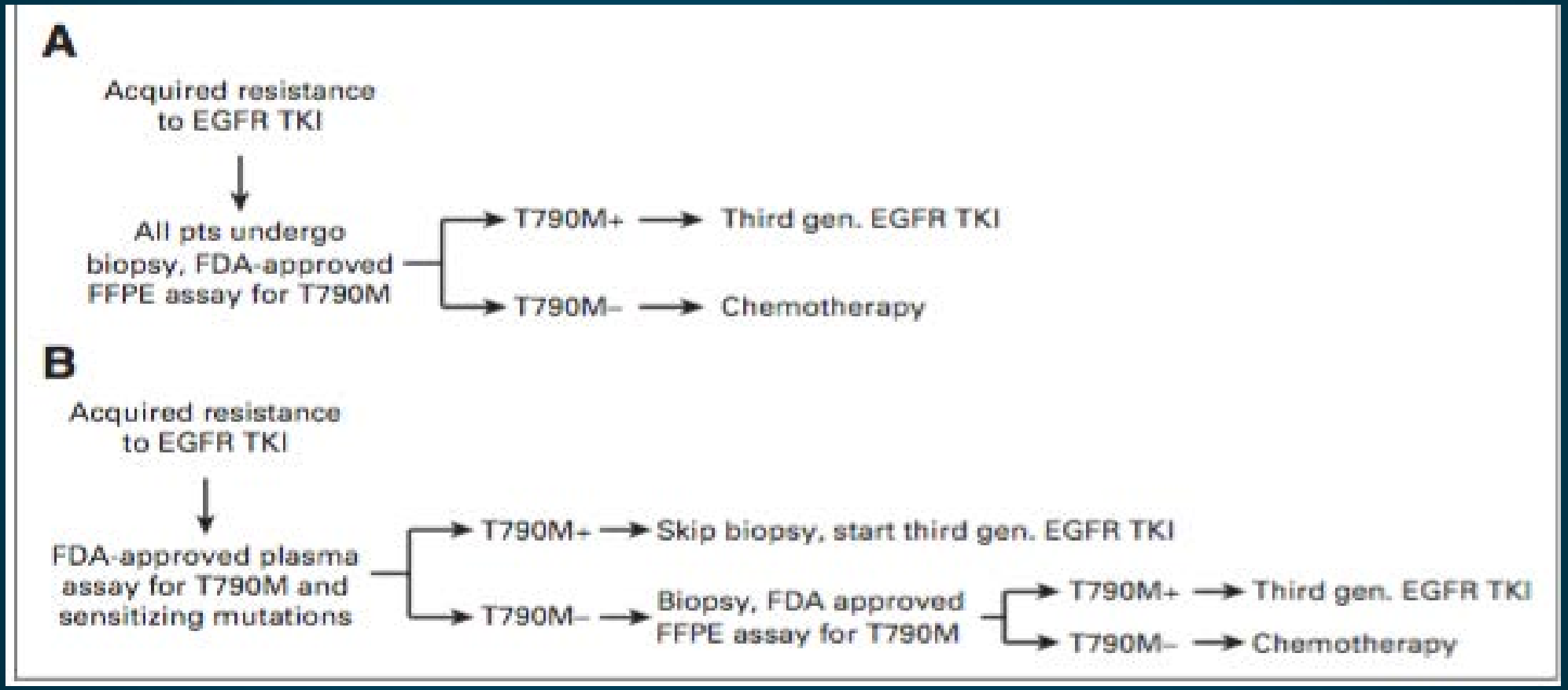
Impact of Bio-Source on Outcome

Sample Type	n	Objective Response Rate,* % (95% CI)
Tissue	443	33.9 (29.5–38.5)
Plasma	374	32.1 (27.4–37.1)
Urine	169	36.7 (29.4–44.4)



Wakelee et al ASCO 2016

Proposed Paradigm for Use With TKI Resistance

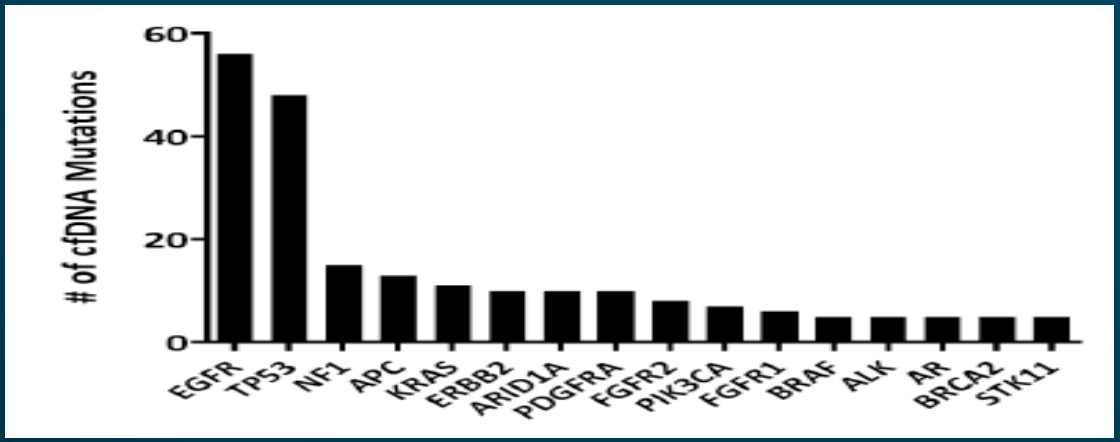


+ Biopsy if Easily accessible

Oxnard et al JCO 2016

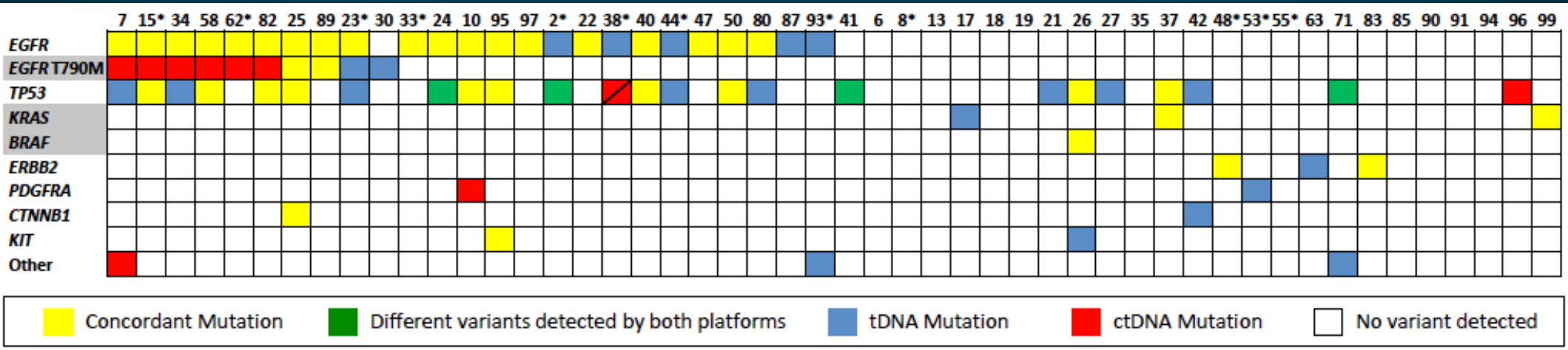
How can we apply this beyond EGFR?

- At Penn, we performed a series of plasma based NGS analyses using the Guardant 360 platform
  - NGS platform covering over 70 genes
    - Can evaluate point mutations, amplifications, fusions, and indels
- 112 plasma samples on 102 patients
- 84% of patients had at least one alteration found in plasma
  - 49% of patients could have tissue analysis

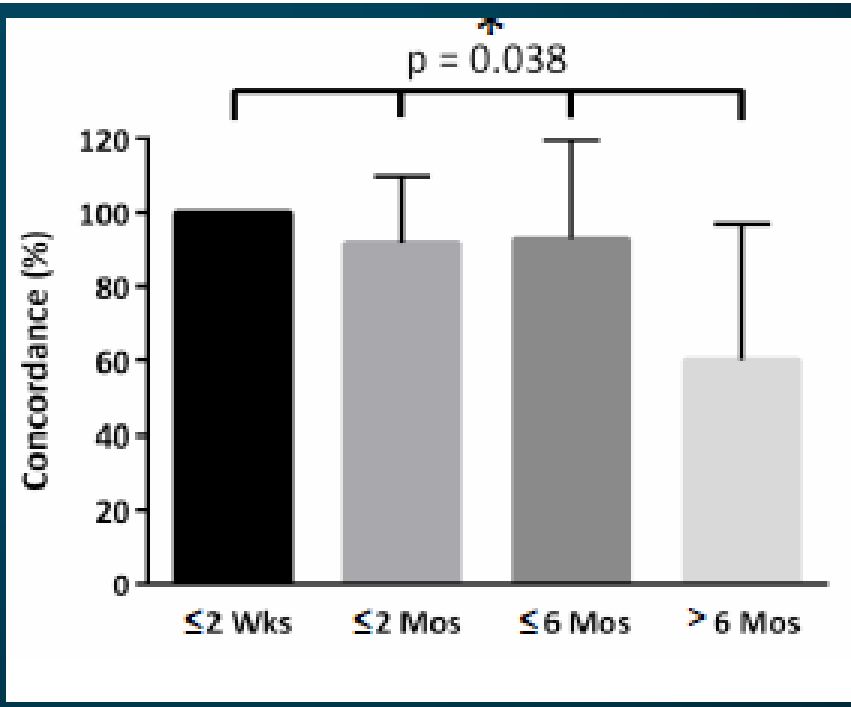


Thompson et al CCR 2016

Tissue and Plasma Concordance

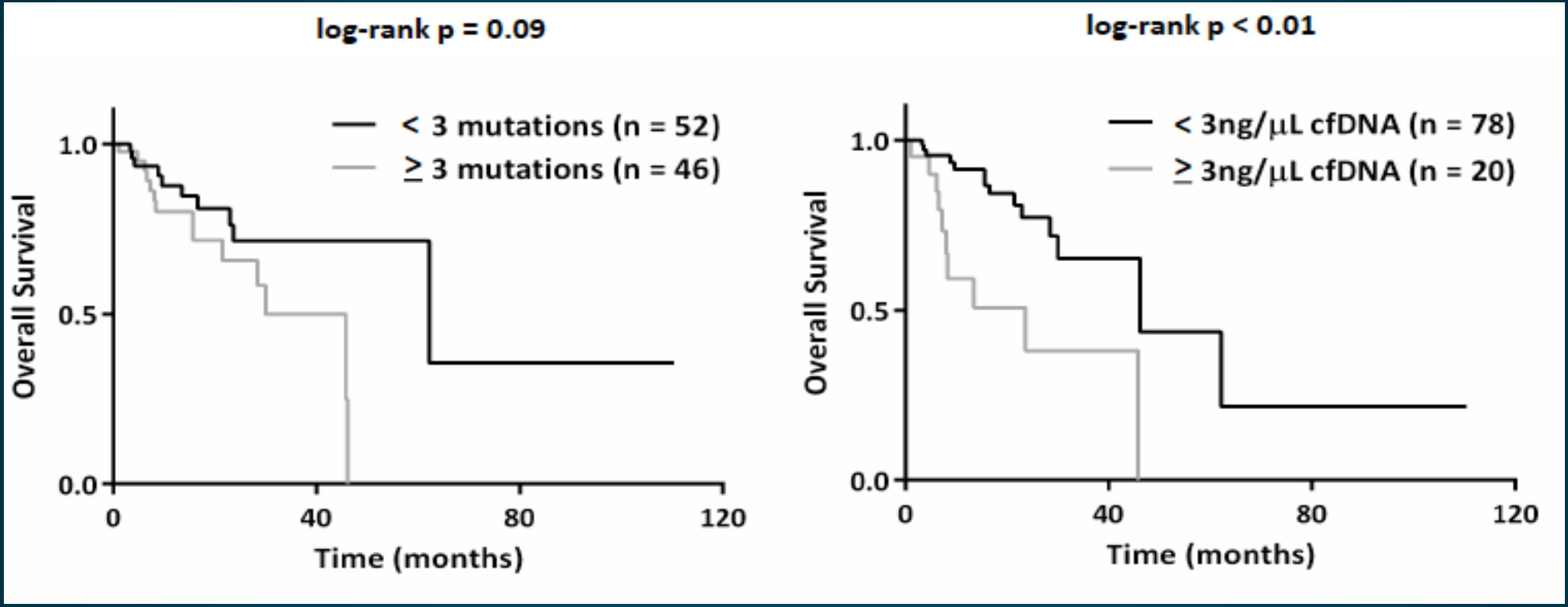


- 79% concordance between plasma and tissue
  - Shorter time between sampling increased concordance
- Temporal change in concordance reflective of tumor evolution



Thompson et al CCR 2016

Impact of Plasma DNA on Outcomes



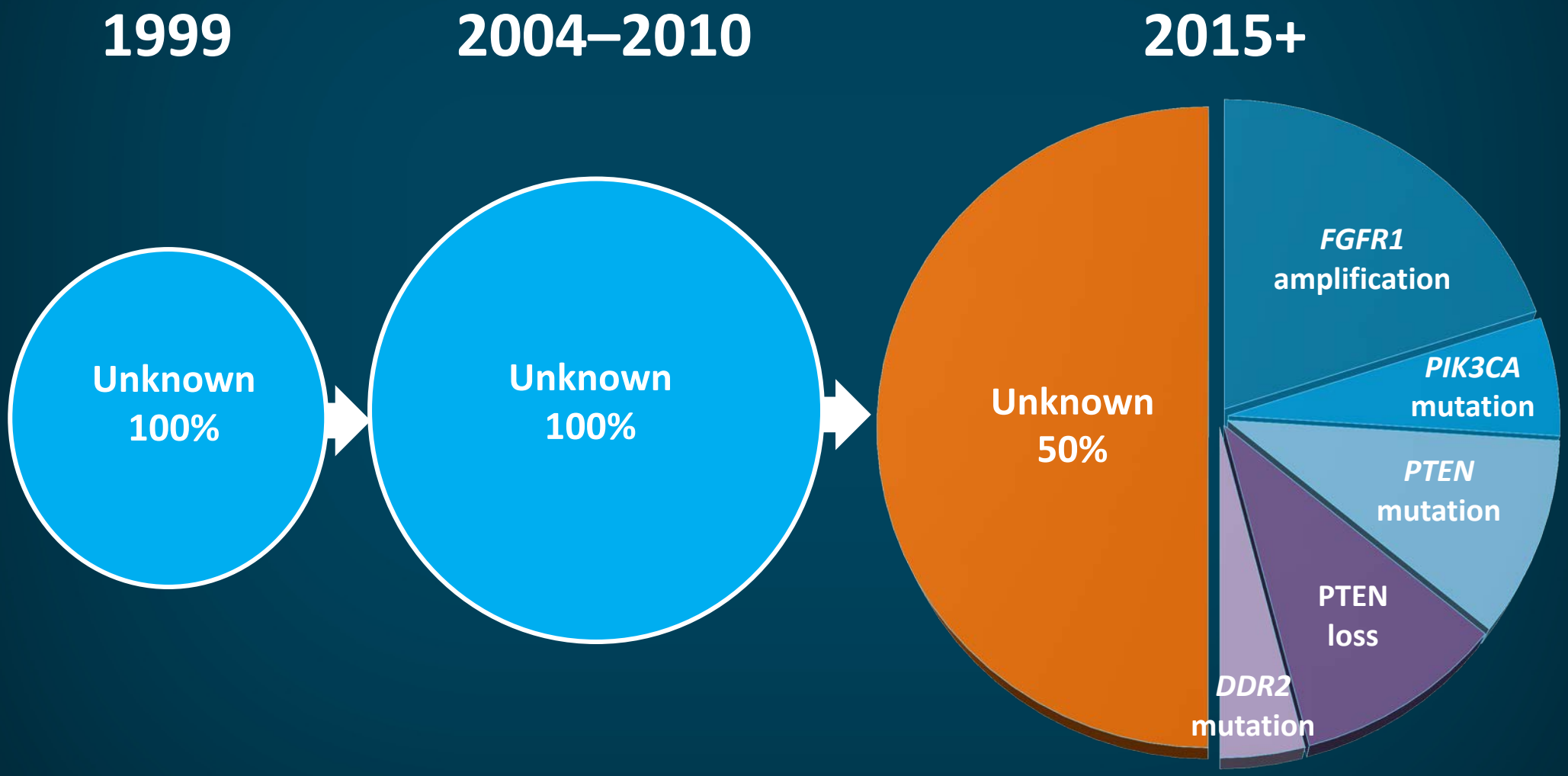
- Trend towards worse outcomes with more mutations
- Significantly worse survival seen with higher concentrations of cfDNA

Thompson et al CCR 2016

Summary

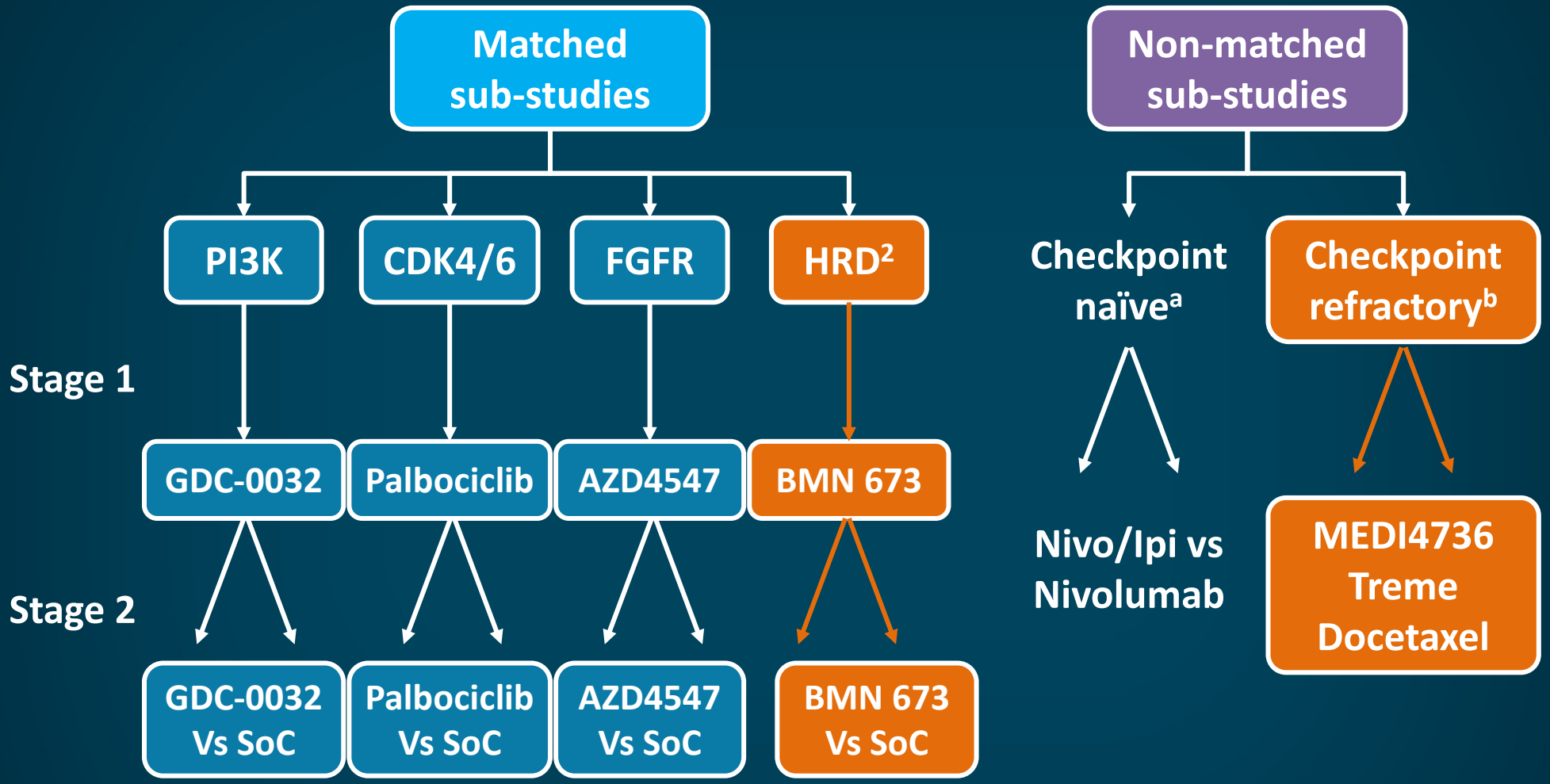
- Personalized Tx has had an enormous impact on the management of advanced NSCLC (primarily adenoca) over the past 10+ years
- Tissue testing remains the “established” gold standard
- Plasma and urine testing are able to detect genetic abnormalities, both at diagnosis and at resistance
- When plasma is positive, tumor testing often is as well
  - Negative predictive value not as high
- NGS assays allow for a comprehensive assessment of genomic landscape
  - More genetic aberrations associated with worse outcomes
  - Greater detected cfDNA associated with worse outcomes
- Serial monitoring affords exciting opportunities
  - Tumors undergo temporal evolution
  - May be a useful adjunct to radiographic surveillance

Actionable Targets (?) in Squamous Cell Lung Cancers



Okudela K et al. *Cancer Res.* 2008. Yamamoto S et al. *Pathol Int.* 2007;57:523-528. Weiss J et al. *Sci Transl Med.* 2010;2:62ra93. Hammerman PS et al. *Cancer Discov.* 2011;1:78-89. The Cancer Genome Atlas Research Network. *Nature.* 2012;489:519-525.

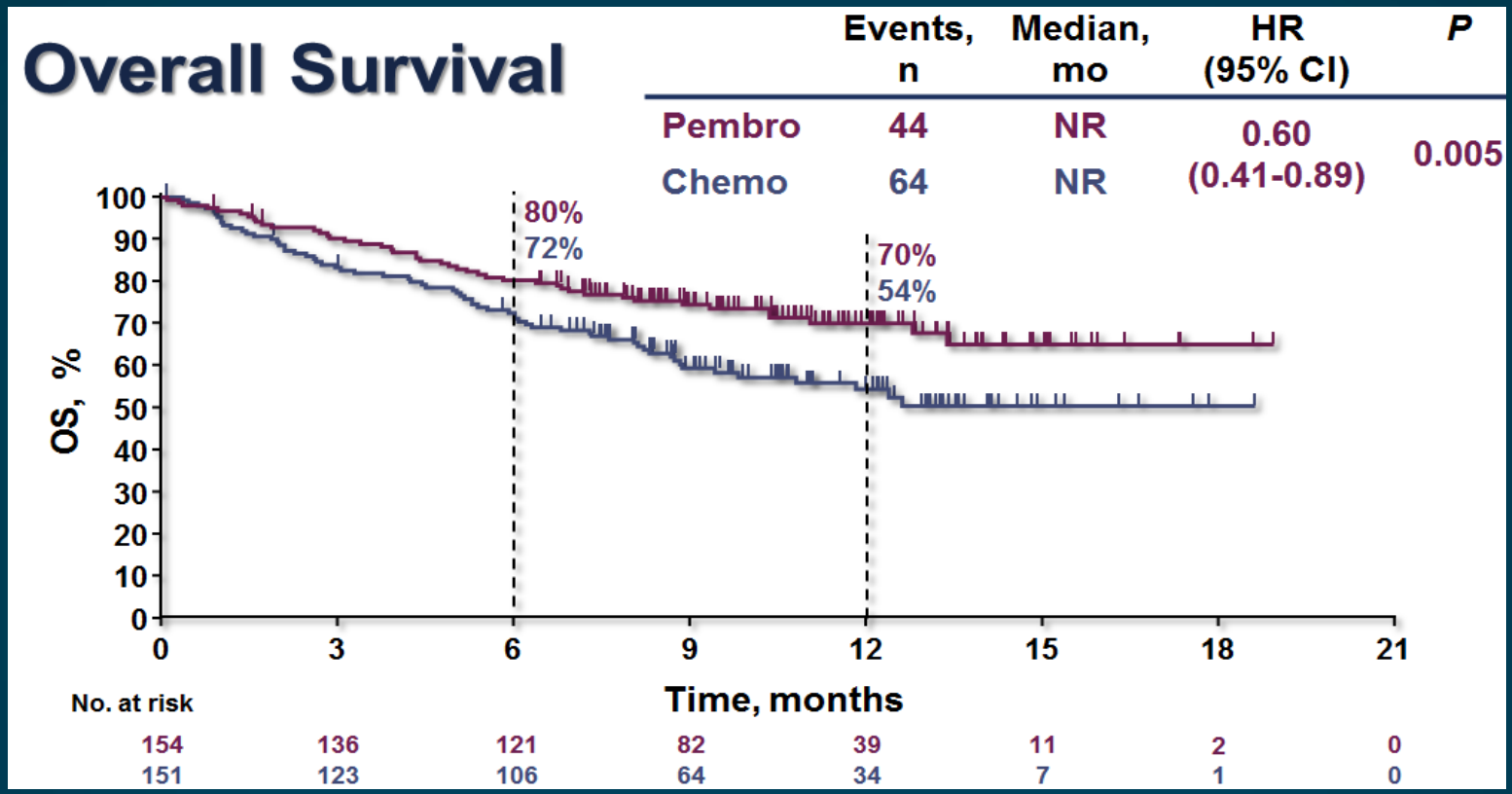
S1400: Revised Lung MAP Scheme



[a]Revision #3 expected September/October 2015; [b]Revision #4 expected December 2015/January 2016.

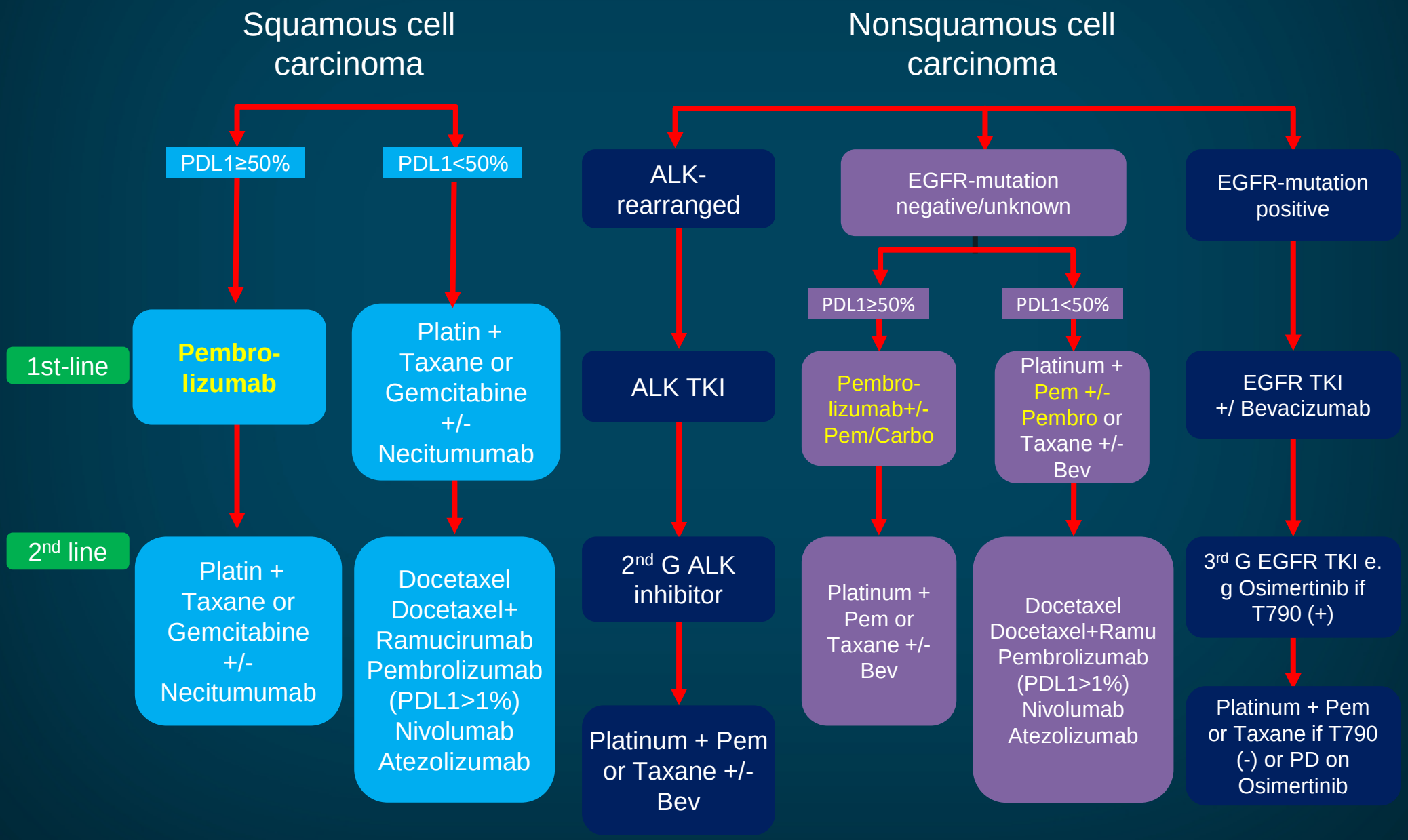
Clinical study reports: NCT02785913 (taselisib/GDC-0032) (https://clinicaltrials.gov/ct2/show/NCT02785913?term=S1400&rank=4). NCT02785939 (palbociclib) (https://clinicaltrials.gov/ct2/show/NCT02785939?term=S1400&rank=3). NCT02154490 (AZD4547) (https://clinicaltrials.gov/ct2/show/NCT02154490?term=S1400&rank=1). NCT02785952 (nivolumab) (https://clinicaltrials.gov/ct2/show/NCT02785952?term=S1400&rank=2). NCT02766335 (MEDI4736) (https://clinicaltrials.gov/ct2/show/NCT02766335?term=S1400&rank=5).

KEYNOTE 24: Survival data



- **Clearcut survival benefit for NSCLC pts with PDL1 ≥ 50%**
  - Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)
  - HR for death: 0.60
  - Despite cross-over in 50% of patients on the control arm

First- and Second-Line Treatment of Metastatic NSCLC (After KEYNOTE 24)



First- and Second-Line Treatment of Metastatic NSCLC (After KEYNOTE 24)