Late Drug Development (Molecular Targeted Therapy)

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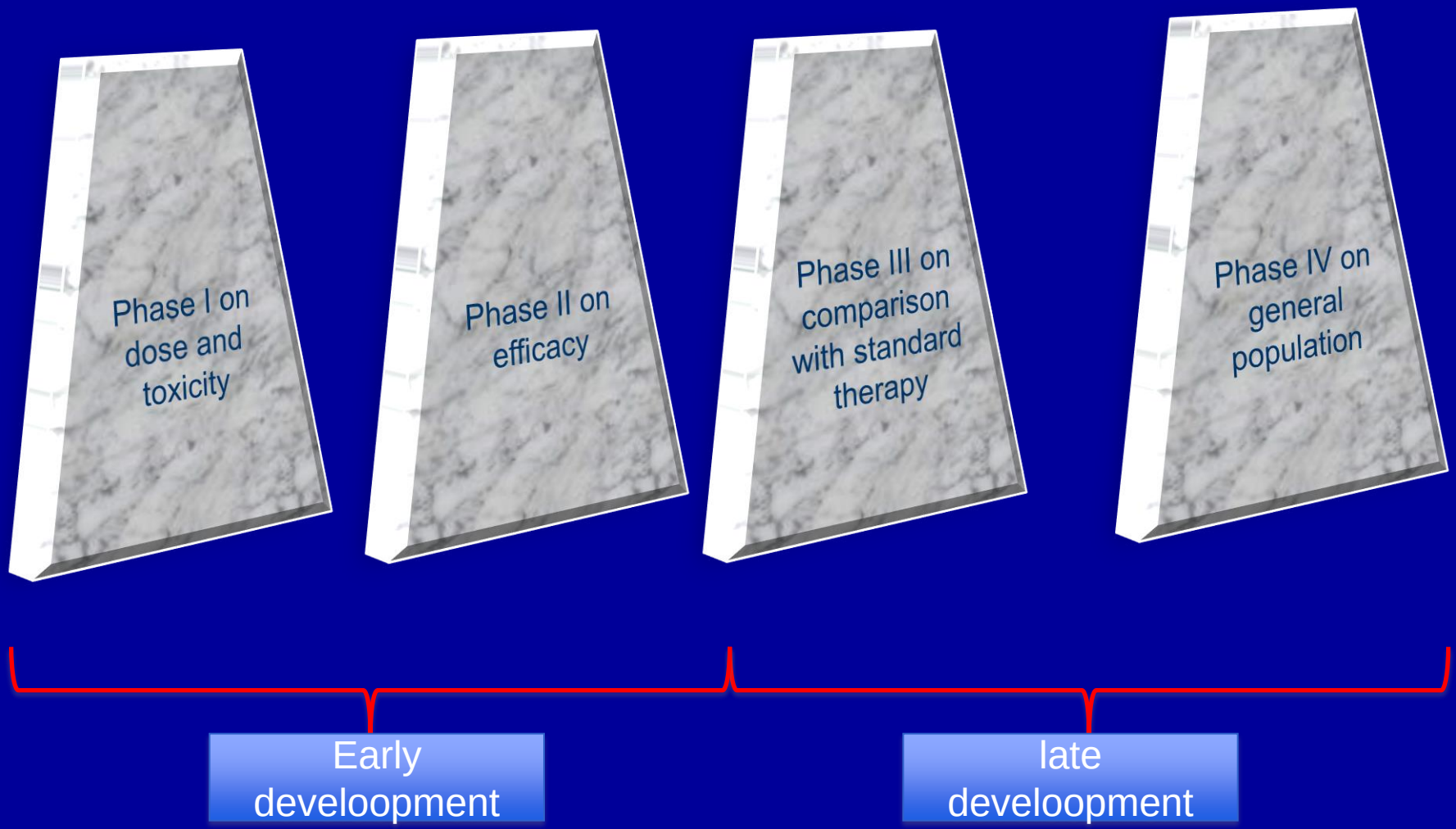
Cornerstone for clinical trial design



Study objectives

- Early development
  - Pharmacokinetic and dosing
  - Proof of concept
  - Identification of biomarker
- Late development
  - Prove to be better than standard treatment
  - Drug approval by regulatory bodies

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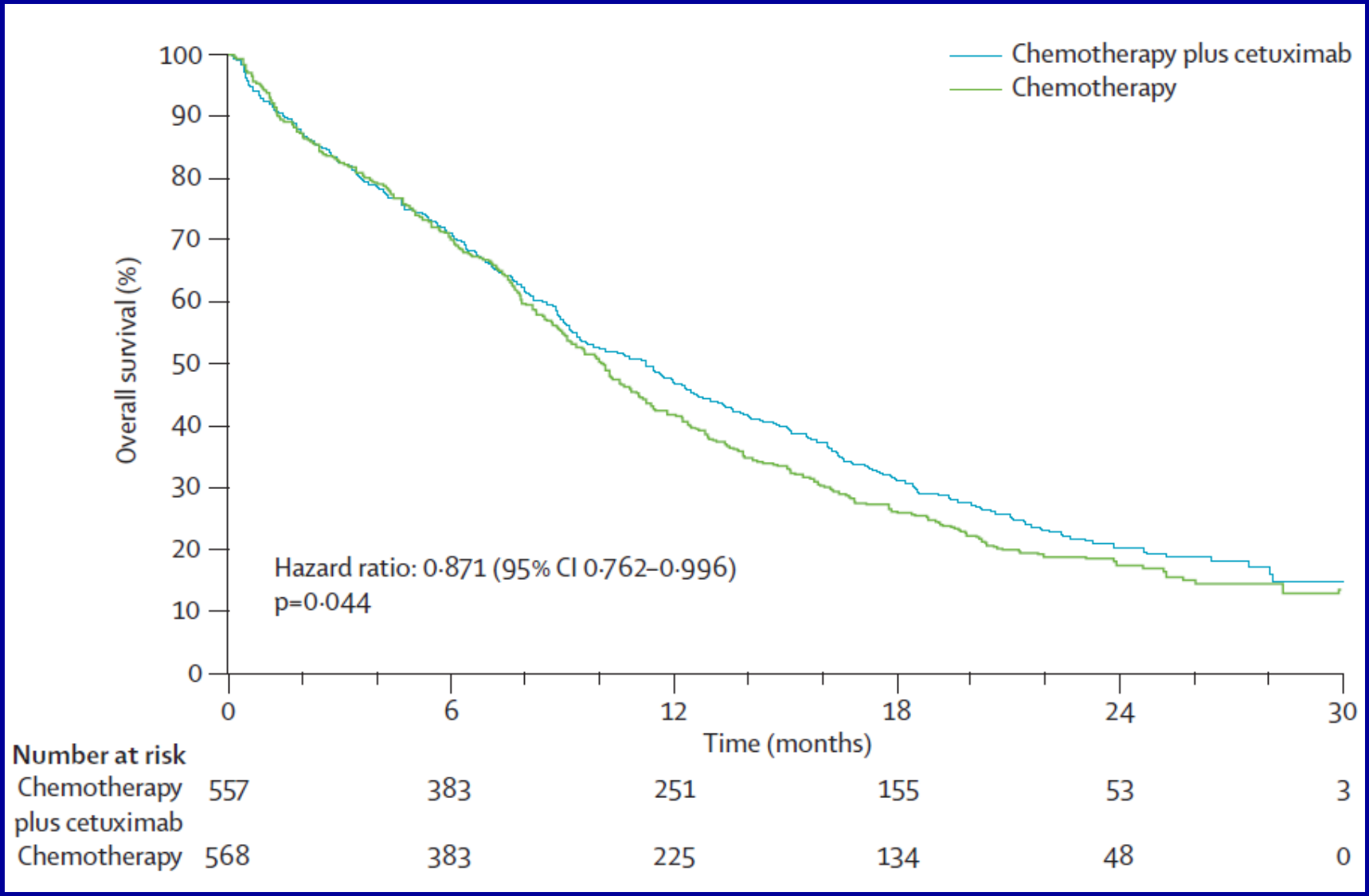
A classic late drug development study on targeted therapy



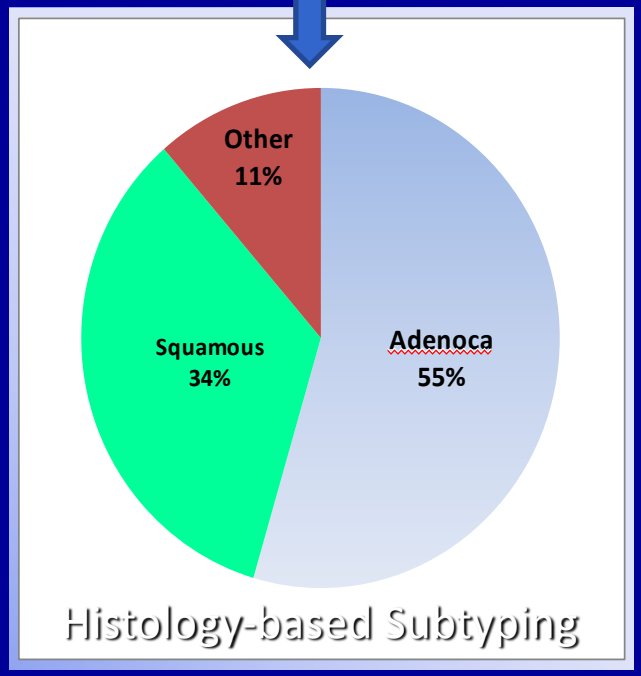
Pirker R et al. Lancet 2009, 373, 1525

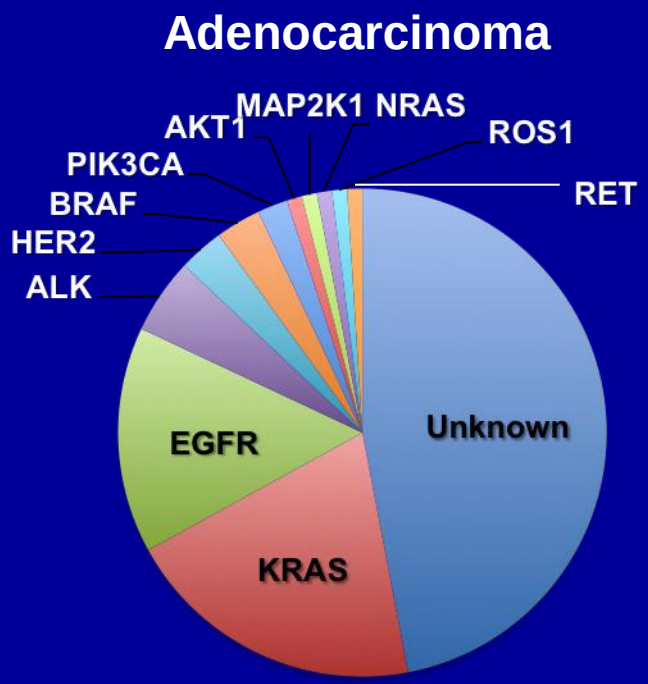
Basic assumptions on phase III design

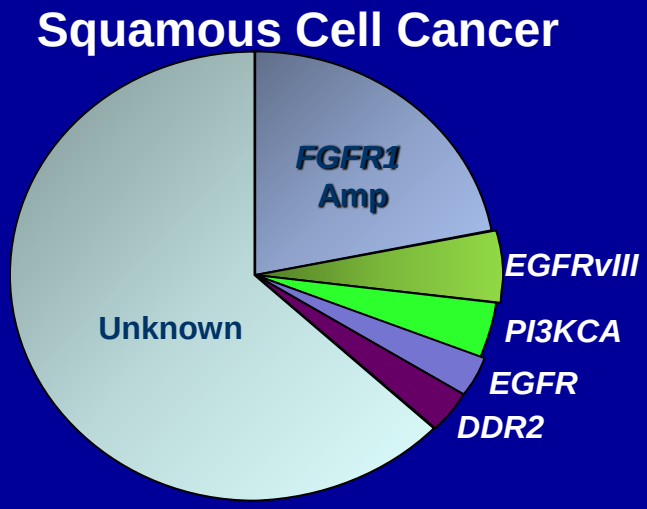
- All patients enrolled to study share similar characteristics (clinically and genonically) **MAY BE**
- Stratification by few clinical criteria trying to assure similarity between the two arms **MAY BE**
- Impact of the study drug at first line would influence the overall survival, ie assuming both the exposure and outcome from subsequent therapy to be similar between the two arms **UNLIKELY**
- Minimal cross over to the other arm **MAY BE**

Histology similarity ≠Genomic similarity

NSCLC as one disease







Li, Gandara et al: JCO (in press) adapted from Pao et al

Oncogene in Chinese Patients with NSCLC

Group	EGFR	PTEN	STK11	ALK	KRAS	c-Met	PIK3CA	BRAF	DDR2	FGFR2
NSCLC	28.4%(147/517)	9.5%(21/220)	7.9%(8/101)	6.3%(15/239)	5.4%(27/498)	4.5%(20/448)	4.4%(20/452)	1.5%(7/452)	1.2%(2/166)	0.6%(1/165)
Non-smoker	40.9%(119/291)	6.3%(7/112)	2.1%(1/48)	6.4%(8/125)	3.6%(10/279)	4.3%(11/255)	4.6%(12/260)	1.5%(4/260)	0%(0/91)	0%(0/90)
Smokers	12.4%(28/226)	13.0%(14/108)	13.2%(7/53)	6.1%(7/114)	7.8%(17/219)	4.7%(9/193)	4.2%(8/192)	1.6%(3/192)	2.7%(2/75)	1.3%(1/75)
AC	40.3%(140/347)	7.0%(8/115)	8.6%(5/58)	7.7%(10/130)	7.1%(24/340)	4.5%(14/308)	4.2%(13/307)	2.3%(7/307)	0%(0/97)	0%(0/96)
SCC	4.4%(6/144)	10.6%(10/94)	6.1%(2/33)	4.1%(4/93)	1.5%(2/132)	5.2%(6/116)	5.8%(7/121)	0.0%(0/121)	3.3%(2/61)	1.6%(1/61)
LCC	3.8%(1/26)	27.3%(3/11)	10.0%(1/10)	8.3%(1/12)	3.8%(1/26)	0.0%(0/24)	0.0%(0/24)	0.0%(0/24)	0%(0/8)	0%(0/8)
NS with AC	49.8%(114/229)	9.1%(7/77)	2.7%(1/37)	9.3%(8/86)	4.5%(10/223)	4.8%(10/207)	5.2%(11/210)	1.9%(4/210)	0.0%(0/71)	0.0%(0/70)
S with AC	22.0%(26/118)	2.6%(1/38)	19.0%(4/21)	4.5%(2/44)	12.0%(14/117)	4.0%(4/101)	2.1%(2/97)	3.1%(3/97)	0.0%(0/26)	0.0%(0/26)
NS with SCC	8.0%(4/50)	0.0%(0/32)	0.0%(0/9)	0.0%(0/35)	0.0%(0/44)	2.8%(1/36)	2.6%(1/38)	0.0%(0/38)	0.0%(0/16)	0.0%(0/16)
S with SCC	2.1%(2/94)	16.1%(10/62)	8.3%(2/24)	6.5%(4/62)	2.3%(2/88)	6.3%(5/80)	7.2%(6/83)	0%(0/94)	4.4%(2/45)	2.2%(1/45)

An SJ,…Wu YL Plos ONE 7(6):e40109

Lung cancer is a heterogenous disease

- Different genomic profile between ethnicity
- Different genomic profile between smoker and non-smoker
- Different genomic profile between histologic cell type

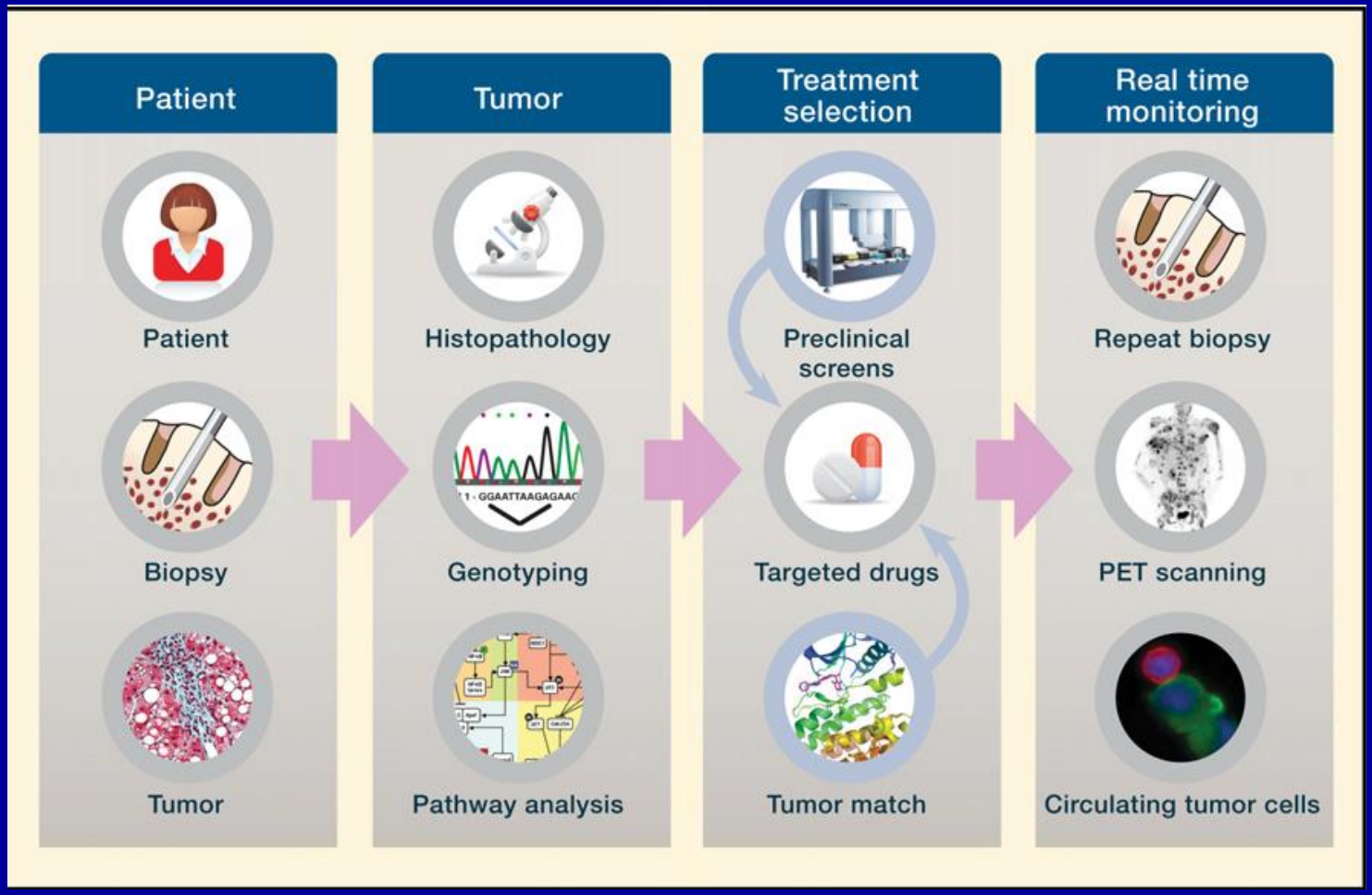
Cross-over rate in NEJ002

	Gefitinib	CBDCA/PTX
EGFR-TKI	100%	98.2%
Gefitinib	100%	98.2%
Erlotinib	27.2%	28.9%
BIBW2992	0	1.8%
Chemotherapy	64.9%	100%
Platinum based	64.9%	100%
CBDCA/PTX	50.0%	100%
Pemetrexed	28.9%	15.8%
Docetaxel	24.6%	19.3%
Others	23.7%	22.8%

Maemondo et al NEJM 2010

The old day late-drug development model may not be applicable to modern day molecular targeted therapy

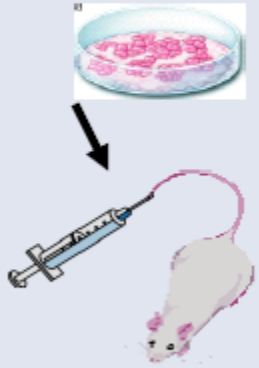
New strategy on drug development



Haber et al Cell 2011

Integrated New Drug-New Biomarker Development Paradigm:

Phases of Development of a New Drug

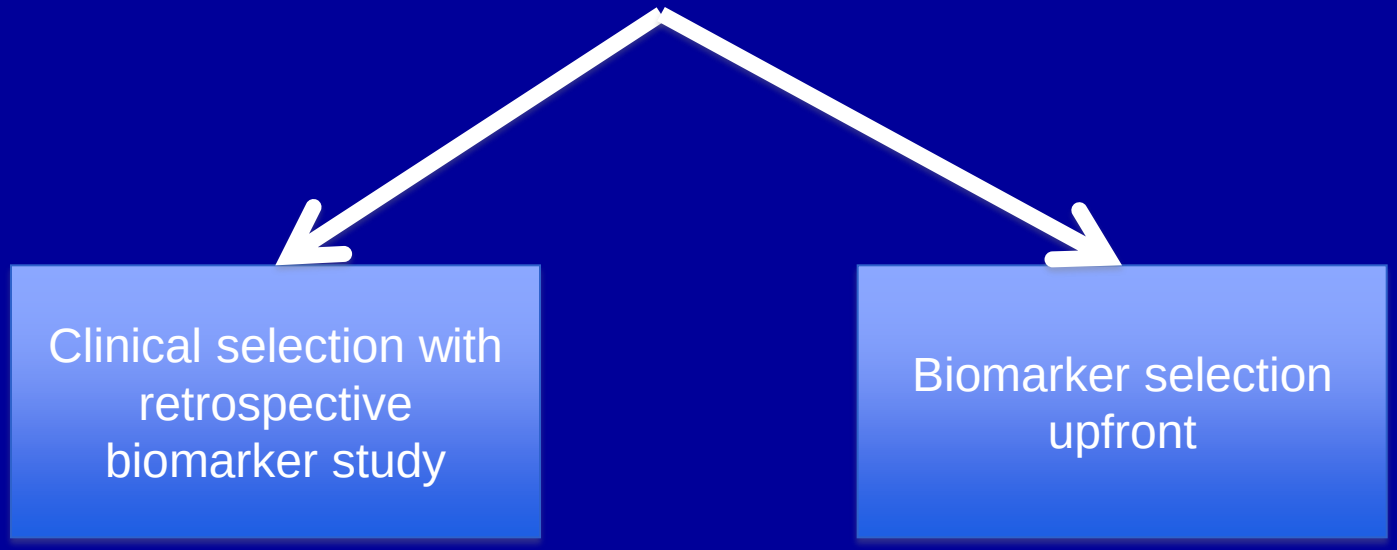
Pre-clinical	Phase I	Phase II	Phase III	Drug Approval
	N=30	N=300	N=1600	Total Time ~90 mos (7.5 years)
~18 mo.	~18 mo.	~18 mo.	~36 mos	

Phases of Development of New Biomarker linked to New Drug

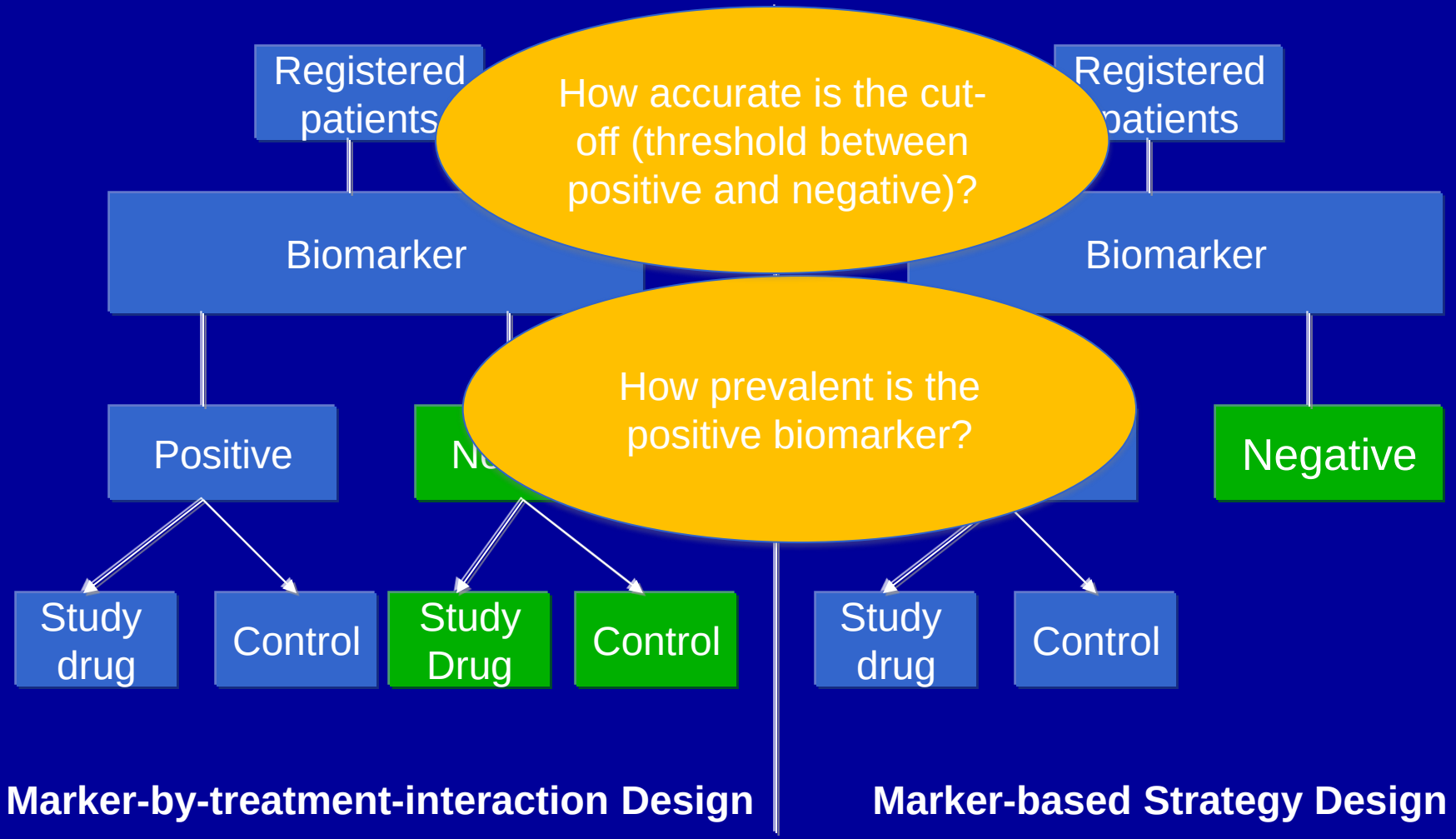
Confirm Target	Integrate Biomarker	Biomarker Informative?	Clinical Validation	Clinical Application of Biomarker
Assay Development	Assay Performance	Assay Validation	Co-Primary Endpoint	

from Gandara et al: Clin Lung Cancer, 2012

Biomarker selection design

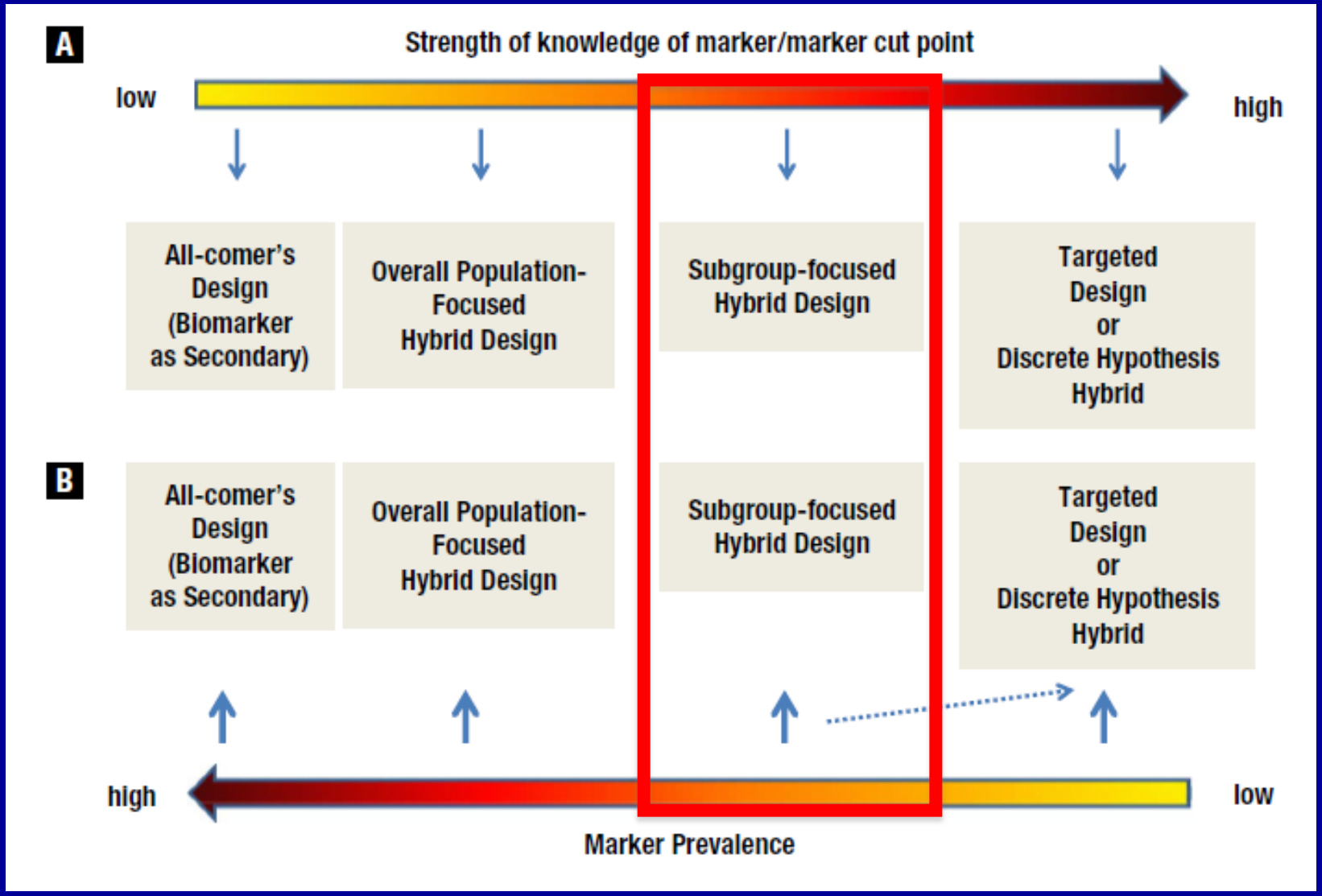


Phase III biomarker-based study design



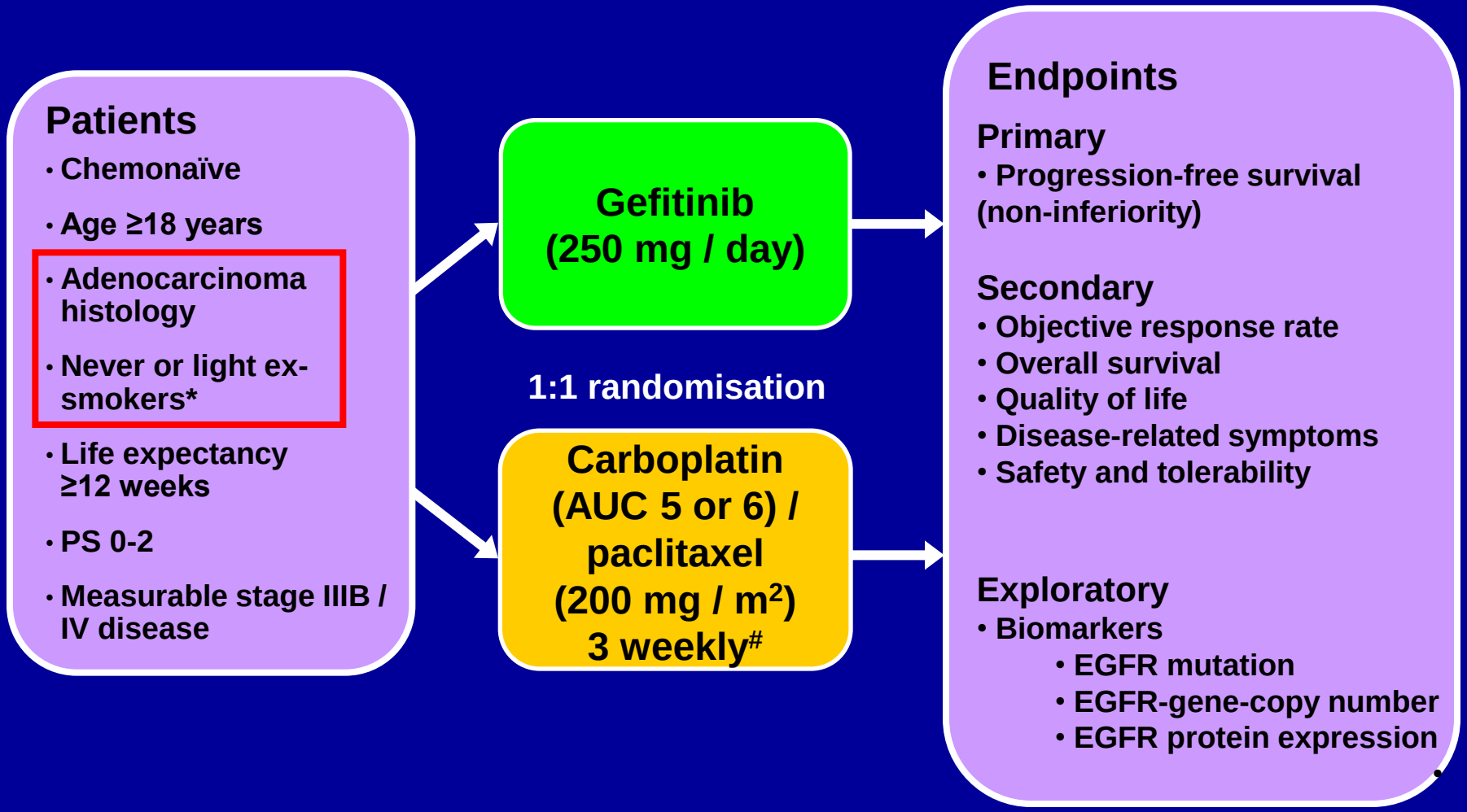
Mandrekar SJ et al J Biopharm Stat 19:530, 2009

When to use which design?



from Redman, Gandara et al: Clin Cancer Res 2012
& Gandara et al: Clin Lung Cancer 2012

IPASS

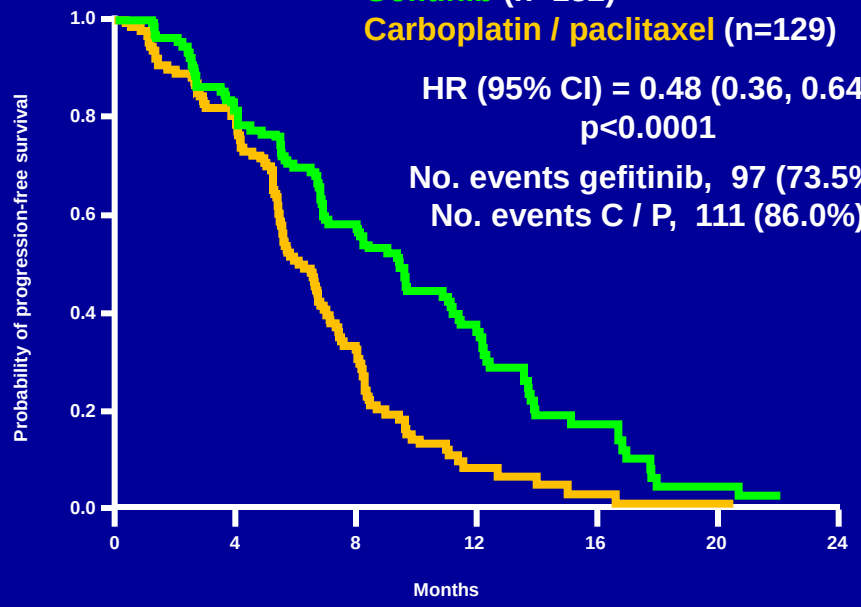


*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

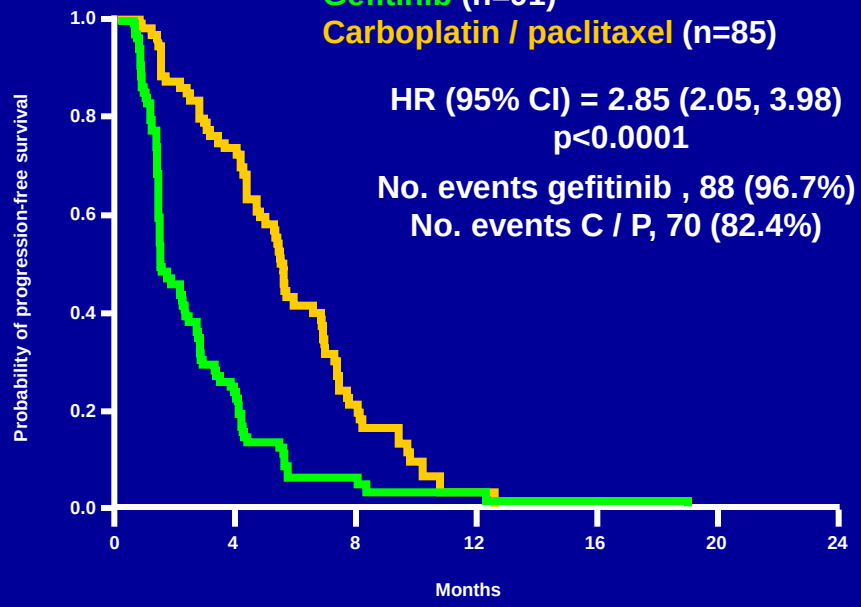
Mok et al NEJM 361:947 2009

IPASS: EGFR Mutation and Progression-free survival

EGFR mutation positive



EGFR mutation negative



At risk :														
Gefitinib	132	108	71	31	11	3	0	91	21	4	2	1	0	0
C / P	129	103	37	7	2	1	0	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok et al NEJM 361:947 2009

Validation of the biomarker

- Retrospective study
  - Existing clinical data base
  - Un-intended retrospective evaluation of biomarker
- Prospective single arm study
  - Able to study the prognostic value only
- Prospective randomized study
  - Intended retrospective biomarker analysis
  - Biomarker selected study
  - Interaction test

Validation of biomarker trial

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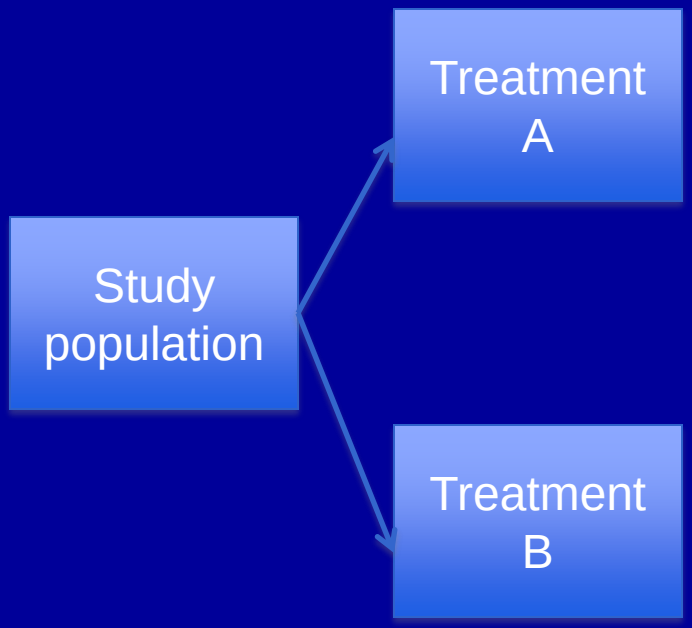
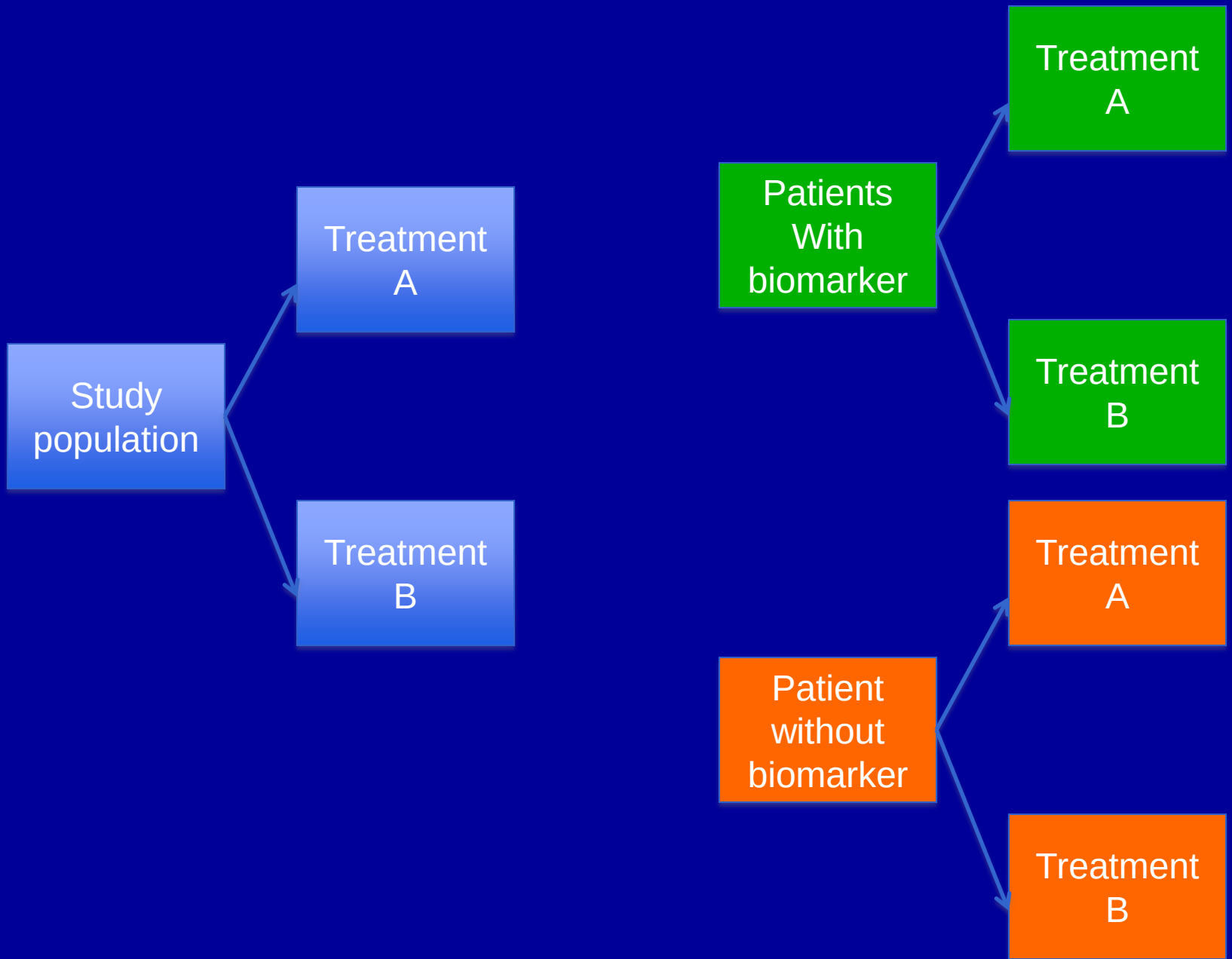
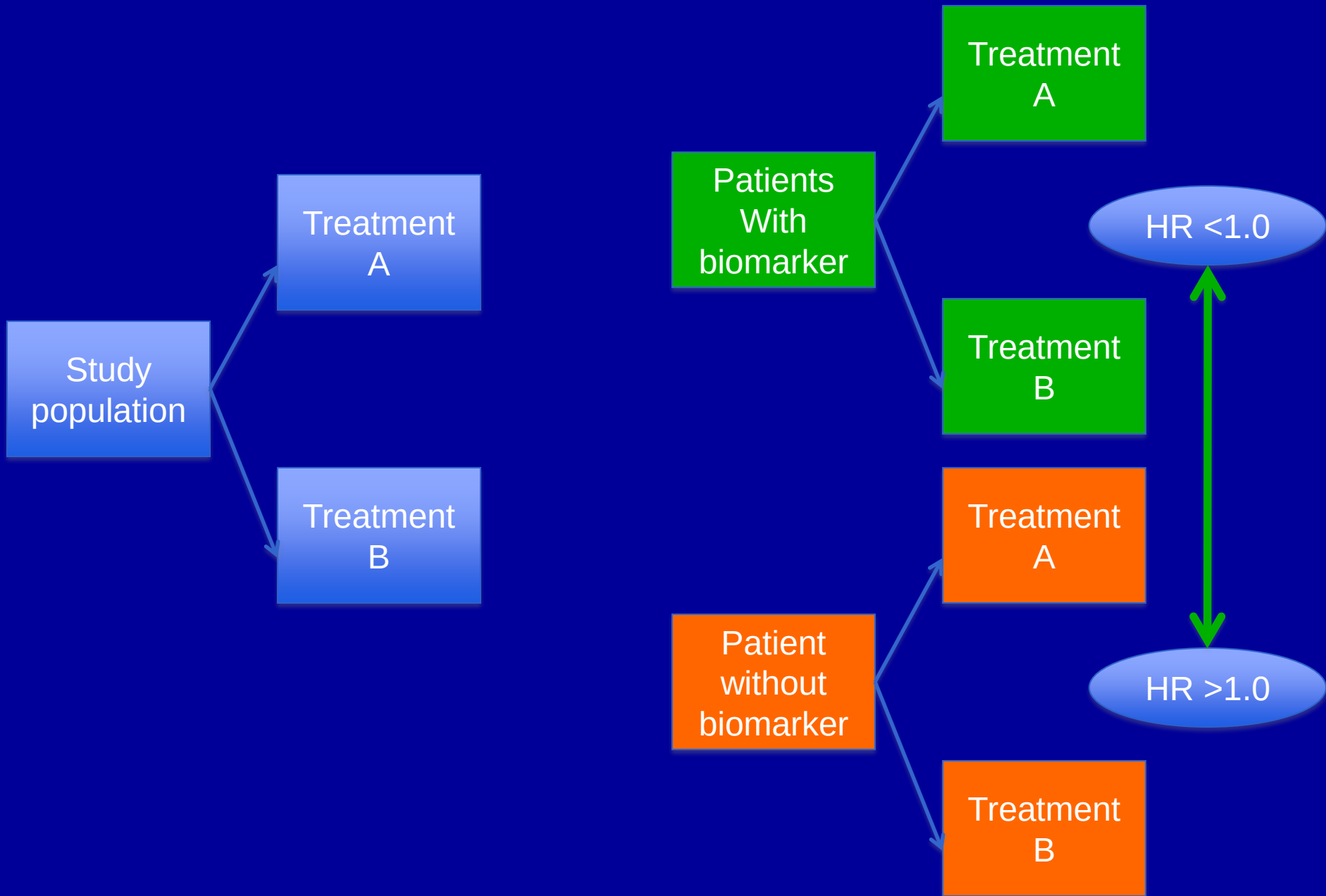
Interaction test



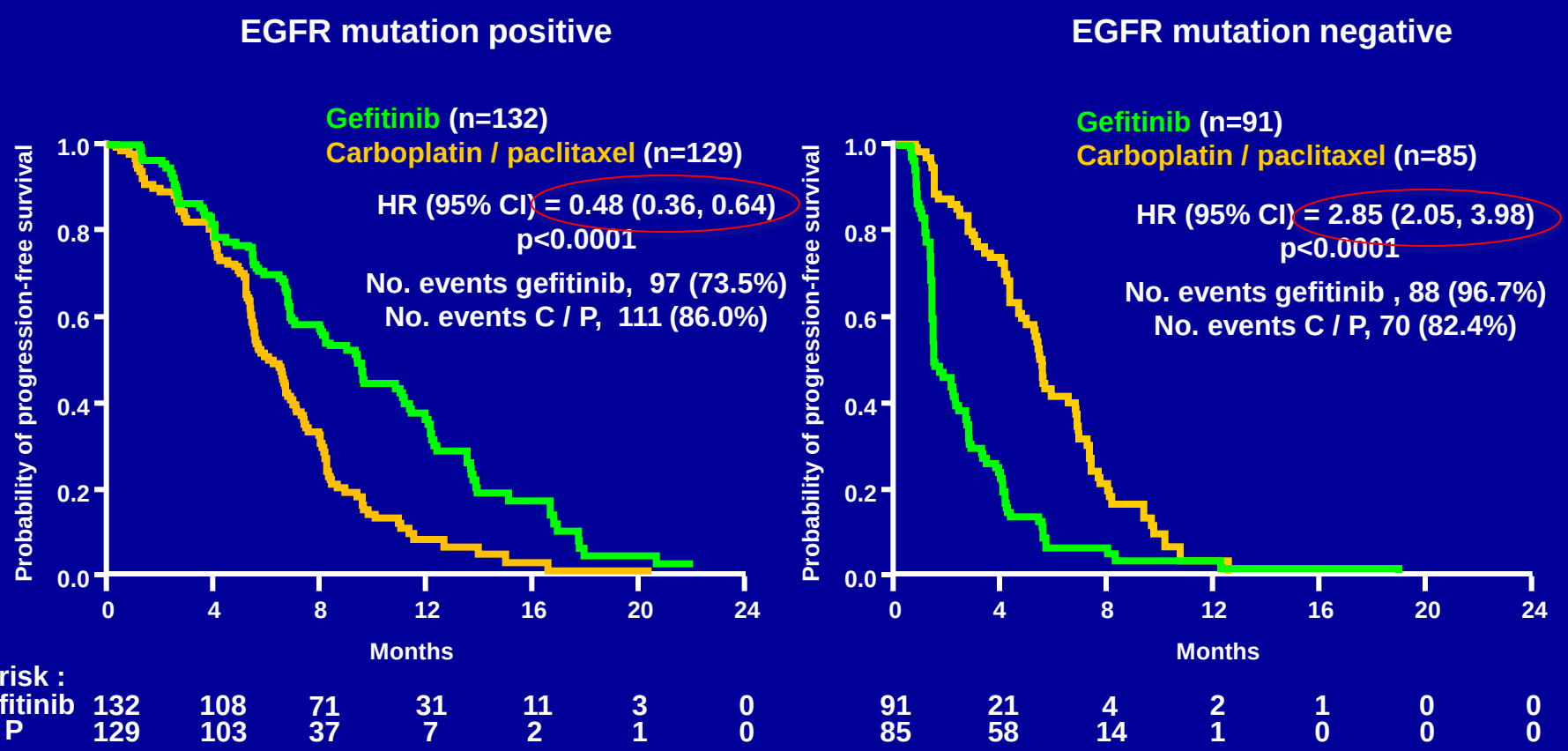
Interaction test



Interaction test



Progression-free survival in EGFR mutation positive and negative patients



Treatment by subgroup interaction test, p<0.0001

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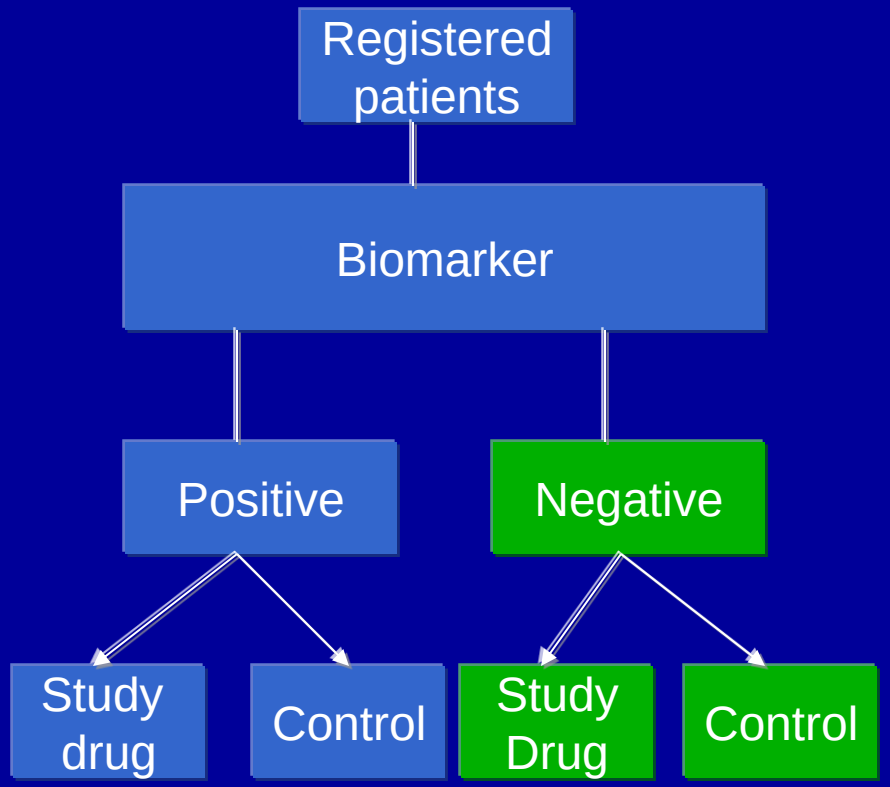
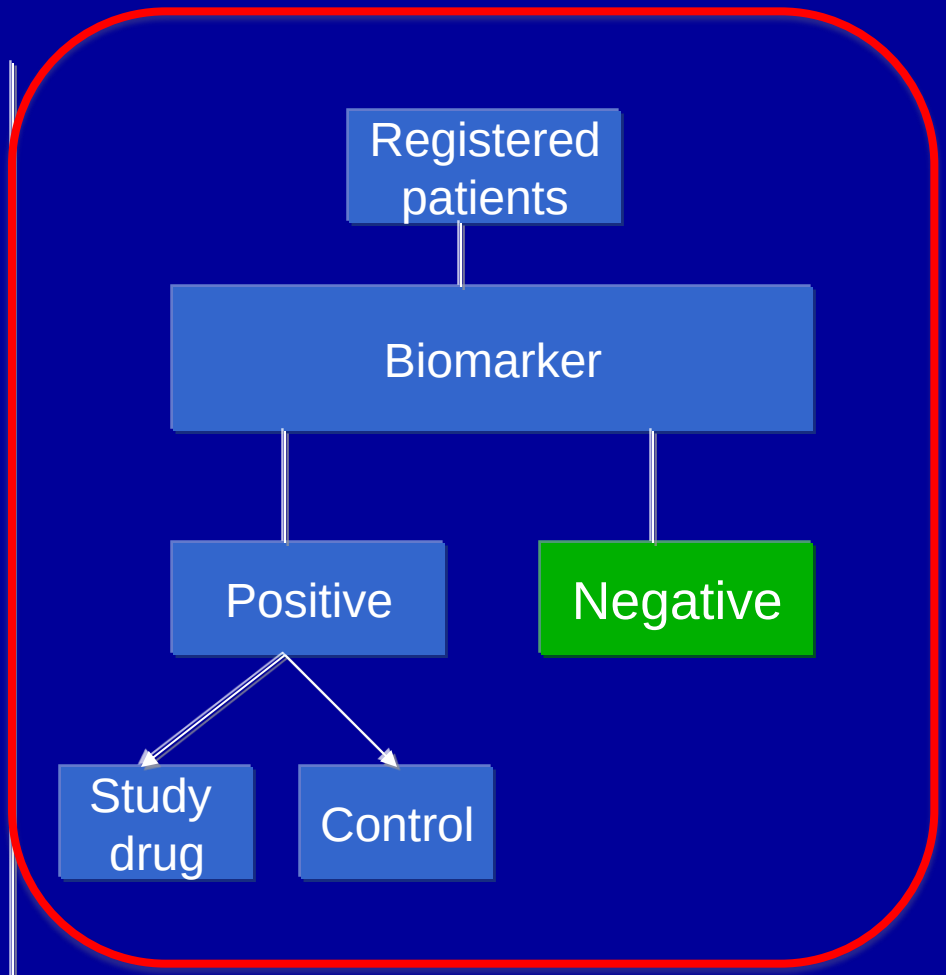
Mok et al NEJM 361:947 2009

Phase III study design



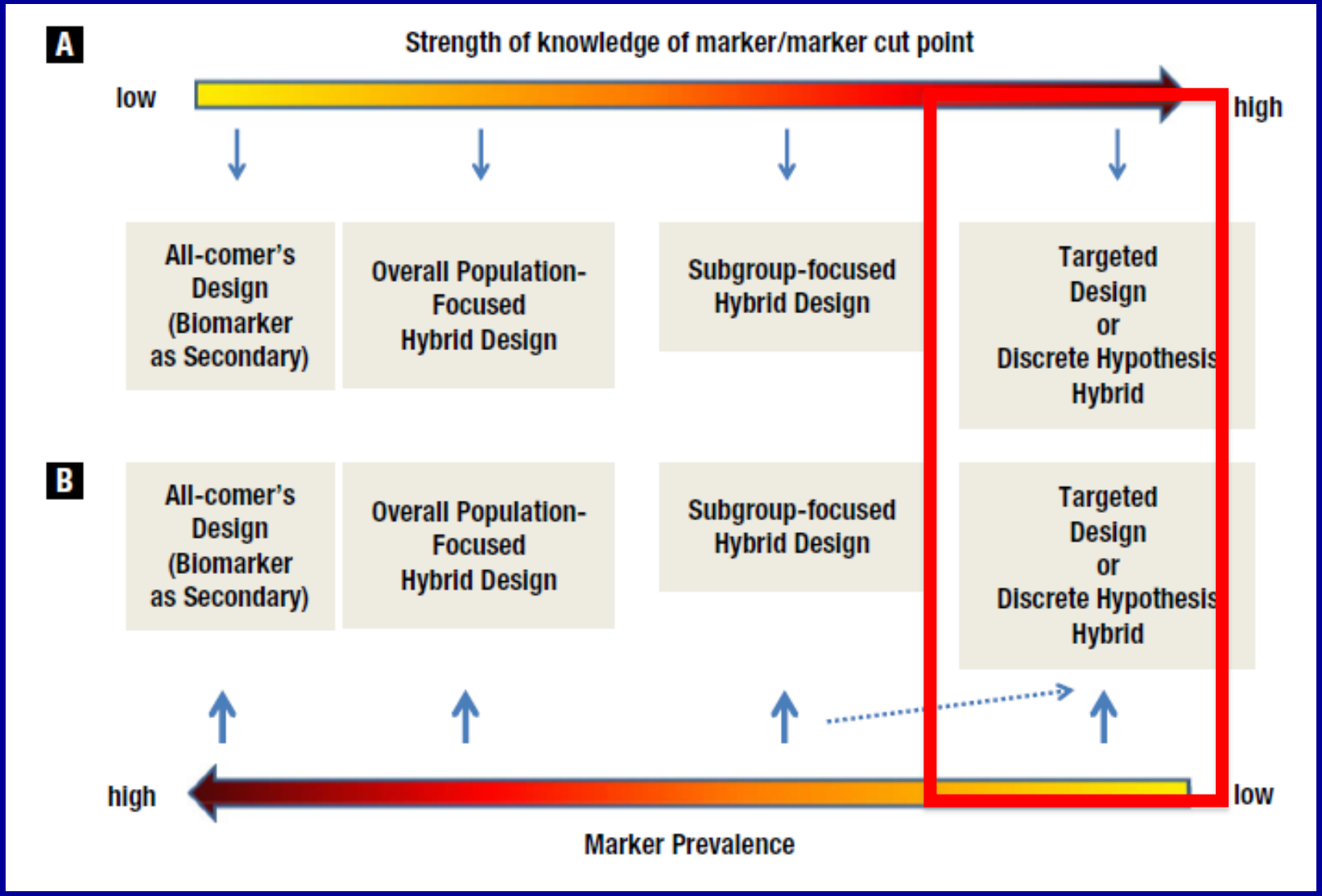
Marker-by-treatment-interaction Design



Marker-based Strategy Design

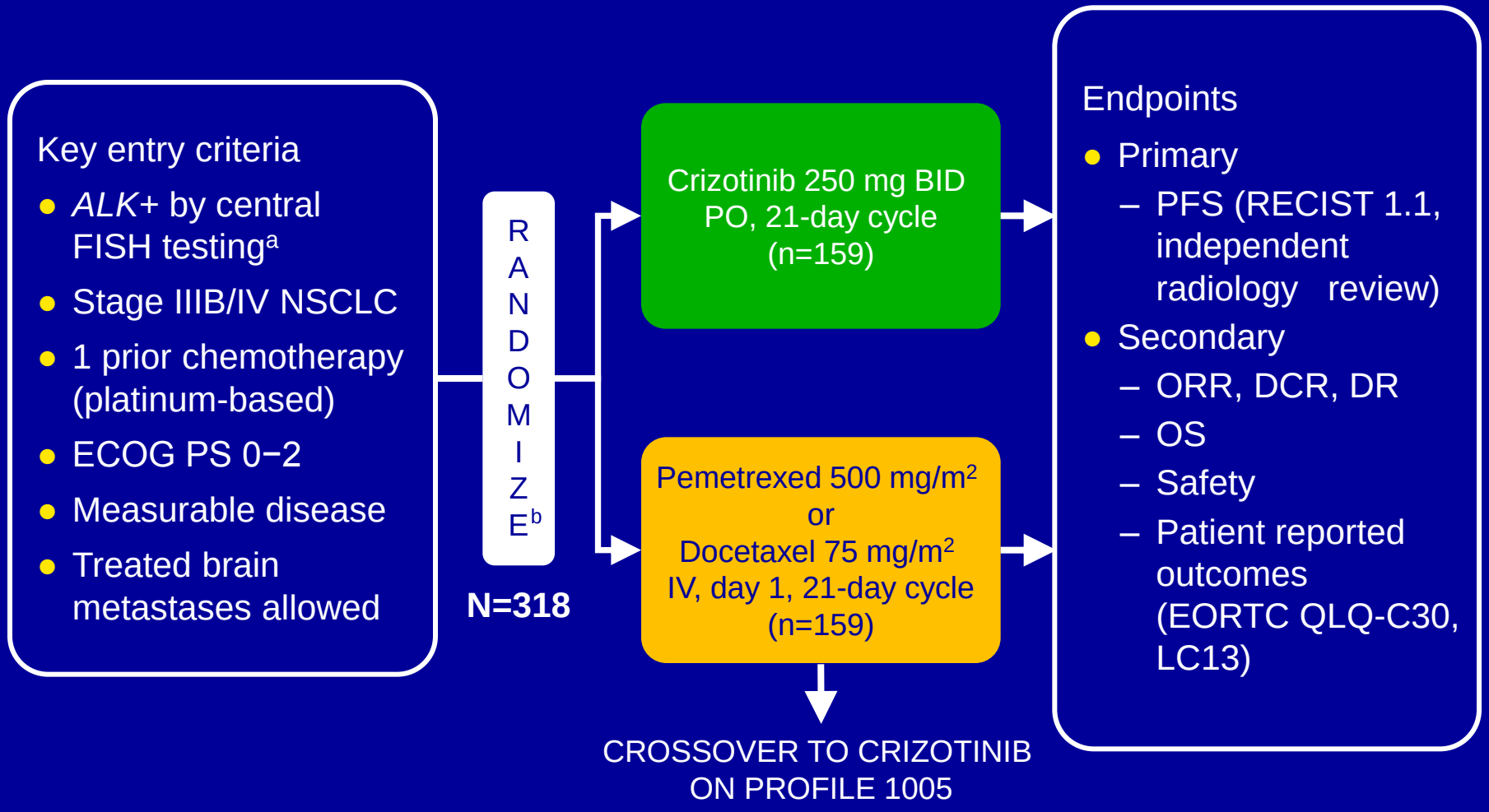
Mandrekar SJ et al J Biopharm Stat 19:530, 2009

When to use which design?



from Redman, Gandara et al: Clin Cancer Res 2012
& Gandara et al: Clin Lung Cancer 2012

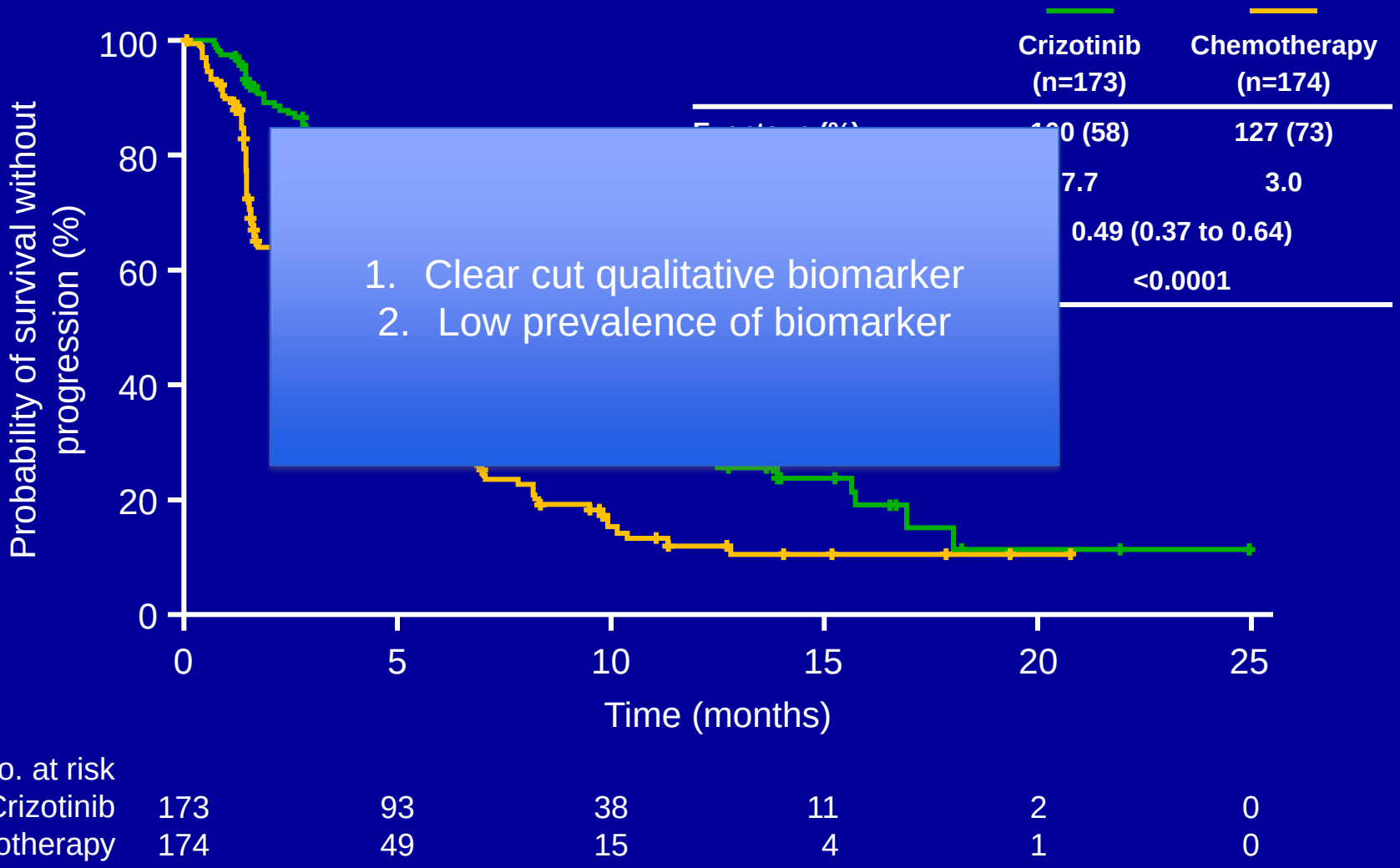
PROFILE 1007



[a]*ALK* status determined using standard *ALK* break-apart FISH assay [b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Shaw et al ESMO 2012

PROFILE 1007: PFS



PROFILE 1014: First line study

Trial design	Endpoints	Stratification
World-wide, multicenter, randomized, open-label, focused screening	Primary: PFS* Secondary: 6- and 12-month OS; OS; ORR*; DCR; DR; Safety; HRQoL; Lung cancer-specific symptoms; General health status; Biomarkers; TTD; HCRU	ECOG PS (0/1 vs 2) Ethnicity (Asian vs non-Asian) Brain metastases

*Based on RECIST v 1.1 and confirmed by independent radiology review

Key entry criteria

- Diagnosis of locally advanced/metastatic non-squamous NSCLC; ECOG 0-2
- Positive for *ALK*
- No prior treatment for advanced disease
- Brain metastases allowed

RANDOMIZE

N=320

N=160 Arm A: Crizotinib 250 mg BID administered on a continuous dosing schedule

N=160 Arm B: Pemetrexed/ cisplatin or pemetrexed/ carboplatin Day 1 of a 21-day cycle

Patients in Arm B who have RECIST-defined PD as determined by the independent radiology review will be allowed to cross over to Arm A

PI: Mok T and Blackhall F

Common factors in positive trials

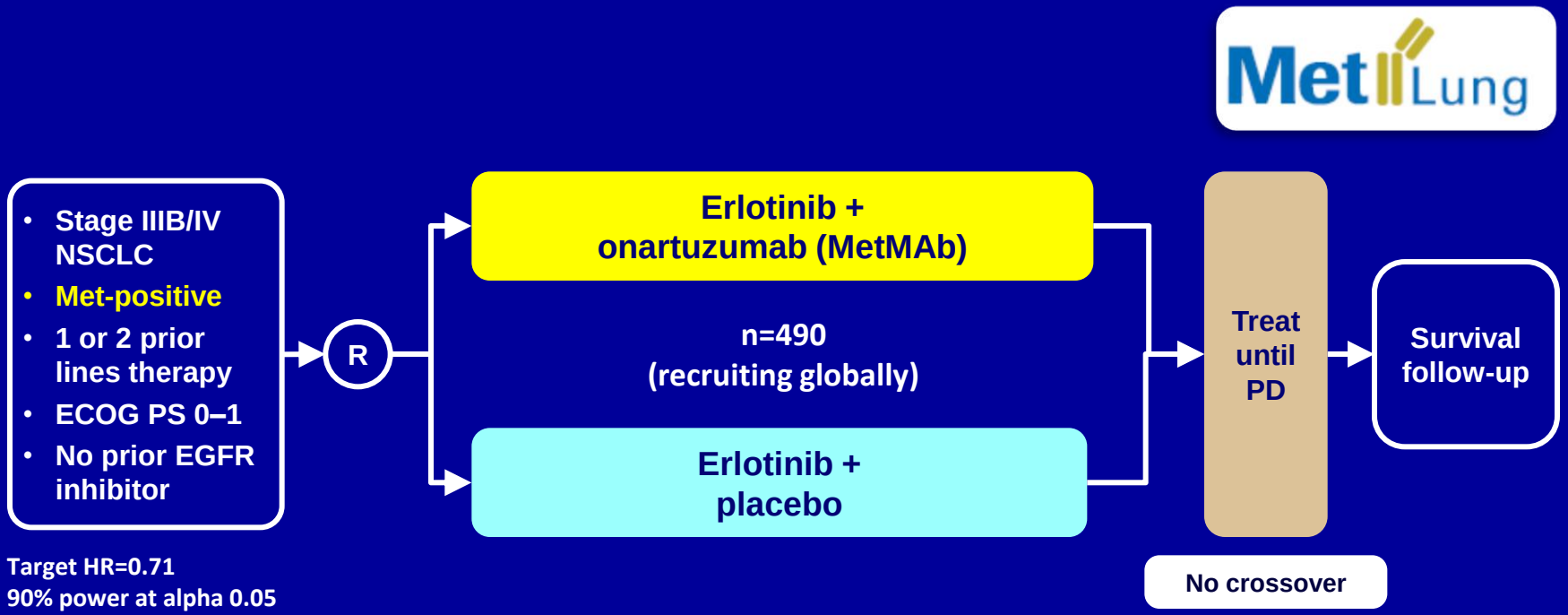
- Proven driver oncogenic
- Known incidence of the driver oncogene in population
- Convincing waterfall plot
- Established predictive biomarker prior to phase III study

Common factors in negative trial

- Unselected population
- Limited translational research from lab to clinic
- Lack of a known potential predictive biomarker before engagement in phase III study
- Chemotherapy +/- targeted drug in unselected population

Can we predict outcome of late drug development trial?

MetLung: global phase III study of onartuzumab (MetMAb) in Met-positive NSCLC



Primary endpoint

- OS

Secondary endpoints

- **PFS, ORR, QoL, safety**

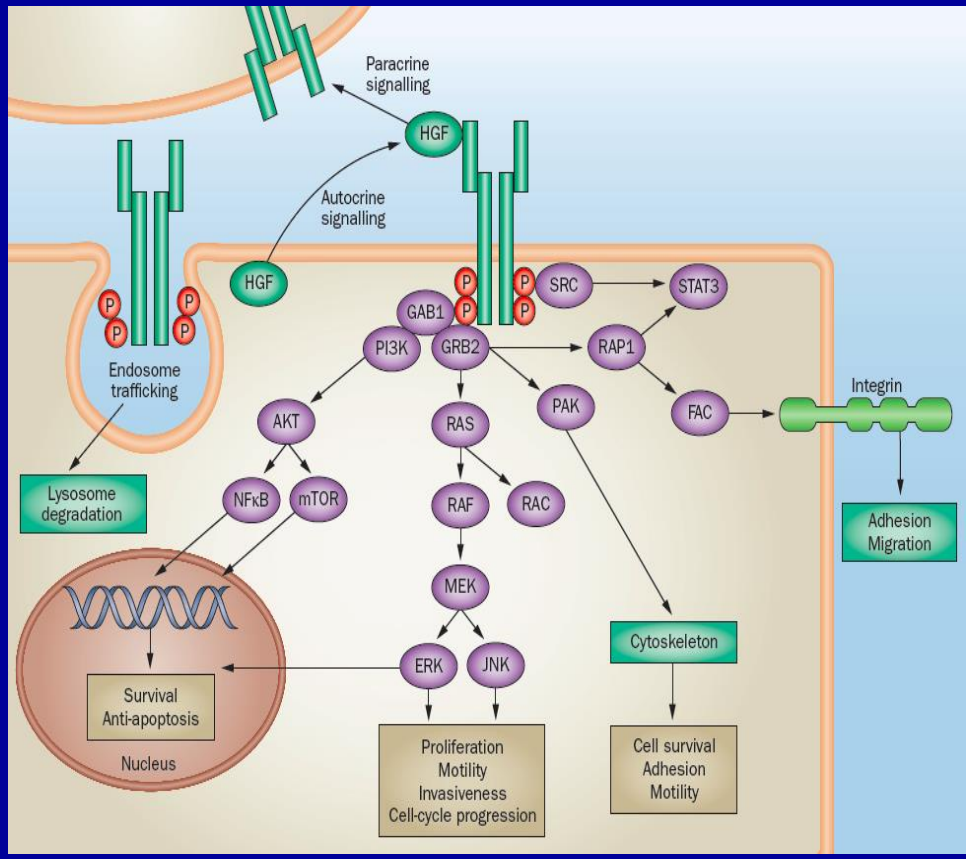
Stratification

- *EGFR* Mut status
- Met 2+ or 3+ score
- Number of prior lines of therapy
- Histology

Erlotinib 150mg/day
Onartuzumab (MetMAb) 15mg/kg iv q3w

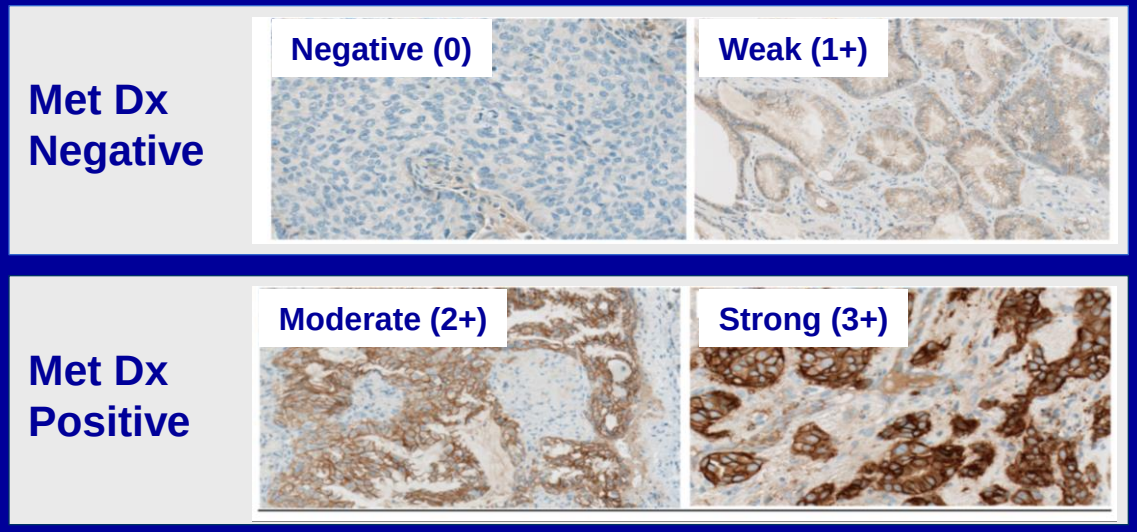
Positive factors

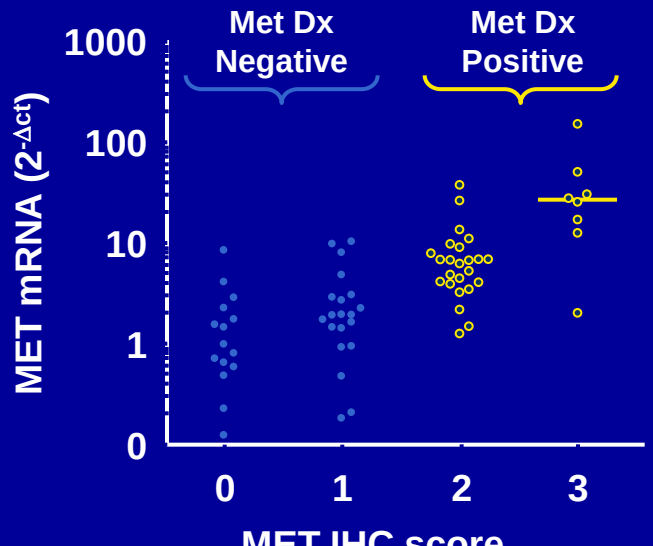
- Known C-MET pathway and its importance to cell proliferation
- Incidence of Met-Positive is known
- Biomarker established in the randomized phase II study
- C-MET and EGFR mutation known in most patients



Negative factors

- C-MET may not be a driver oncogene
- Met-positive by IHC is semi-quantitative subjective biomarker
- Limited sample size (n=66) of met-positive patient in the randomized phase II study
- Role of erlotinib in EGFR mutation wild type is debatable





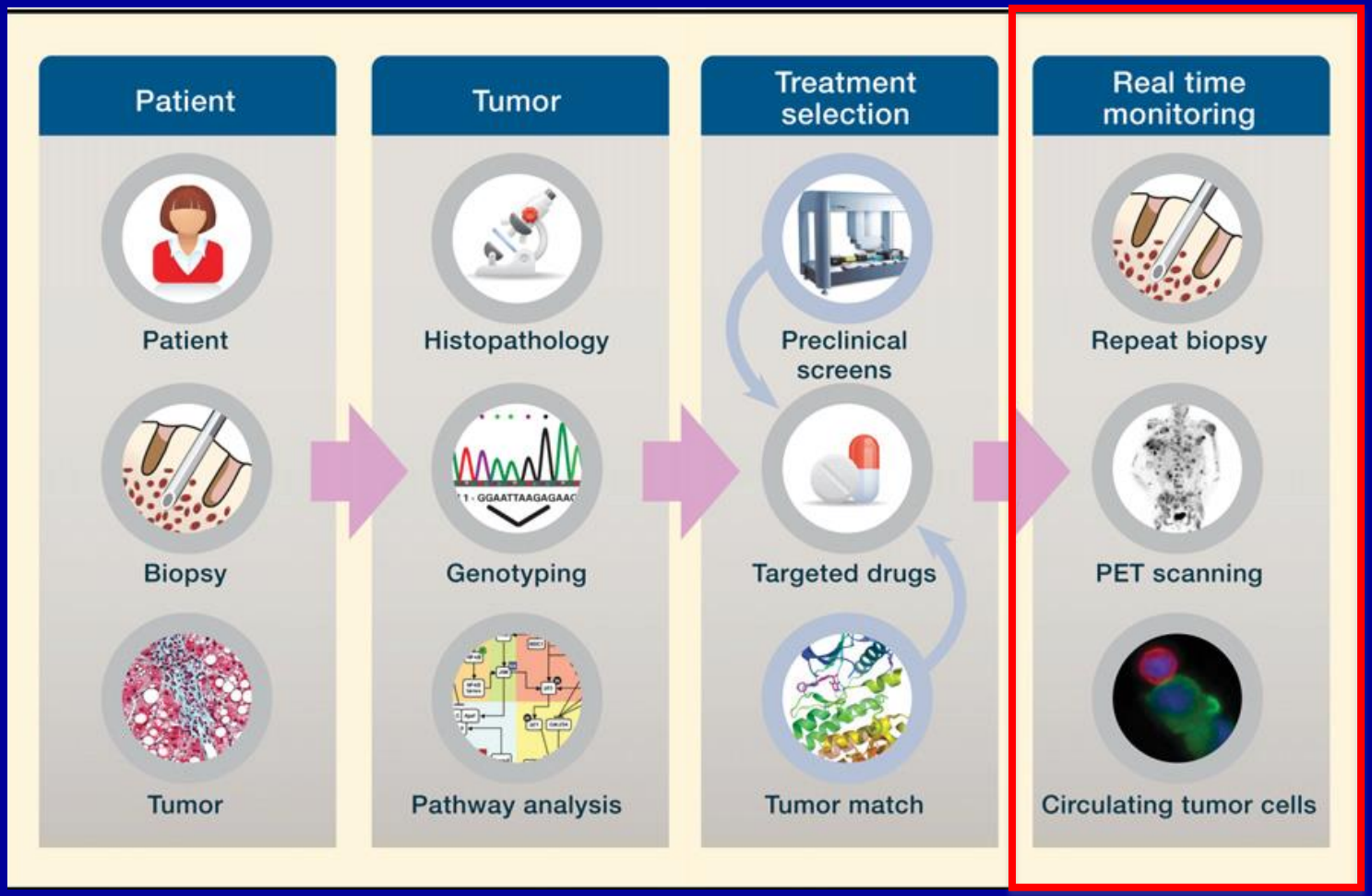
Media Release

Basel, 3 March 2014

Roche provides update on phase III study of onartuzumab in people with specific type of lung cancer

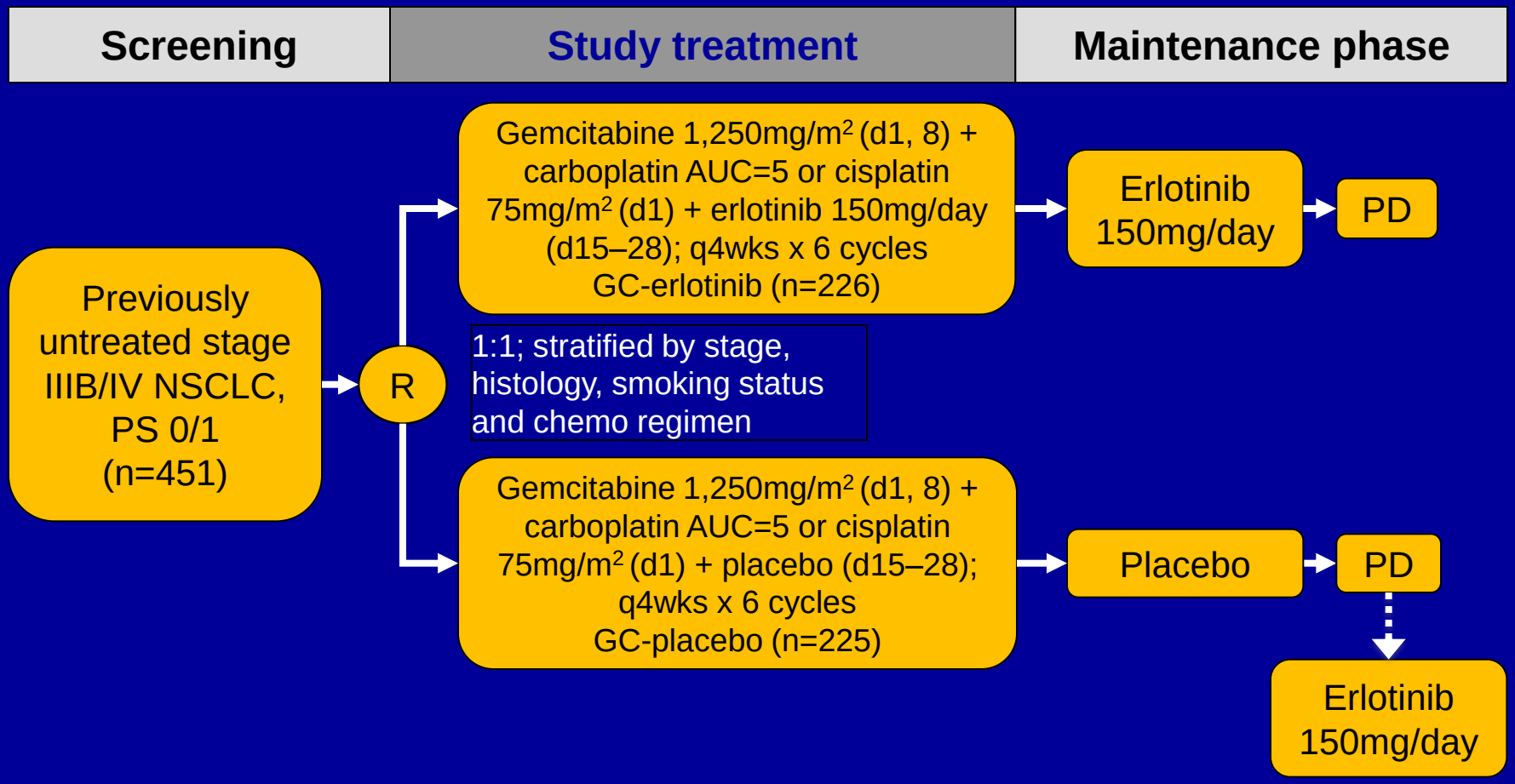
Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that an independent data monitoring committee has recommended that the phase III METLung study be stopped due to a lack of clinically meaningful efficacy.

Can we do real time monitoring?



Haber et al Cell 2011

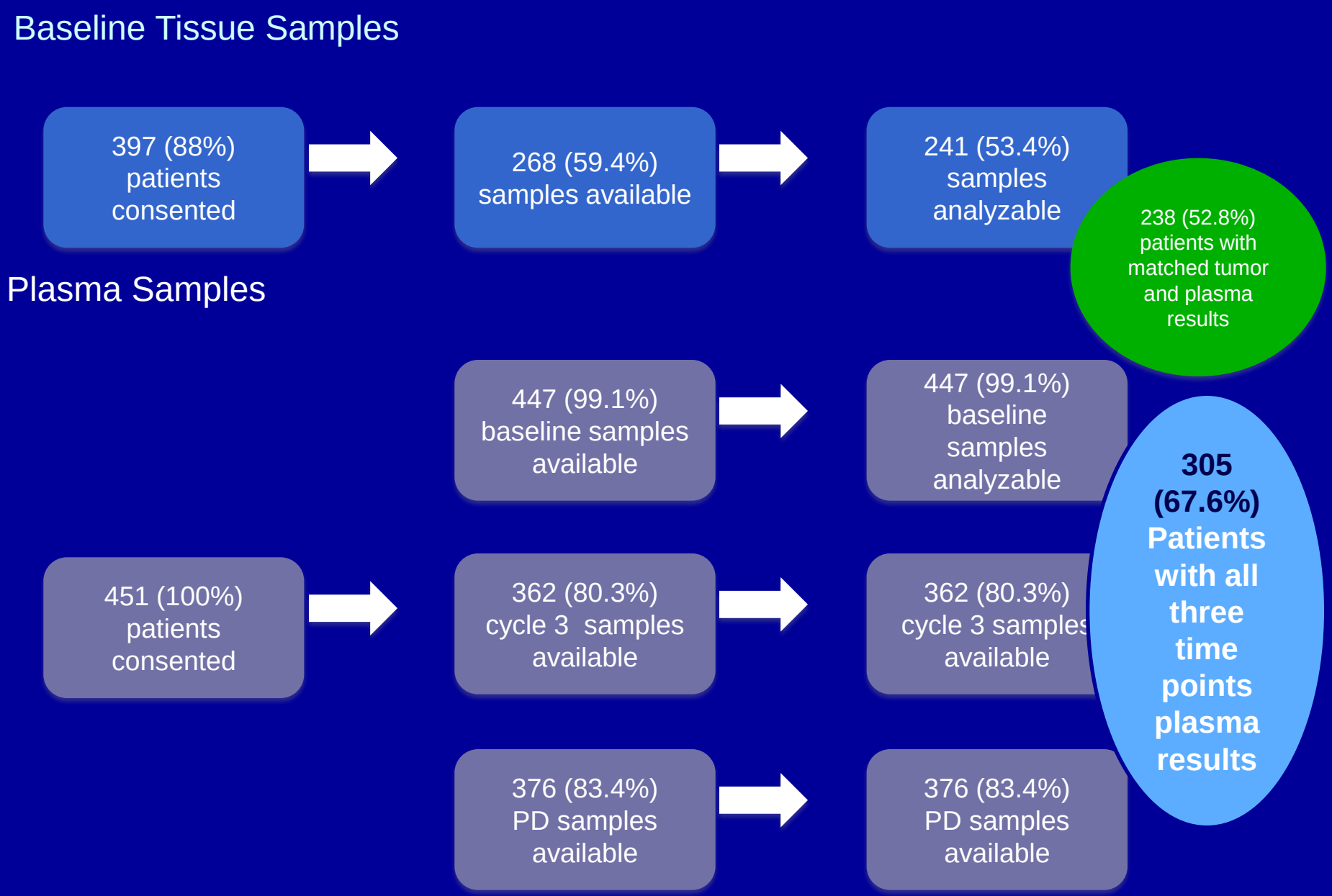
FASTACT-2 study design



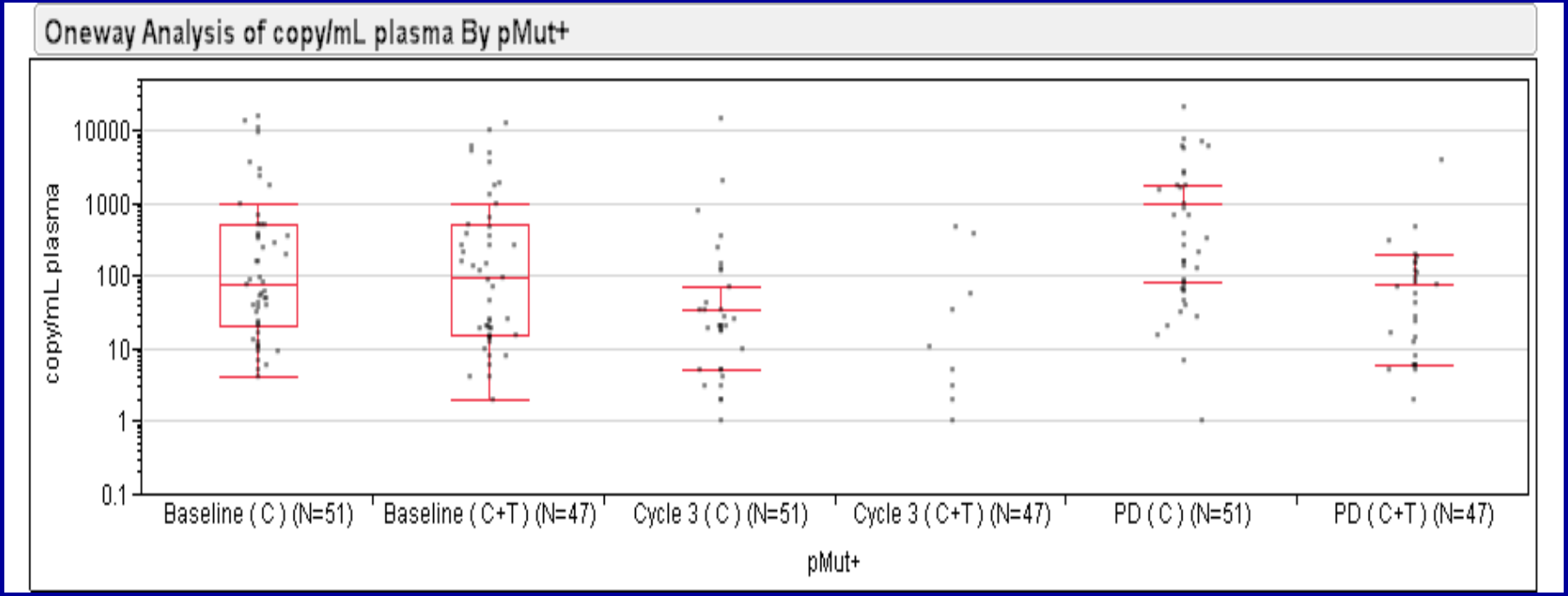
IRC = independent review committee

Wu YL et al Lancet Oncology 2013

Serial plasma sample at baseline, C3 and PD



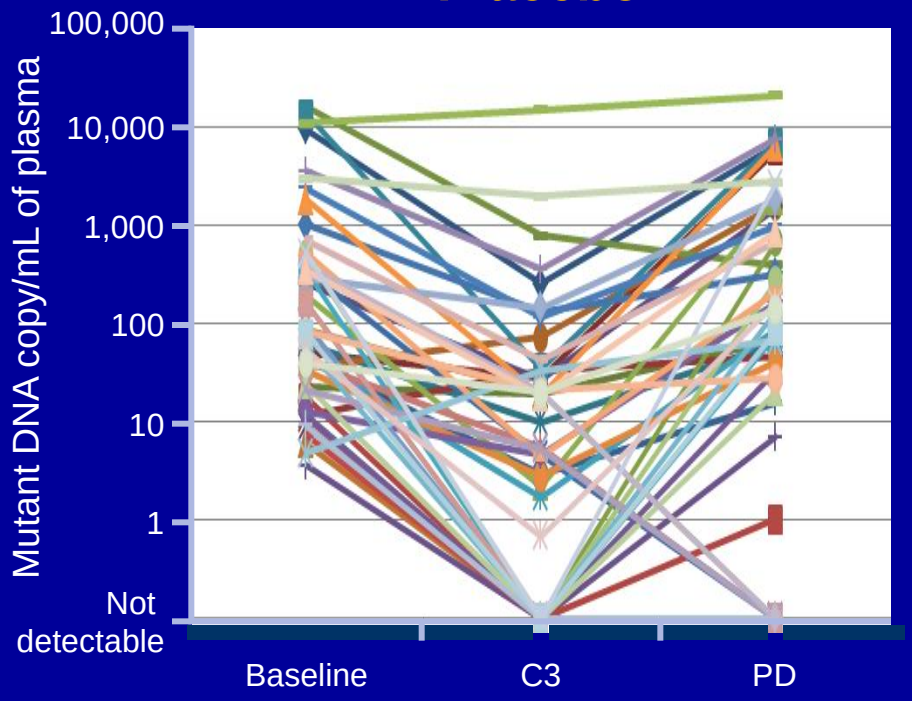
Semi-quantitation change in plasma EGFR mutation DNA during treatment



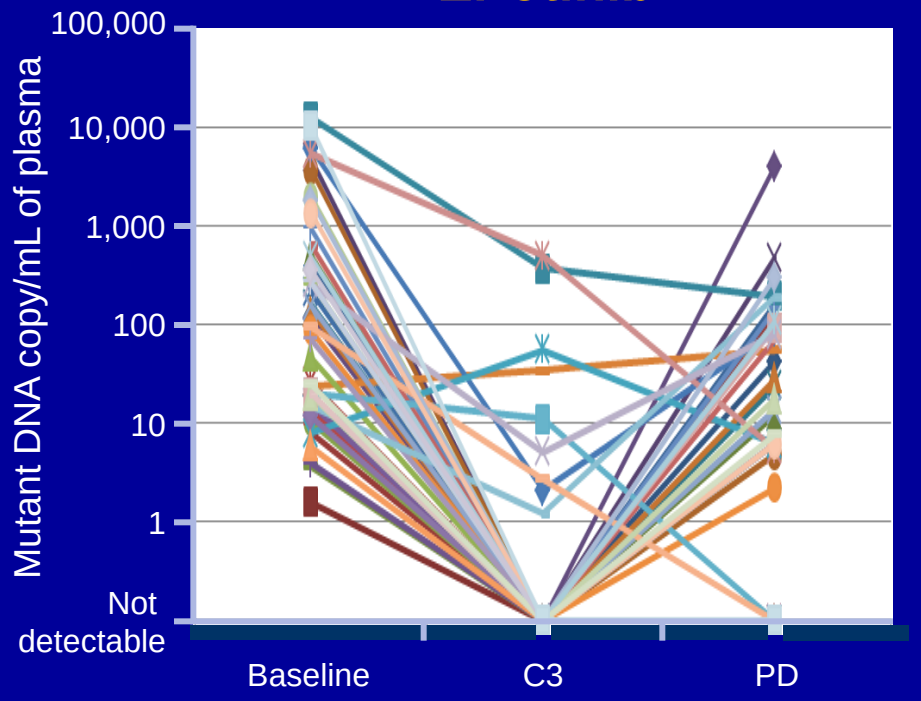
Median EGFR mutant DNA (copy/mL plasma)	C	C+T
Baseline	78	94
Cycle 3	5	0
PD	83	6

Dynamic change in plasma EGFR status during therapy

Patients treated with GC+ Placebo



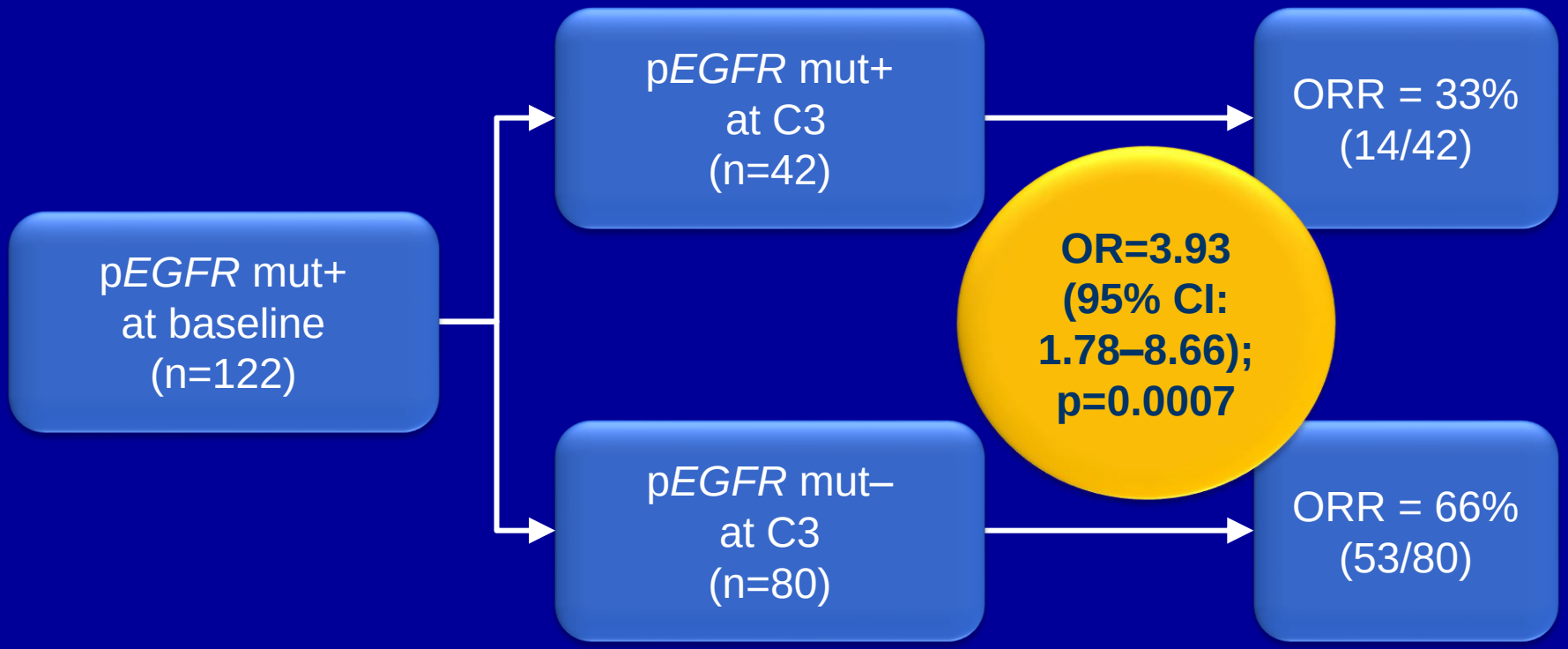
Patients treated with GC+ Erlotinib



Mok et al WCLC 2013

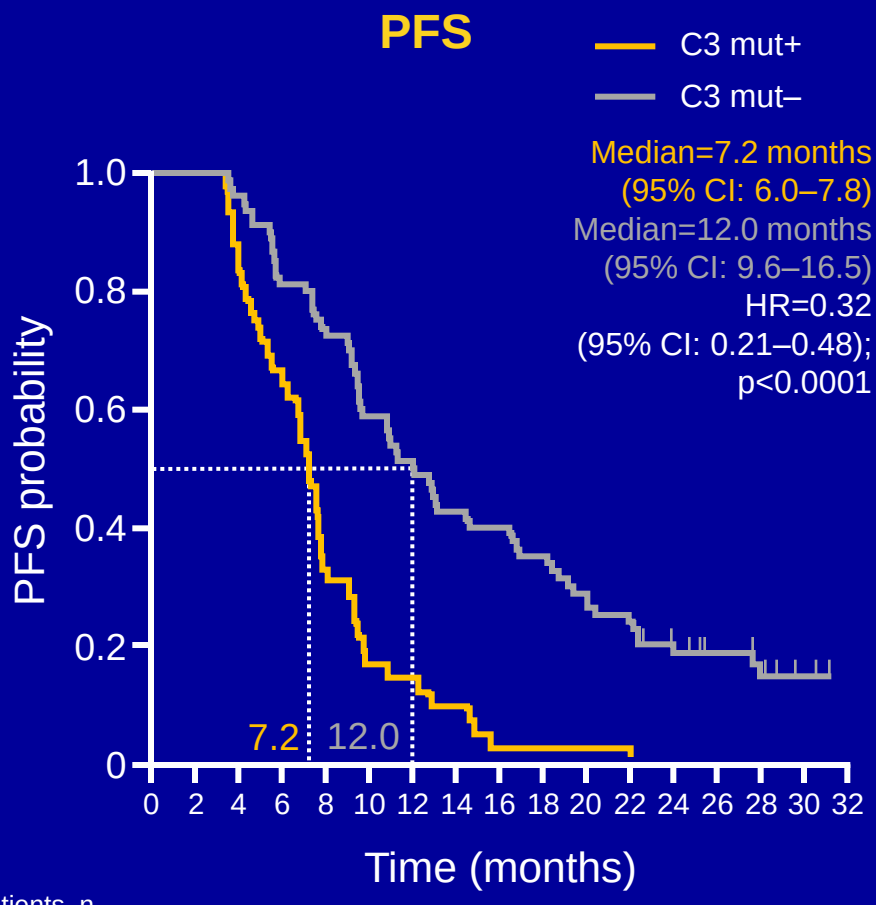
What happened to patients with persistent EGFR mutation at cycle 3?

Positive versus negative p*EGFR* mut status at C3 (both treatment arms combined)

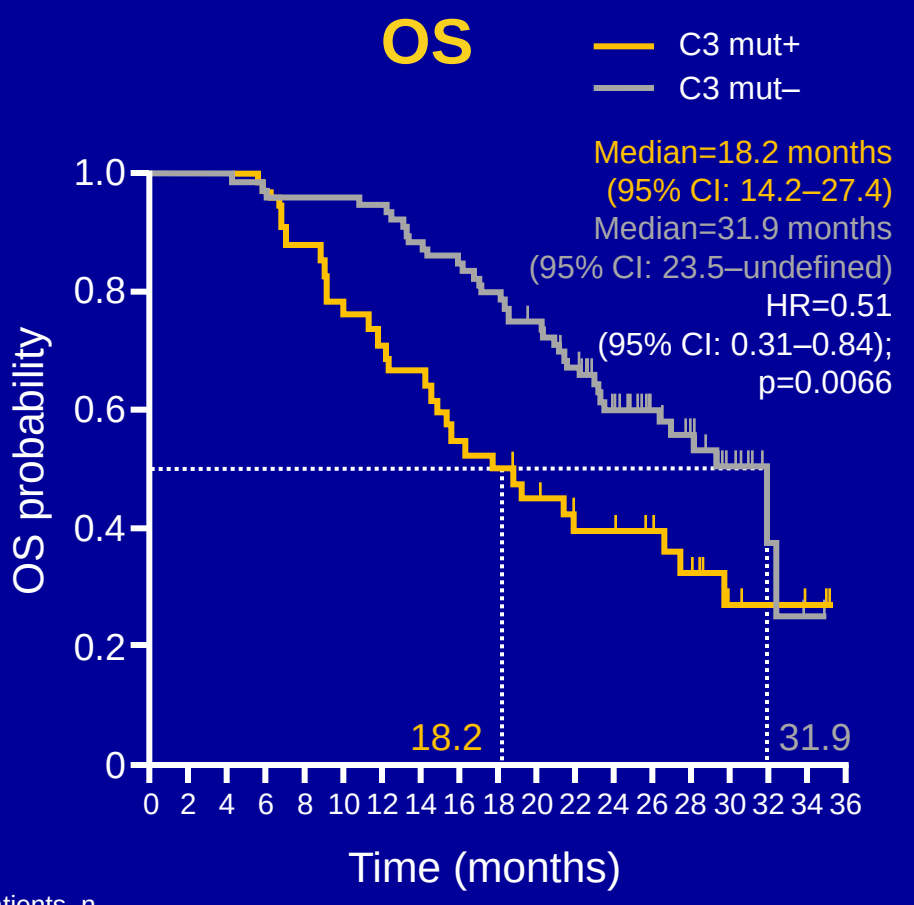


ORR = objective response rate; OR = odds ratio

Association between p*EGFR* mut+ at C3 and PFS/OS (both treatment arms combined)



Patients, n																	
C3 mut+	42	42	35	28	14	7	6	4	1	1	1	1	0	0	0	0	0
C3 mut–	80	80	77	65	59	47	40	34	32	28	23	19	13	10	7	3	0

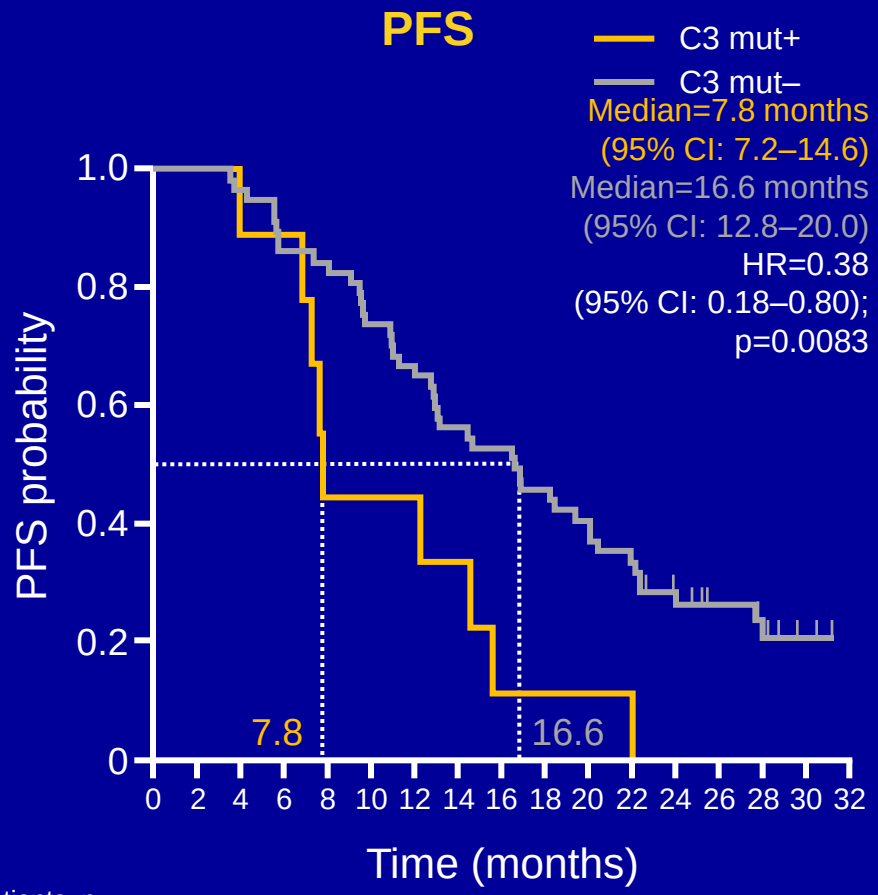


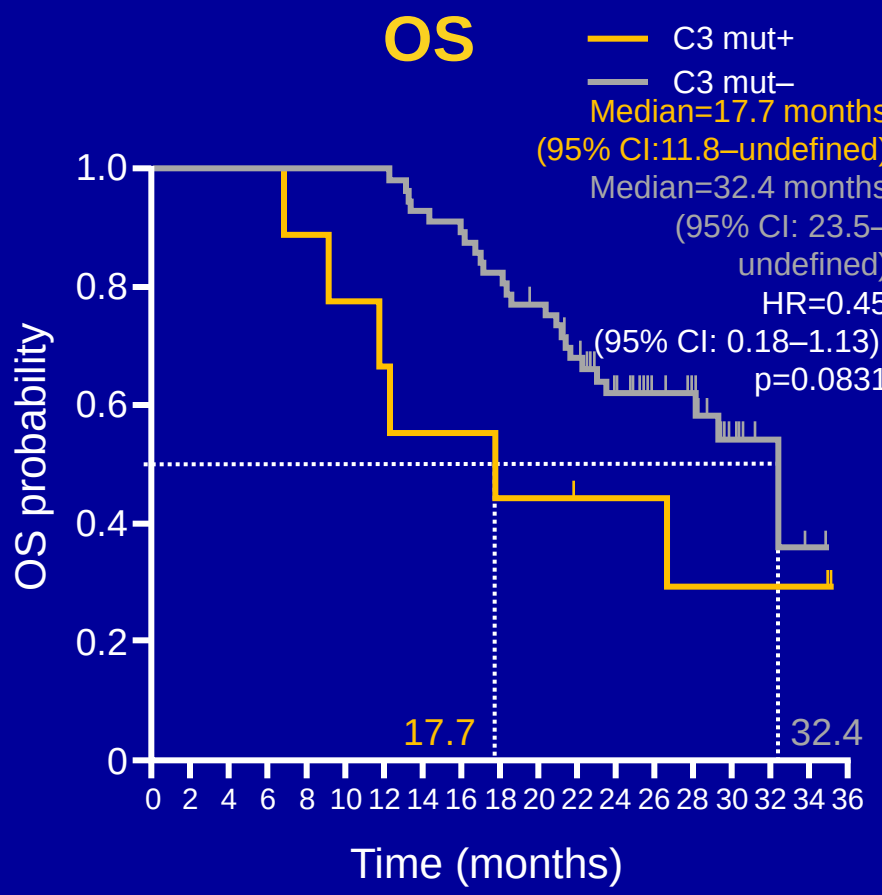
Patients, n																			
C3 mut+	42	42	42	41	37	32	30	28	23	21	18	14	14	12	9	4	3	2	0
C3 mut–	80	80	80	77	77	77	76	71	68	64	59	52	38	29	22	12	3	1	0

Positive p*EGFR* at baseline followed by negative p*EGFR* at C3 is associated with improved outcomes; patients positive at baseline and still positive at C3 experienced worse outcomes

OS = overall survival

p*EGFR* mut+ at C3 predicts PFS and OS (GC+E arm only)





Patients, n																	
C3 mut+	9	9	8	8	4	4	4	3	1	1	1	1	0	0	0	0	0
C3 mut–	57	57	55	49	48	42	37	32	30	26	23	19	13	10	7	3	0

Patients, n																					
C3 mut+	9	9	9	9	8	7	6	5	5	4	4	3	3	3	2	2	2	2	0
C3 mut–	57	57	57	57	57	57	57	53	51	47	43	37	28	22	18	8	3	1	0

Positive p*EGFR* at baseline followed by negative p*EGFR* at C3 is associated with improved outcomes; patients positive at baseline and still positive at C3 experienced worse outcomes

Conclusion

- The traditional phase I-IV study design may not be directly applicable to biomarker-based molecular targeted therapy
- Biomarker driven design is the trend
- Understanding the epidemiology of driver oncogene is essential to clinical study design
- It is best to have a known biomarker before engaging in late drug study (retrospective analysis could be risky)
- Avoid chemotherapy +/- targeted as much as you can
- Plasma DNA (or CTC) may provide real time monitoring of treatment outcomes

New versus old design