Disclosures

- Consulting for:
  - Genentech/Roche
  - Pfizer
  - Novartis
  - BioDesix
  - Merck
  - EMD Serono
  - GSK
  - Boehringer Ingelheim
  - Amgen

Clinical trial design and perspectives

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Historical Clinical Trial Design

- Phase I – Maximum tolerated dose assessment
- Phase II – Response signal generation
- Phase III – Comparison to the standard or added to the standard in unselected patients

Oncology history is paved with failed Phase III trials

- **Negative NSCLC Trials**
  - Erlotinib X2
  - GefitinibX2
  - MMPI x2 AG3340, BMS 275291
  - MMPI (Prinomostat AG3340)
  - FTI X3 (SCH66336, R115777,BMS)
  - PKC Antisense (ISIS 3521) X2
  - Bexarotene x2
  - Bevazizumab
  - Cetuximab
  - Sorafanib
  - PF Toll9 X2
  - Trail agonists
  - IGF-1R inhibitors
  - ASA404
  - Thalidomide
  - Multiple vaccines

Negative SCLC Trials

- Pemetrexed
- Picoplatin
- Thalidomide
- GDC-0449
- IMC-A12

Avg of 1,000 patients each

Modified from Paul Bunn and Solange Peters

Breast Cancer
Adjuvant Endocrine Therapy (ER)

Study	No of patients	Control	Experimental	Median FU (Years)	DFS	OS
EBCTCG [1]	≈80 000	Obs	Tamoxifen	15	0.61 (SE±0.04)	0.69 (SE±0.05)
ATAC [2]	9366	Tamoxifen	Anastrozole	8.3	0.85 (95% CI:0.76-0.94)	0.97 (95% CI:0.86-1.11)
BIG 1-983 [3]	4922	Tamoxifen	Letrozole	4.3	0.82 (95% CI:0.71-0.95)	0.91 (95% CI:0.75-0.11)

Huge trials to uncover small differences in OS!

1. Lancet 365 (9472):1687-717, 2005
2. Lancet 365 (9453): 60-62, 2005
3. JCO 25(5):486-92,2007

Times have changed

- There are new science-based ways to develop therapeutics
- New challenges posed by the new classes of therapeutics
- New trial designs needed to test them

Drug development is Evolving

- We are now going after defined targets with rationally-designed drugs and combinations
- Biologics commonly have flatter dose-effect curve
- *A priori* patient selection strategies for patients make sense, and are based on target identification
- Efficacy is improving and the bar for efficacy is getting higher – HR of 0.7 or better is the norm

Novel Clinical Trial Designs

- Phase I – Limited number of doses, drug combinations, and selected populations of patients
  - Expansion cohorts for signal finding
- Phase II – Randomized designs
- Phase III – Smaller and smarter
- Adaptive, Bayesian designs
- "Basket" designs – multiple diseases for a given marker
- "Umbrella" designs – multiple markers for a given disease

Checkmate 012: Phase I Trial of Nivolumab

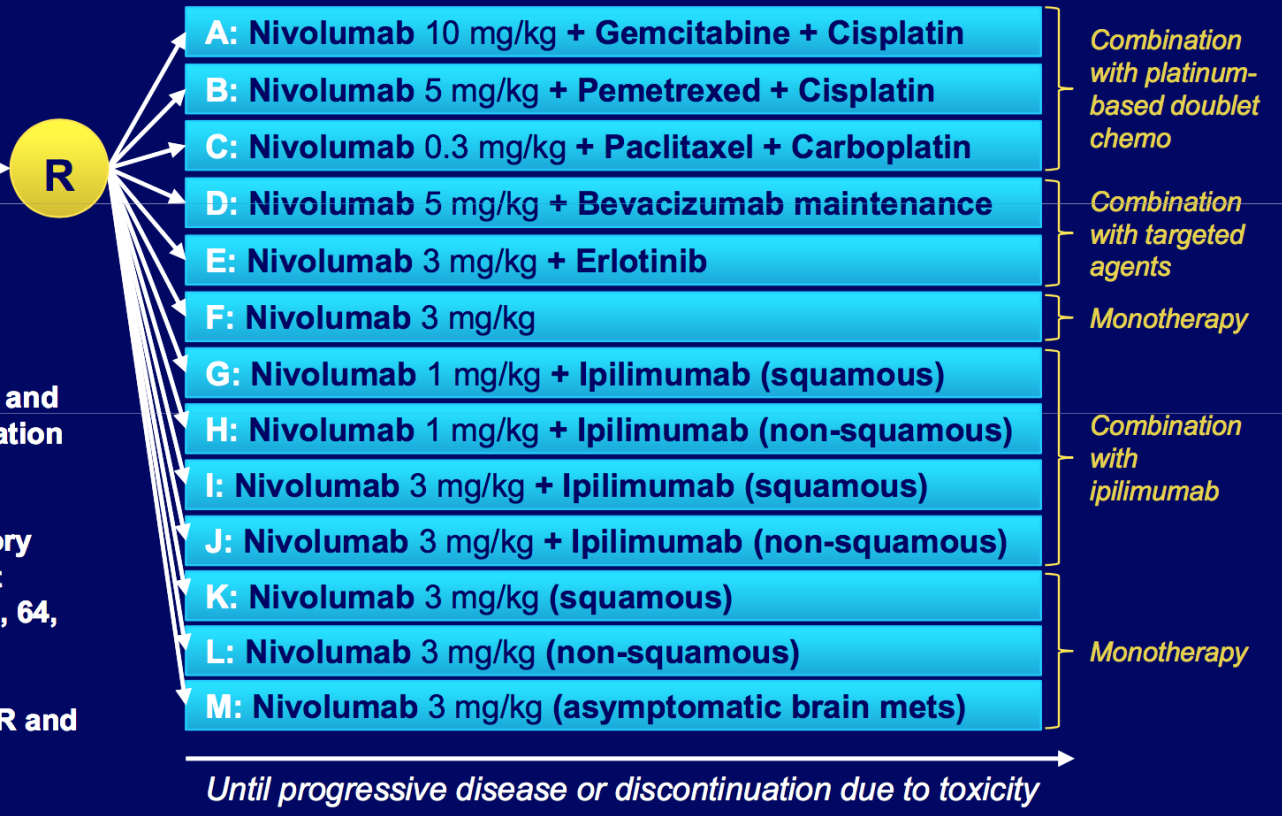
An open-label, randomized, multi-arm, phase I trial of nivolumab in combination with chemotherapy or targeted agents, or as monotherapy in first-line subjects with Stage IIIb/IV NSCLC

N=190

Key Inclusion Criteria

- Newly diagnosed and confirmed Stage IIIb/IV NSCLC
- ECOG PS ≤1
- Chemotherapy-naïve (except Arm D)
- Prior EGFR TKI acceptable

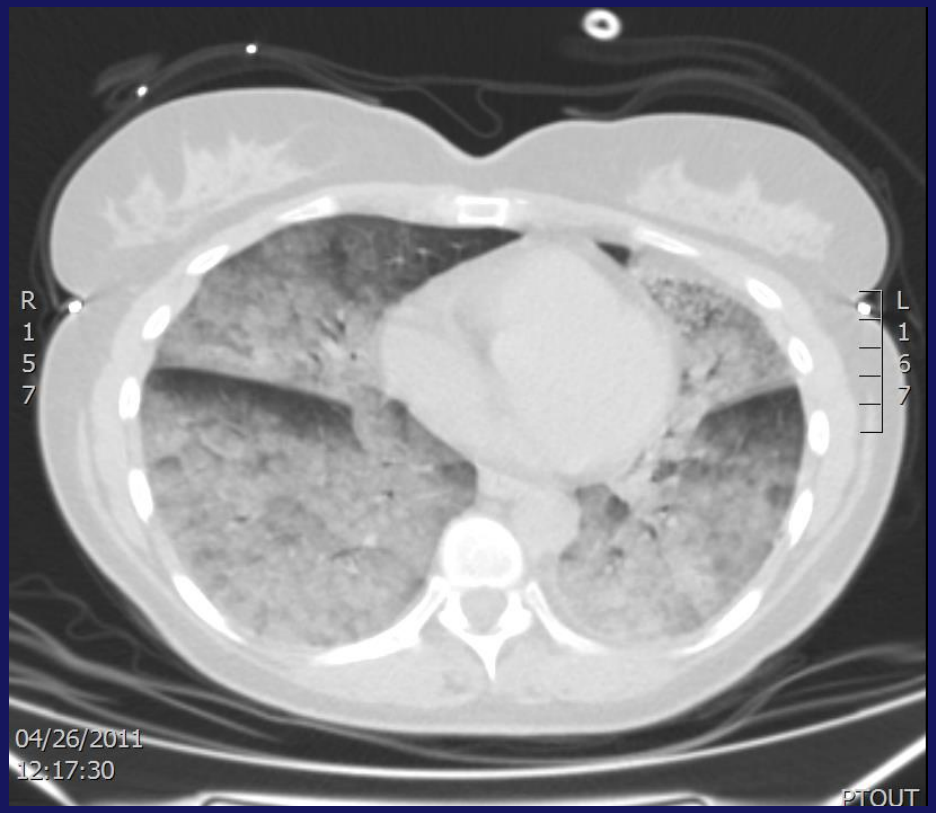
- **Primary outcome measures: Safety and tolerability of nivolumab in combination with chemotherapy measured by:**
  - **Frequency of AEs and SAEs**
  - **Frequency of clinical laboratory test by worst toxicity grade at screening, Day 1, 8, 15, 22, 43, 64, and Day 1 of each cycle until progressive disease**
- **Secondary outcome measures: ORR and PFS rate in combination or as monotherapy**

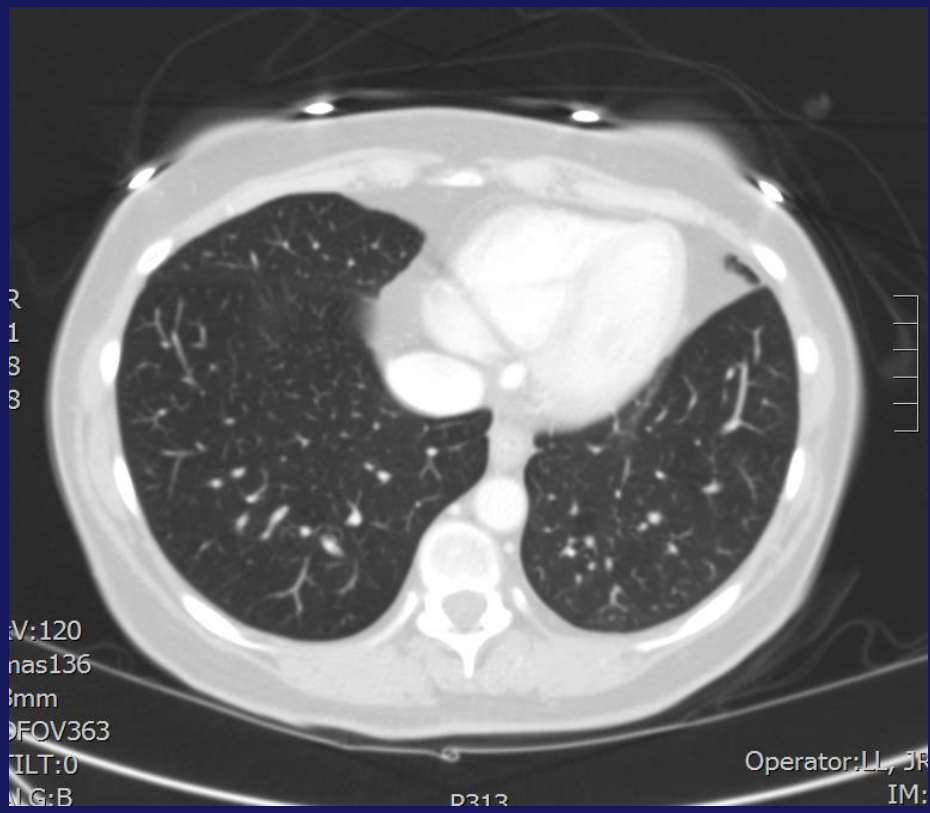


AE=adverse event; ECOG PS=Eastern Cooperative Oncology Group Performance Status; Mets=metastases; NSCLC=non-small cell lung cancer; ORR=objective response rate; PFS=progression-free survival; R=randomized; SAE=serious adverse event; TKI=tyrosine kinase inhibitor.

Clinicaltrials.gov. NCT01454102.

Response to crizotinib (Xalkori)



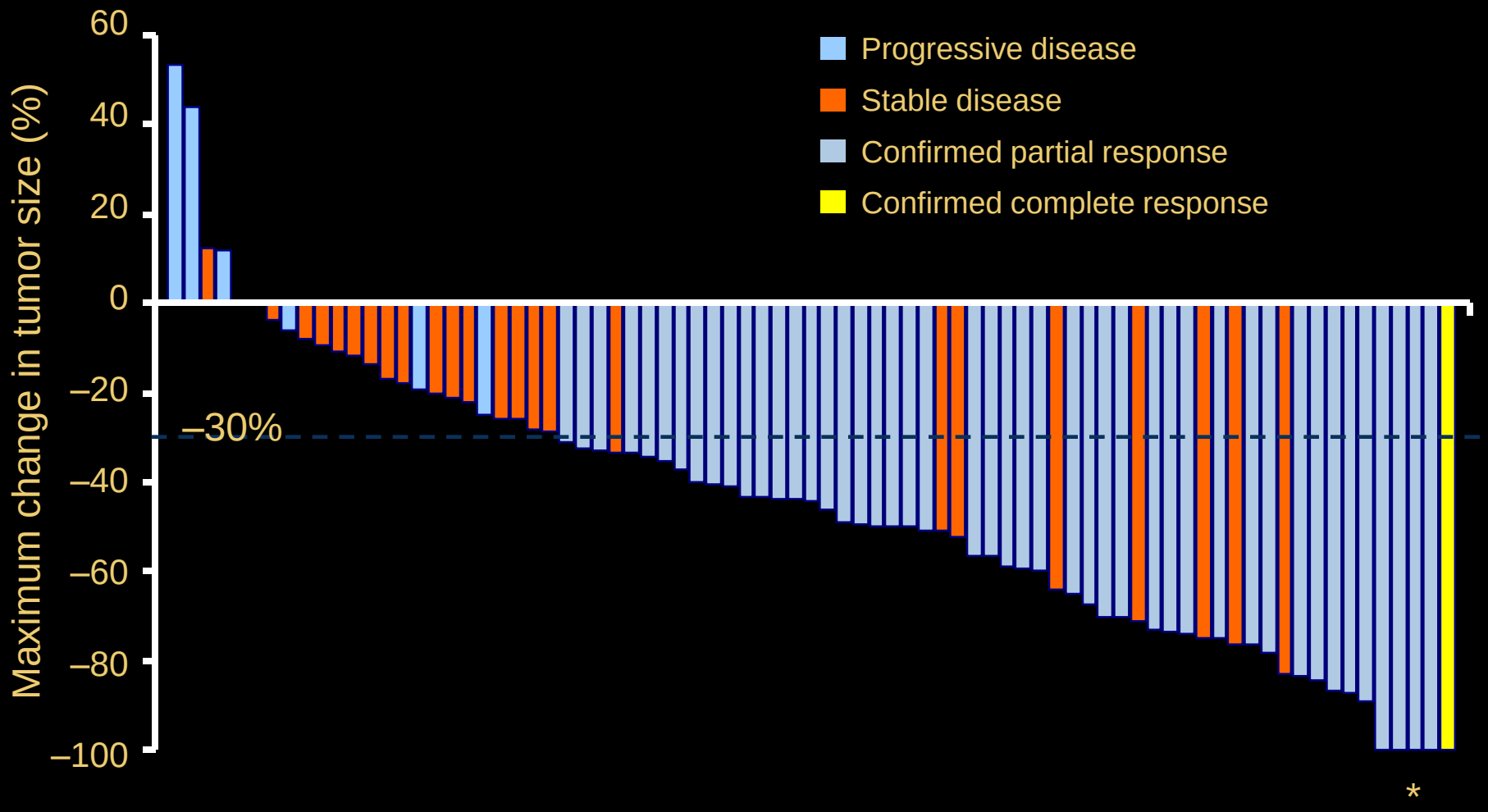


4/26/2011

9/27/2011

Marked Activity of Crizotinib in Patients with Advanced, ALK-positive NSCLC (N=82)

Kwak et al. NEJM 2010;363:1693–703; Bang et al. JCO 2010;28:18S abstract 3



When you know the driver, and have an effective drug, tumors respond!

CLINICAL TRIALS IN CANCER
- Endpoints and Study Design -

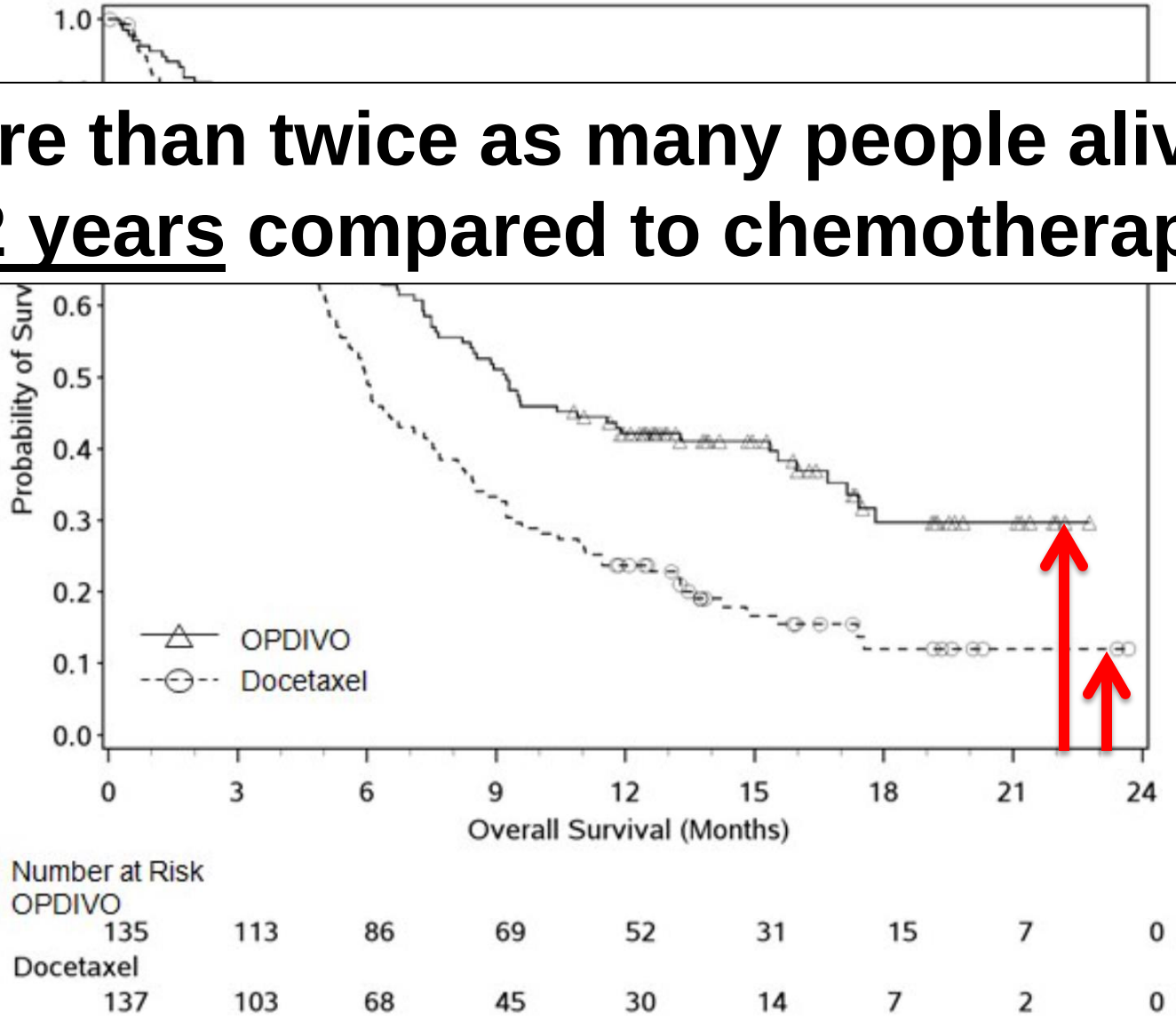
Survival:	**Primary end-point for most large, randomized studies, especially if survival differences are likely. FDA accepted endpoint for NDA**
Progression-free survival	**Primary end-point for many randomized phase II and some phase III studies, often not sufficient evidence for clinical benefit for FDA**
Response:	**Primary end-point mainly in smaller and exploratory Phase II studies**
Quality of Life/Symptoms:	**Often a secondary end-point; appropriate as primary when survival differences are unlikely**

Clinical endpoints – my opinions

- Overall survival is best – PFS a compromise
- It has been difficult to show survival differences with clear PFS differences, and even with only partial crossover
- 5-year overall survival numbers have improved VERY slowly
- Truly effective therapies should show survival benefits, and optimum benefits when used in first line

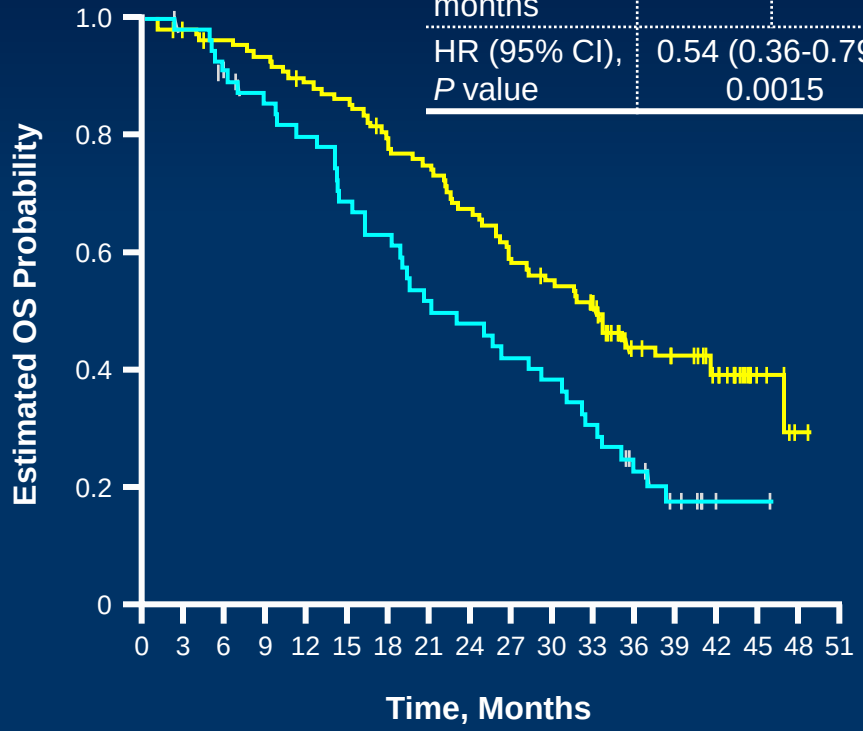
Survival in patients with previously treated squamous cancer

More than twice as many people alive at ~<u>2 years</u> compared to chemotherapy!!



Starting with targeted therapy rather than chemotherapy improves survival

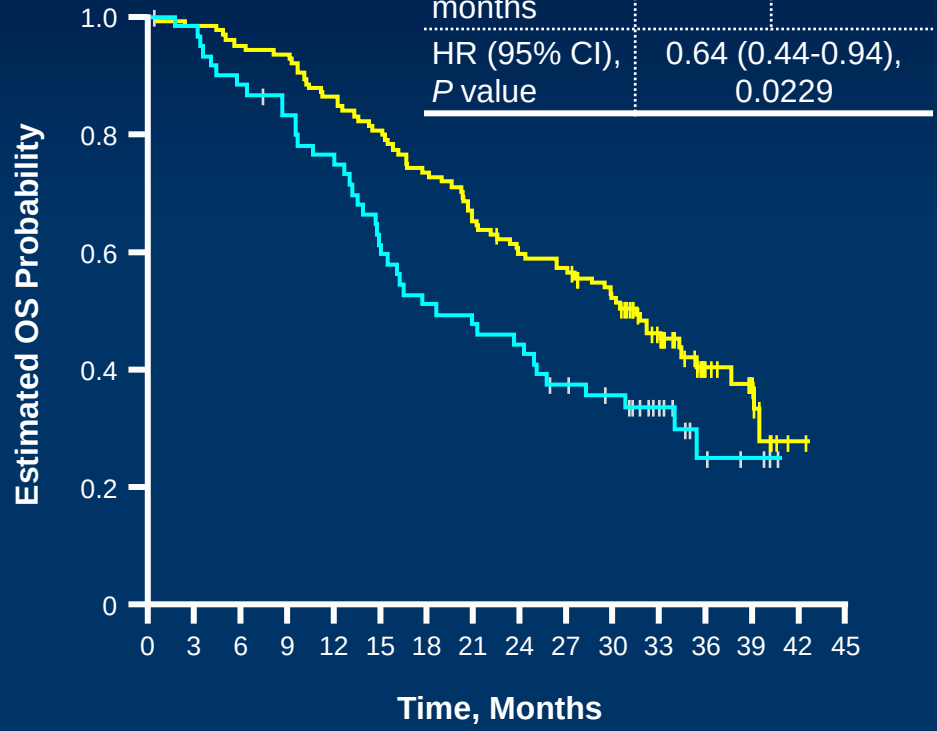
LUX-Lung 3	Afatinib (n=112)	Pem/Cis (n=57)
Median, months	33.3	21.1
HR (95% CI), *P* value	0.54 (0.36-0.79), 0.0015	



Number of patients

Afatinib	112	108	105	102	96	93	83	80	72	62	58	51	34	30	21	6	1	0
Pem/Cis	57	55	50	46	43	37	33	27	25	22	20	16	10	6	1	1	0	0

LUX-Lung 6	Afatinib (n=124)	Gem/Cis (n=62)
Median, months	31.4	18.4
HR (95% CI), *P* value	0.64 (0.44-0.94), 0.0229	



Number of patients

Afatinib	124	122	118	115	106	99	90	80	73	69	59	39	16	8	1	0	
Gem/Cis	62	58	53	49	44	35	30	28	26	21	18	11	4	3	0	0	

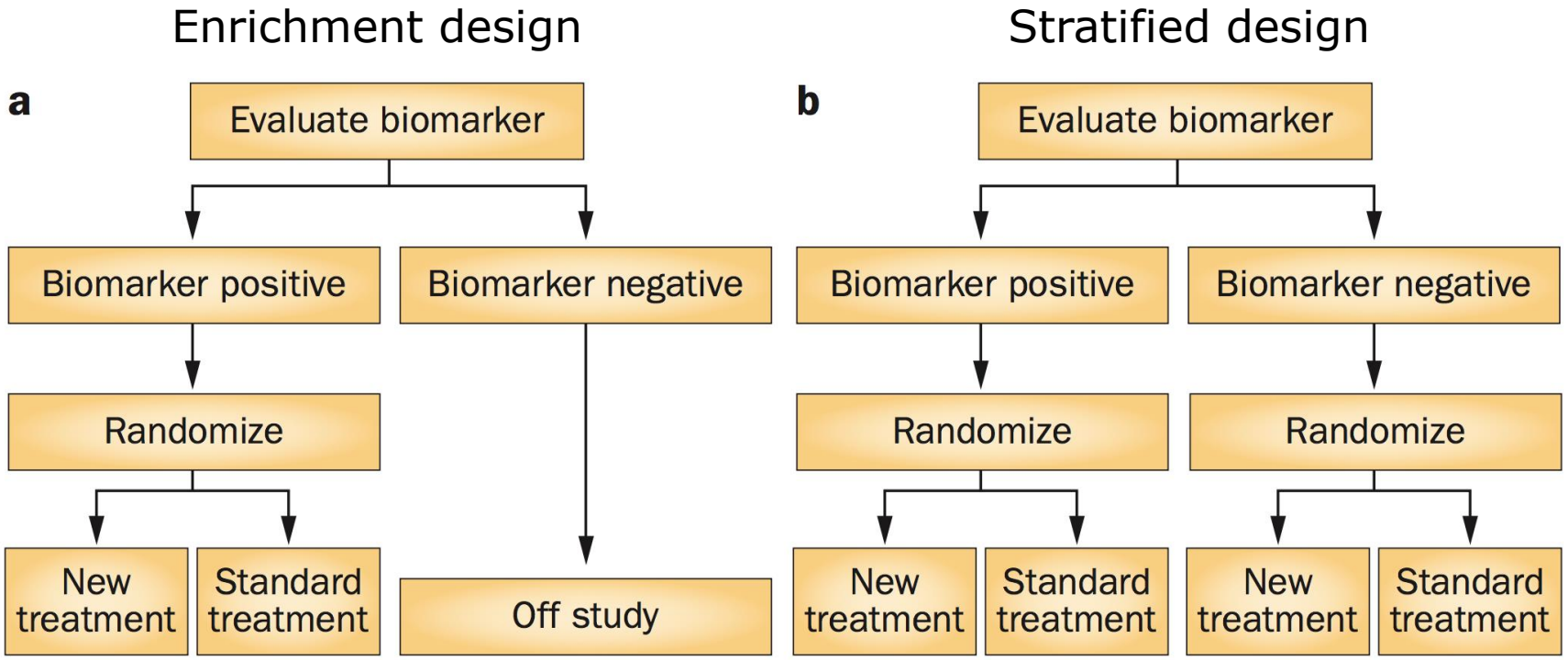
Yang J, et al. Presented at: ASCO. 2014 (abstr 8004).

Biomarker evaluation trial designs

- Theoretical biomarkers are not always correct
  - Selecting patients for KRAS status in MEKi studies
- Biomarker negative populations are not homogeneous just because they lack your biomarker
  - Tumors lacking EGFR mutations are heterogeneous too!
- Taking response rate and PFS too seriously
  - MEKi + docetaxel, for example

Biomarker evaluation strategies

It is often a difficult decision to rigorously test a biomarker



Unless a biomarker is highly predictive, better to choose the latter

Freidlin, B. & Korn, E. L. *Nat. Rev. Clin. Oncol.* 11, 81–90 (2014)

Example of a weak biomarker…

MPDL3280A responses by PD-L1 biomarker expression

PD-L1 IHC expression category[a]	ORR[b] (n=88)	SD
TC3 or IC3	50% (11 of 22)	18.2% (4 of 22)
TC3 or IC2/3	31.6% (12 of 38)	28.9% (11 of 38)
TC0/1/2 and IC0/1/2	12.1% (7 of 58)	36.2% (21 of 58)
TC0/1/2 and IC0/1	14.3% (6 of 42)	33.3% (14 of 42)
All patients[c]	20.5% (18 of 88)	34.1% (30 of 88)

[a]IC3: ≥10% tumor immune cells (IC) positive for PD-L1; IC2/3: ≥5% tumor immune cells positive for PD-L1; IC1/2/3: ≥1% tumor immune cells positive for PD-L1; IC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status; TC3: ≥50% tumor cells (TC) positive for PD-L1; TC0/1/2: <50% tumor cells positive for PD-L1.
[b]ORR = objective response rate. All objective responses were PR.
[c]All patients includes patients with IHC 0/1/2/3 and 8 patients have an unknown diagnostic status.
Patients first dosed at 1–20 mg/kg by Oct 21, 2013; data cut-off Apr 21, 2014.

Herbst, Nature 2015

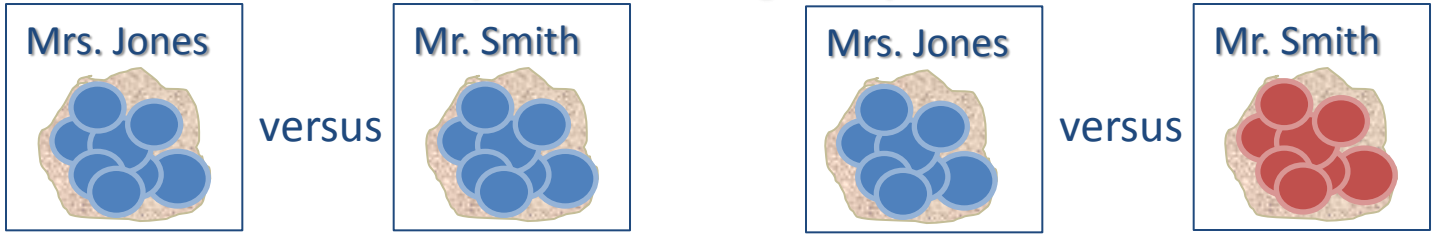
New challenges for targeted therapies

- Targeted therapies drive targeted escape mechanisms
  - E.g. T790M
  - Tumor heterogeneity, even within a single patient
- Targeted therapies may have unexpected effects due to physiologic pathway interactions
  - Inhibiting one pathway can activate another

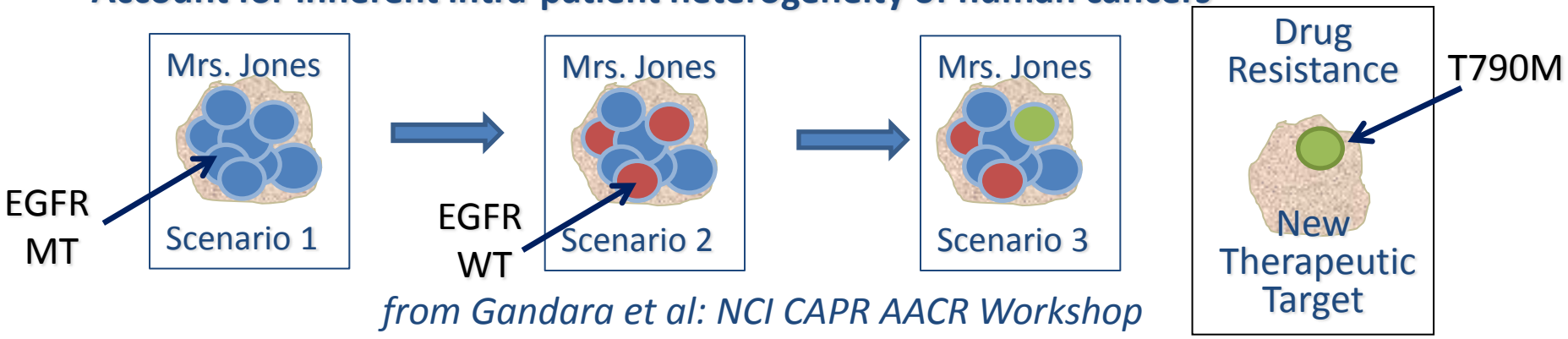
Accounting for both Inter-patient & Intra-patient Heterogeneity of Human NSCLC

Unmet Needs in Biomarker Assessment:

- **Account for complexity of underlying biologic systems in human cancers**
- **Account for inherent inter-patient heterogeneity of human cancers**

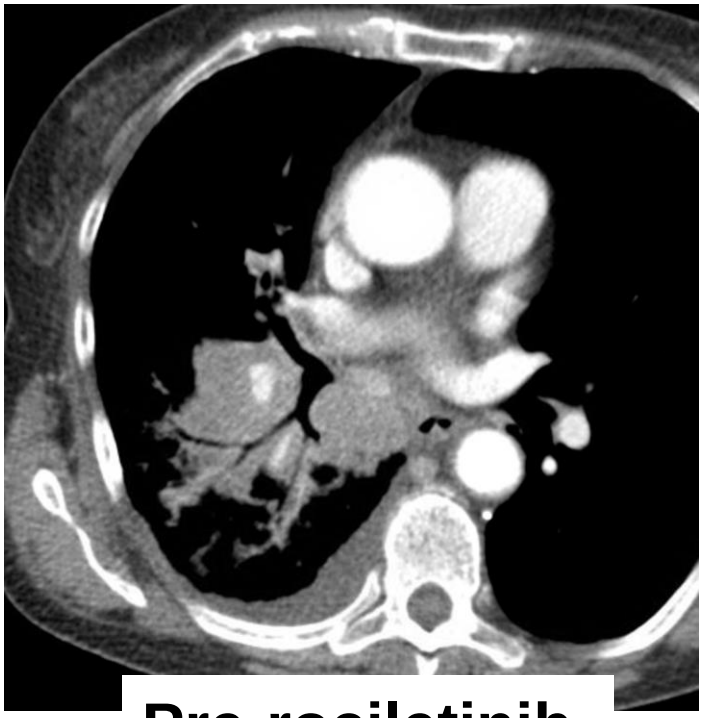


- **Account for inherent intra-patient heterogeneity of human cancers**

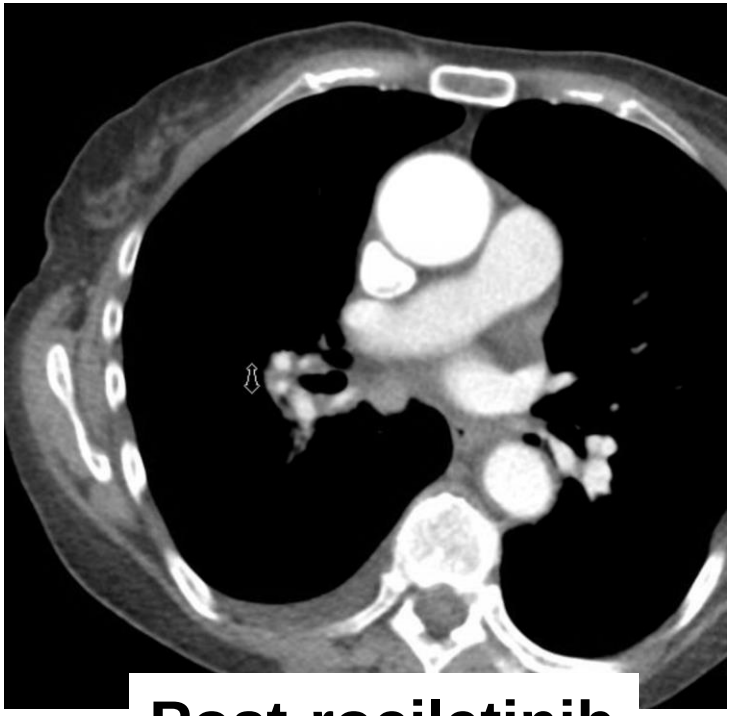


from Gandara et al: NCI CAPR AACR Workshop

T790M pos

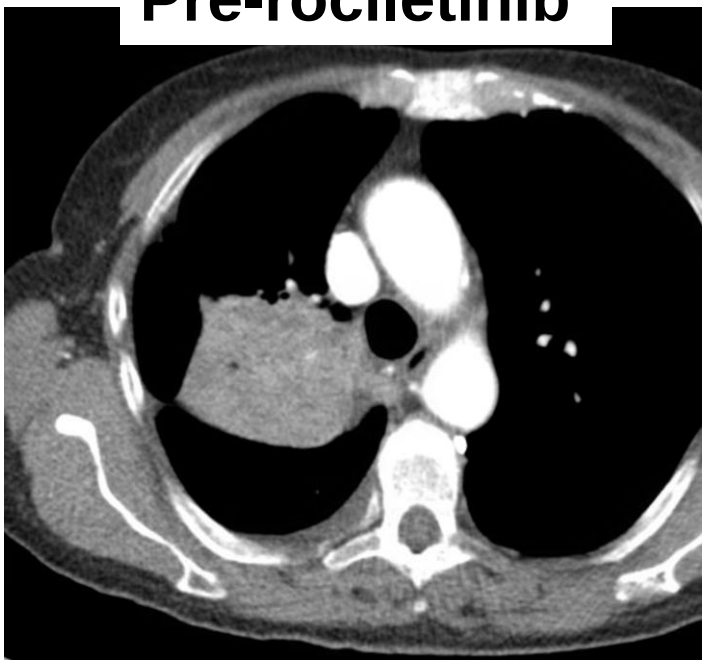


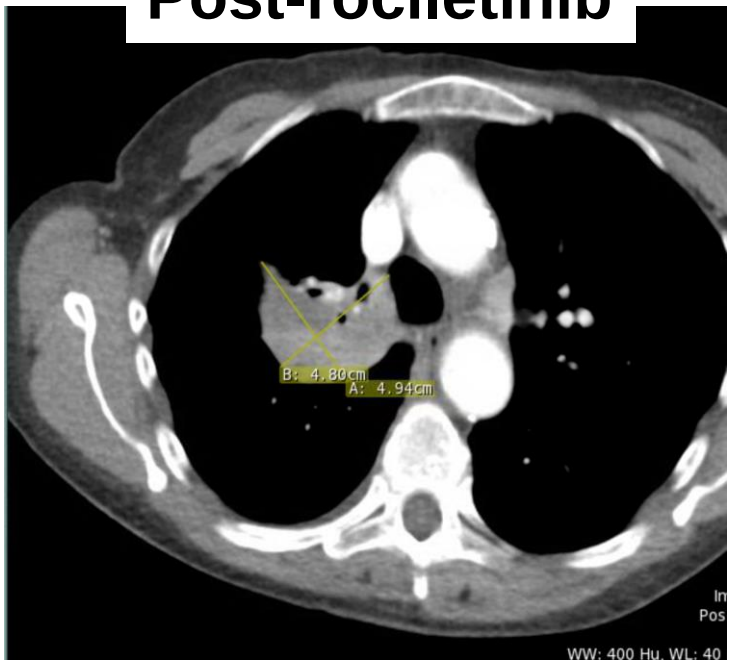
Pre-rociletinib



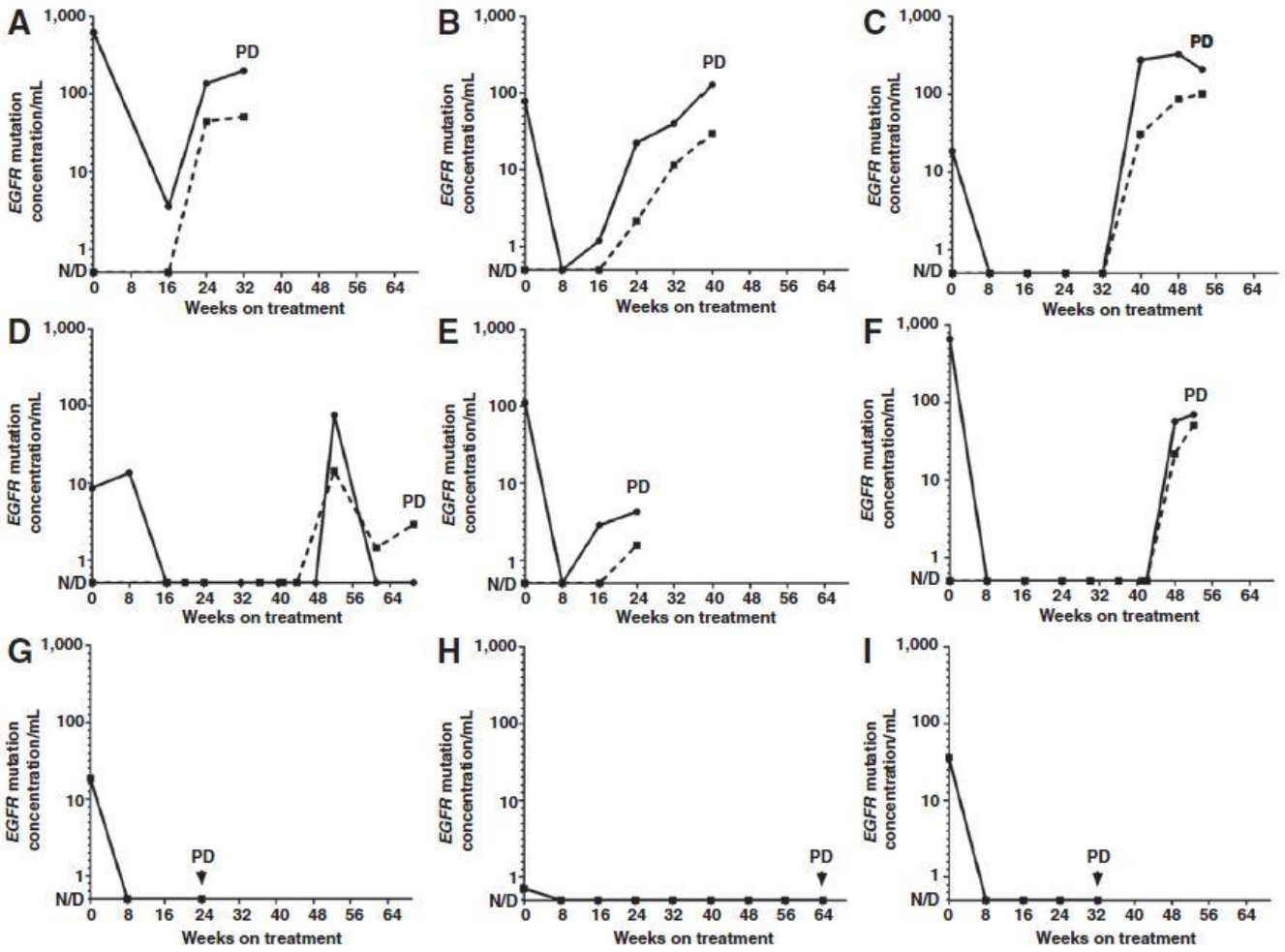
Post-rociletinib

T790M neg





Plasma Levels of Mutant *EGFR* in Patients Receiving 1st Line Erlotinib Until Disease Progression



Solid lines: sensitizing mutation, dashed lines T790M

Reference: Oxnard GR et al. Clin Cancer Res. 2014;20(6):1698-705.

VERY GOOD CONCORDANCE BETWEEN BEAMING & TISSUE

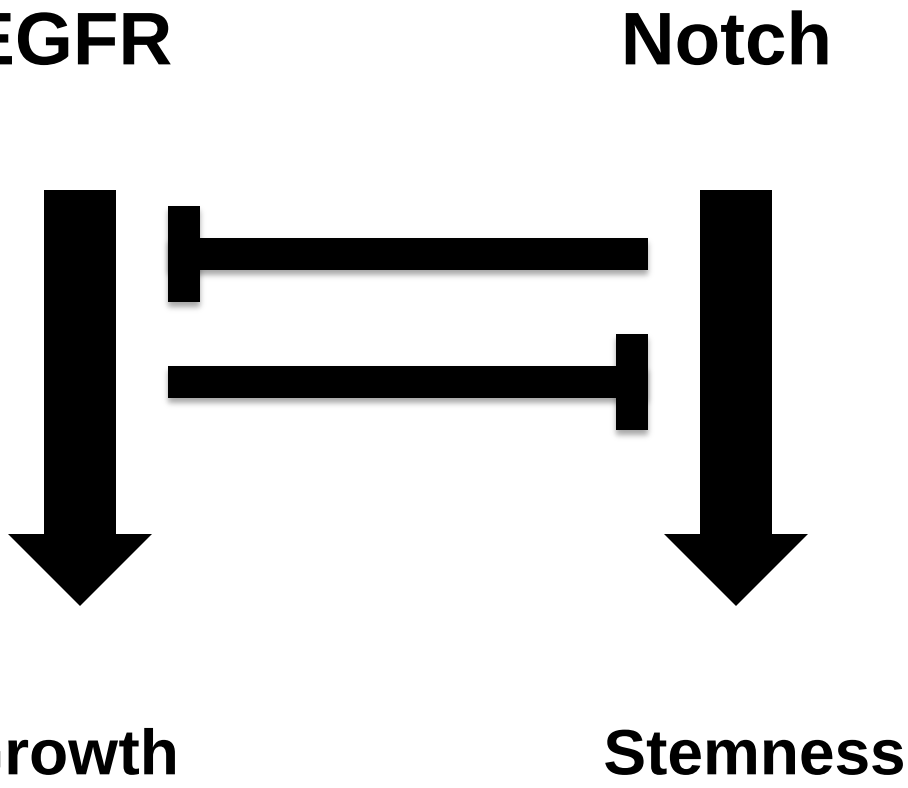
Table 3. Concordance of plasma (BEAMing) and tumor (cobas® FFPET test) in a 45 patient subset from the PhI/II clinical trial

		Tissue							
		Activating Mutations				T790M			
		Positive	Negative	Inadequate tissue	Total	Positive	Negative	Inadequate tissue	Total
Plasma	Positive	28	0	7	35	19	4	6	29
	Negative	7	0	3	10	8	4	4	16
Total		35	0	10	45	27	8	10	45

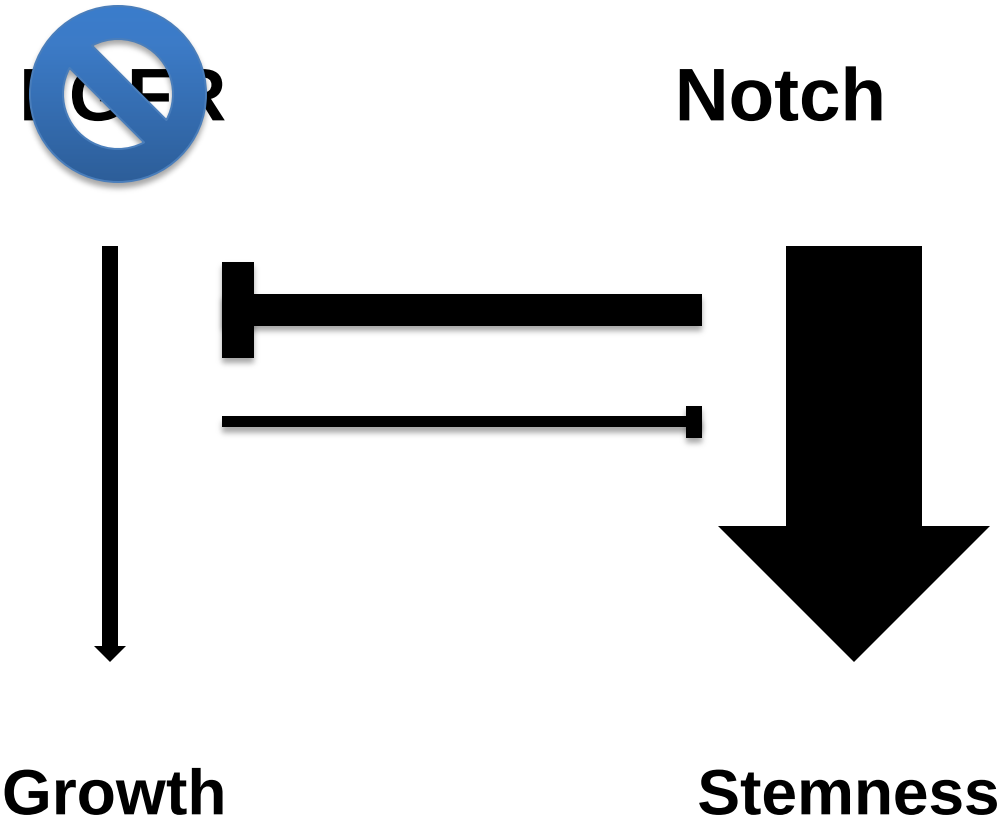
Plasma analysis can detect T790M in cases where tissue is inadequate, or even negative for T790M. These discordant patients responded to rocelitinib

Dziadziuszko et al, AACR 2014

Physiologic pathway interaction is made apparent with highly targeted therapies

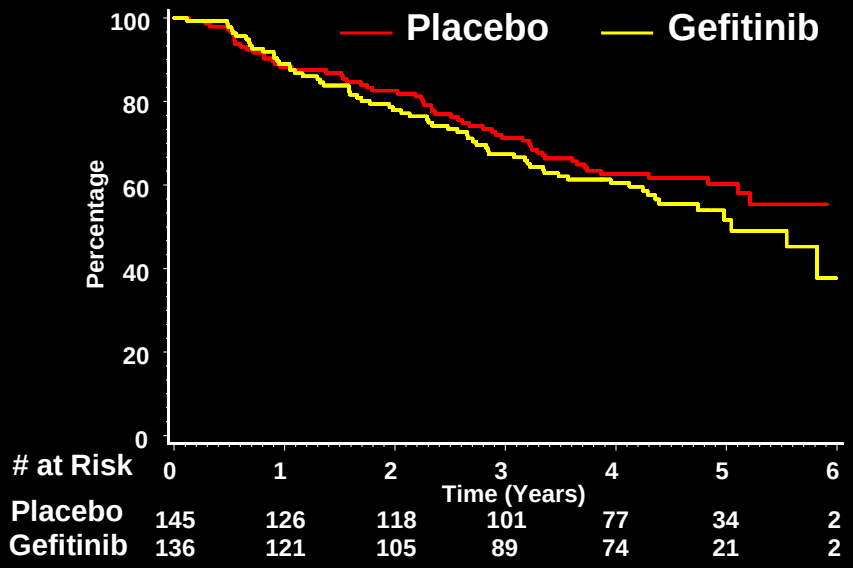


EGFR and Notch pathways interact



BR.19 EGFR TKI after surgery, by mut status

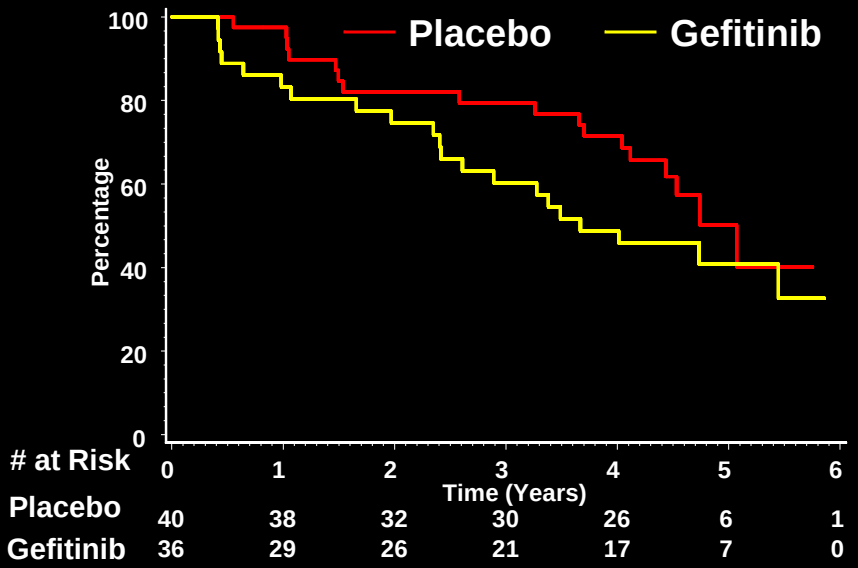
Wild type



HR (95% C.I.)
Gefitinib/Placebo: 1.21 (0.84, 1.73)
Log Rank: p=0.301 Median (95% C.I.)

-Placebo: Not reached (5.1, inf.)
-Gefitinib: 5.0 (4.3, inf.)

Sensitizing mutation

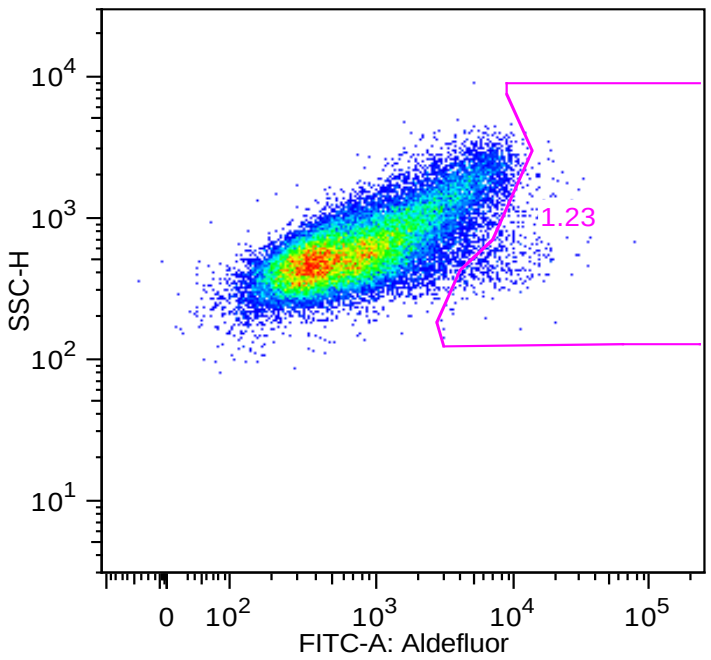


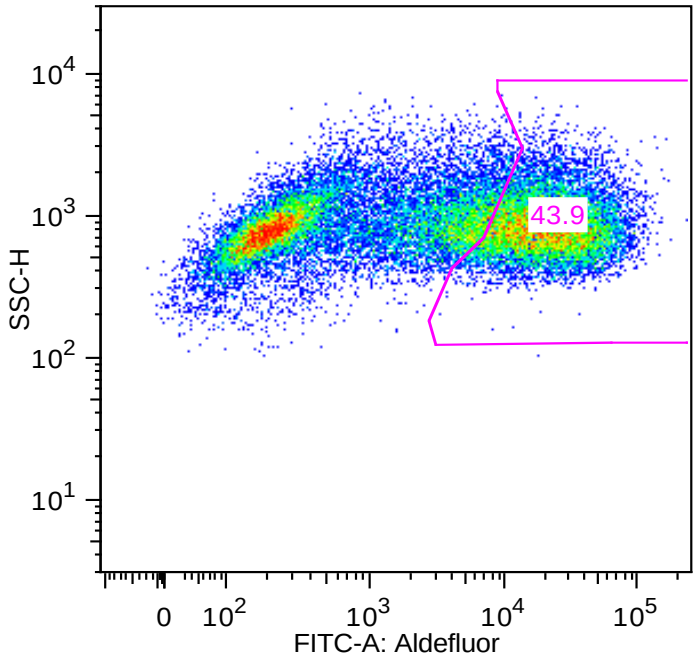
HR (95% C.I.)
Gefitinib/Placebo: 1.58 (0.83, 3.00)
Log Rank: p=0.160 Median (95% C.I.)

- Placebo: 5.1 (4.4, inf.)
- Gefitinib: 3.7 (2.6, inf.)

Final analysis (Goss, JCO 2013) OS HR 3.6 worse for mutation positive pts

Erlotinib and ALDH+ in HCC827





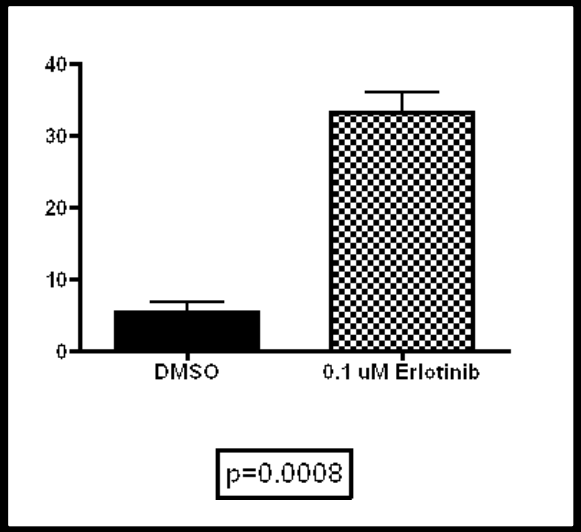
DMSO alone 1.2%

4 days of erlotinib 43.9%

Arasada and Carbone, CR 2014

Erlotinib treatment increases absolute number of clonogens in HCC 827

Colony forming



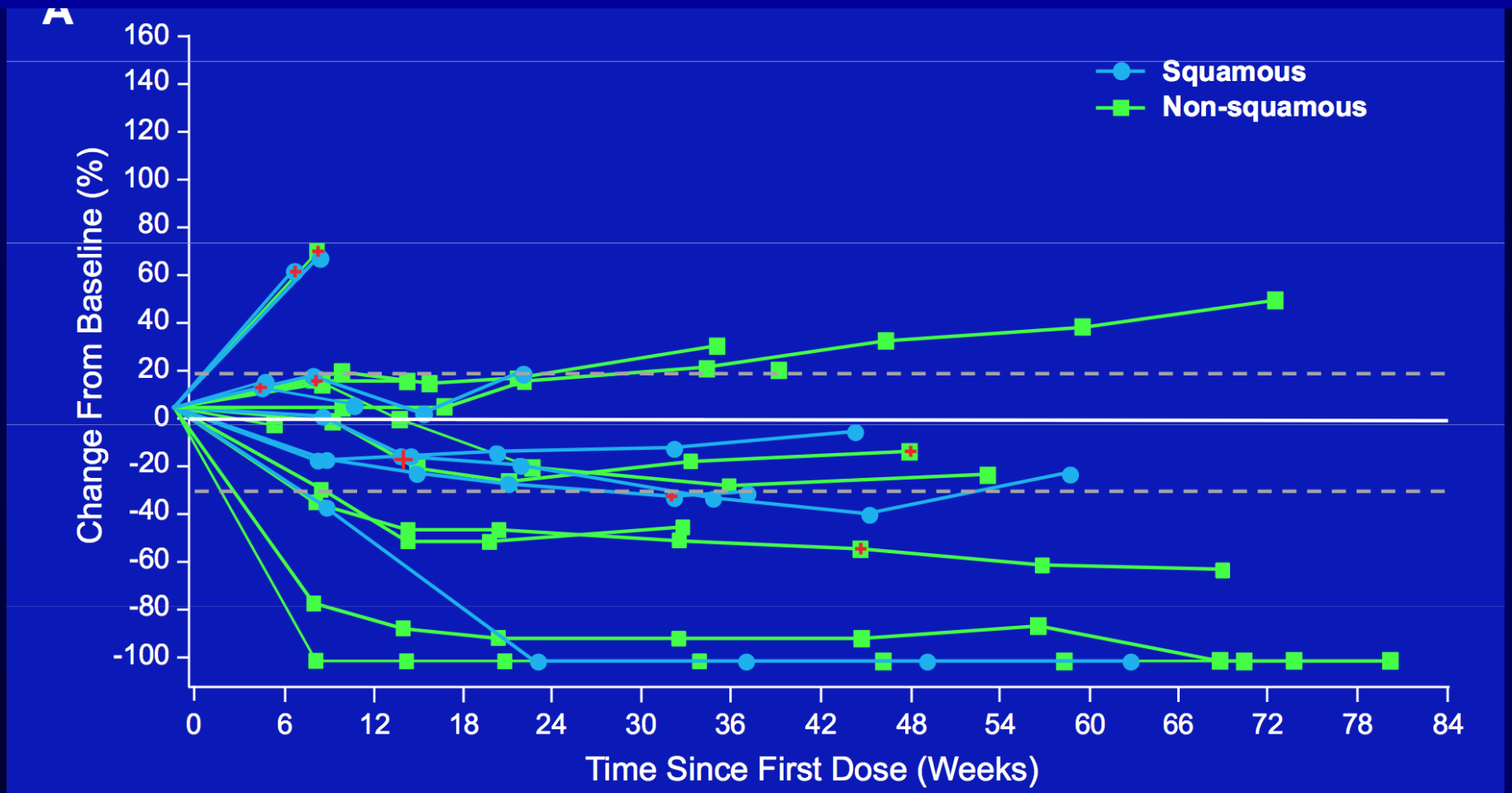
Treatment	Total number of live cells	% of Cell death	ALDH+ cells	% ALDH+ cells
NTC-DMSO	2,570,000	0	177,330	6.9
NTC-siRNA pool (0.5 μM) Erlotinib (3 day)	958,000	63	547,976	57.2
Notch1-siRNA pool (0.5 μM) Erlotinib (3 day)	1,310,000	49	547,580	41.8
Notch3-siRNA pool (0.5 μM) Erlotinib (4 day)	303,000	88	19,270	6.36

Arasada and Carbone, CR 2014

Needs for new trial designs in complex times!

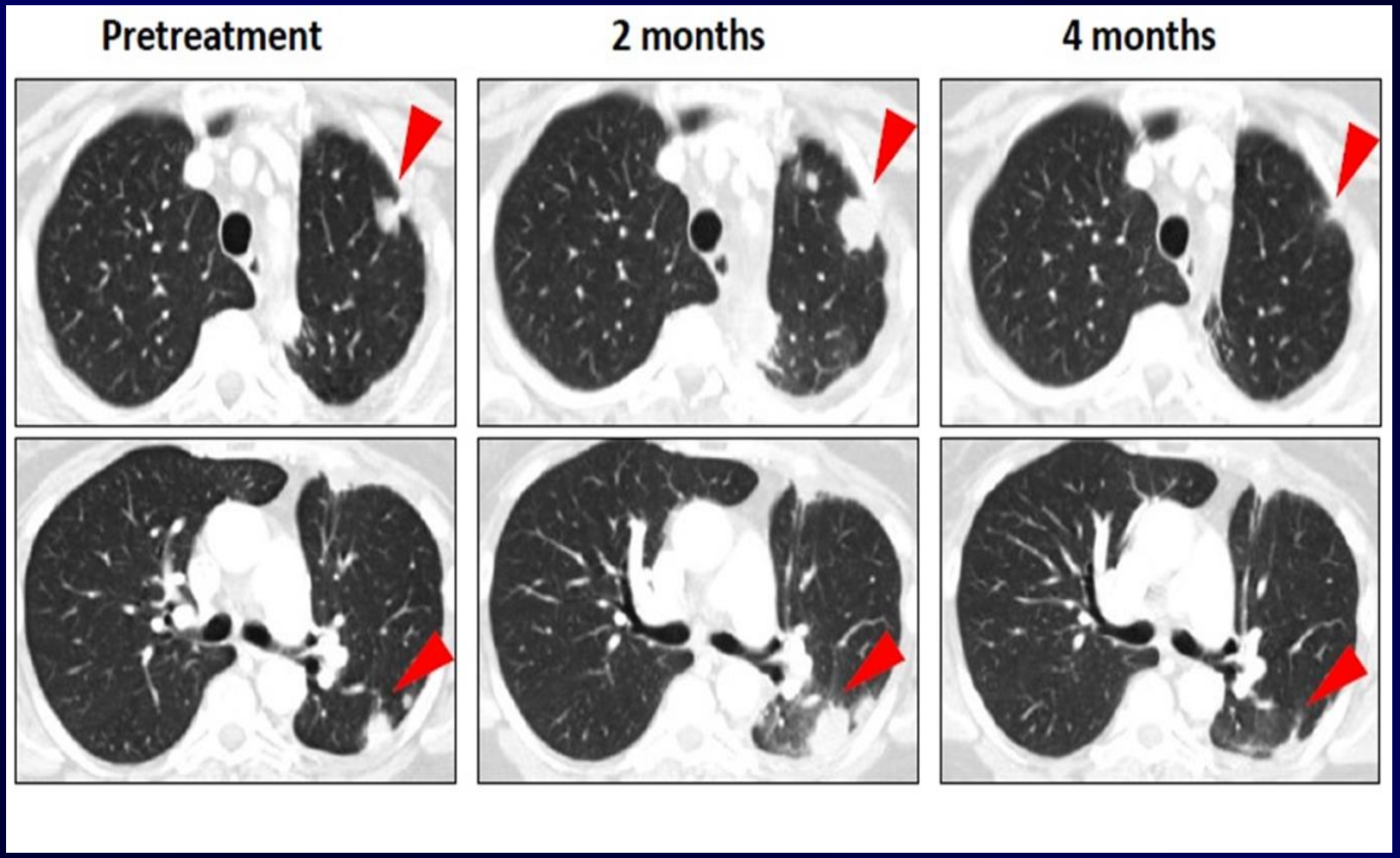
- Account for "pseudo progression"
- Detect survival benefit in the absence of response, landmark survival
- Account for manageable intra-patient heterogeneity
  - Brain metastases
  - Single site progressions
- Designs able to define optimal sequencing
  - Sequenced or newest-first targeted therapies
- "Real-time" genetic monitoring

Nivolumab monotherapy in first line – a substantial proportion have unexpectedly prolonged stable disease



Red + indicates first appearance of new lesion

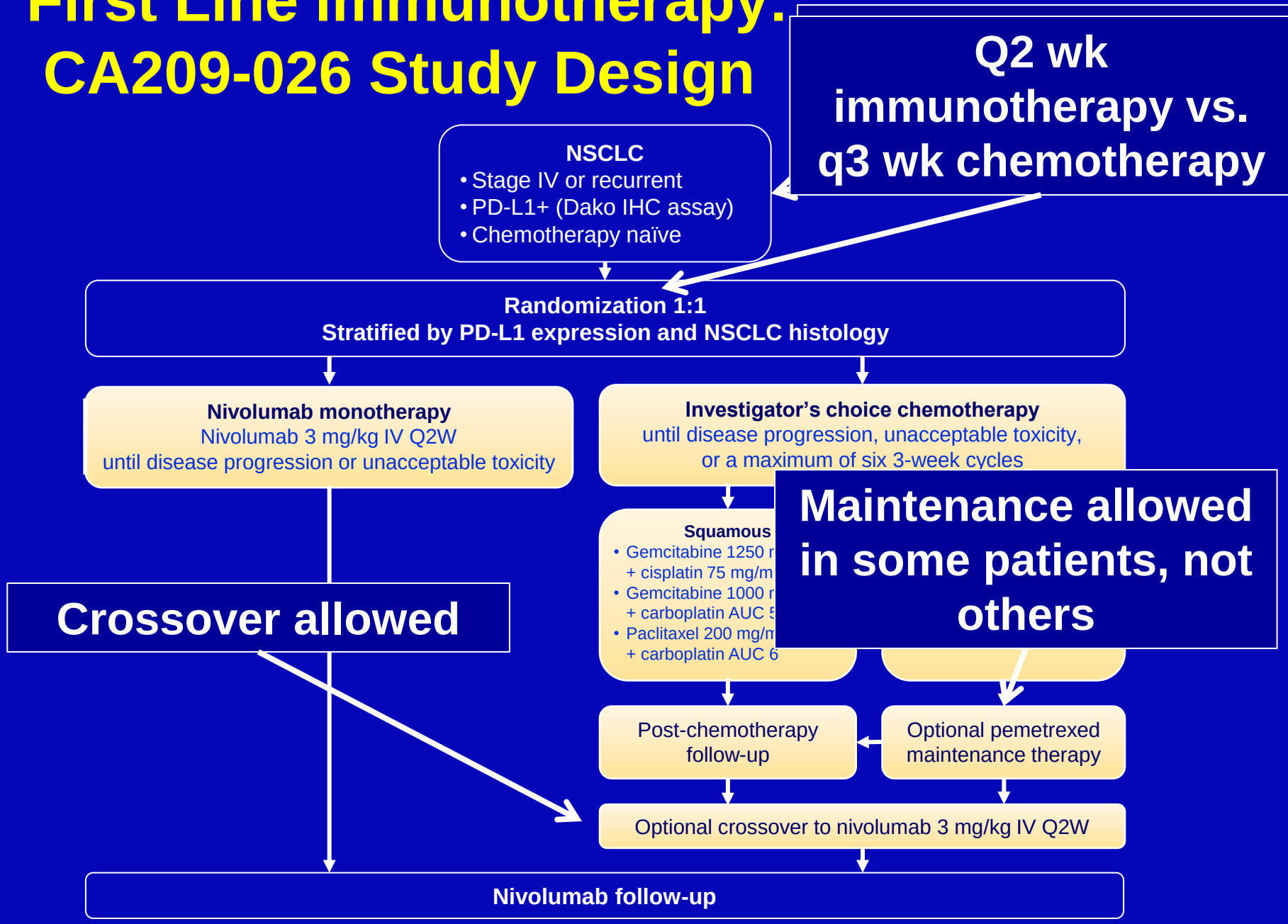
Pseudoprogression in Metastatic NSCLC (BMS-936558)



- **Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression**
- **Dx ‘04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed**

Antonia S, Moffitt Cancer Center

First Line immunotherapy: CA209-026 Study Design



My conclusions

- Modern therapies are starting to improve long-term survival – the "tail" of the curve, not just medians or HRs.
- Until we cure everybody, selecting the right patient for the right therapy is still a crucial goal
  - Even when some benefit is seen in unselected populations
- Randomized strategies are still crucial, but allowing crossover both reflects reality and is more ethical

End