elcc European Lung Cancer Conference

Overcoming resistance in oncogenic-driven disease

BRAF – HER2

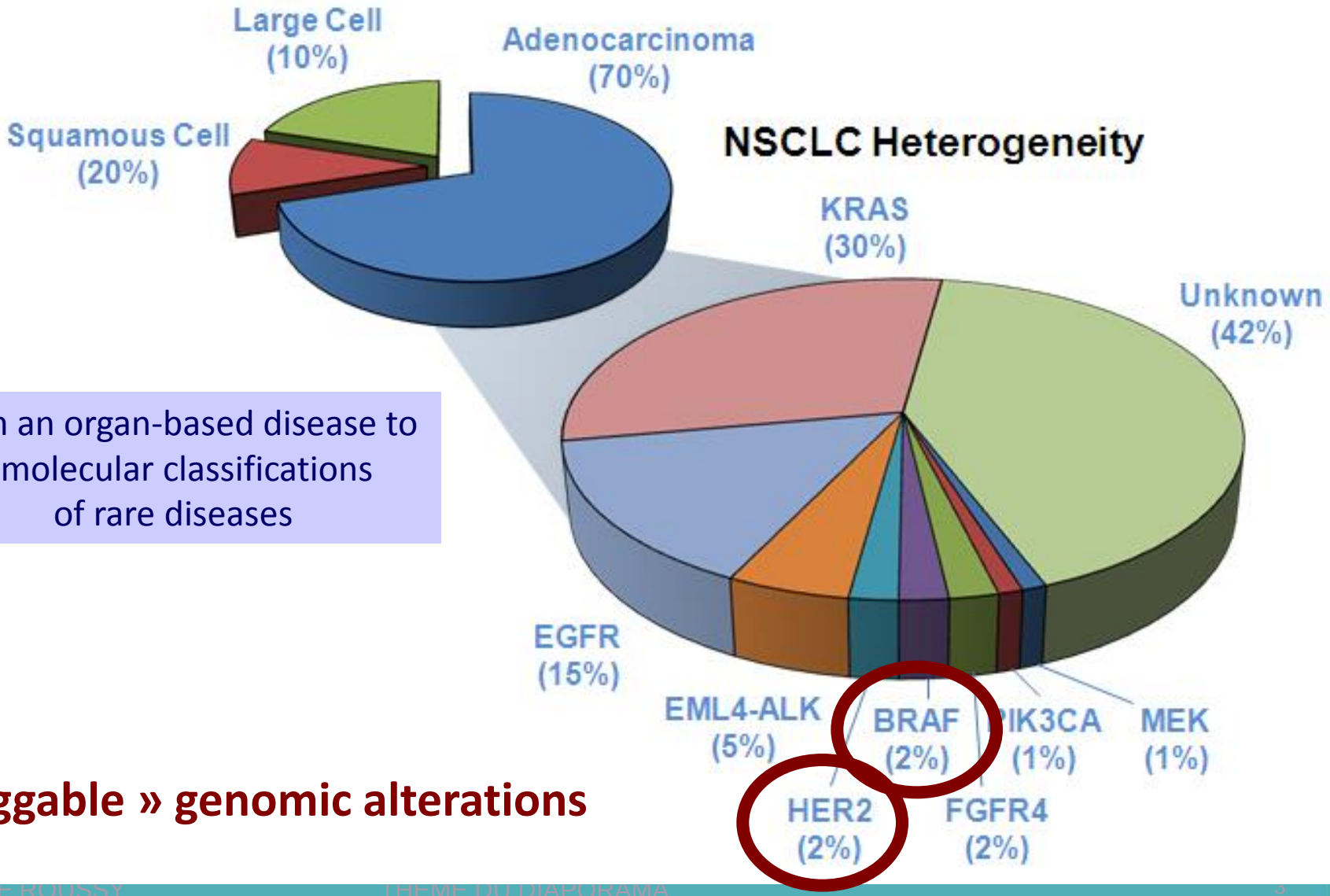
Benjamin Besse, MD, PhD

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Disclosures

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
  - Abbott, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS

Disease segmentation based on oncogenic events



From an organ-based disease to a molecular classifications of rare diseases

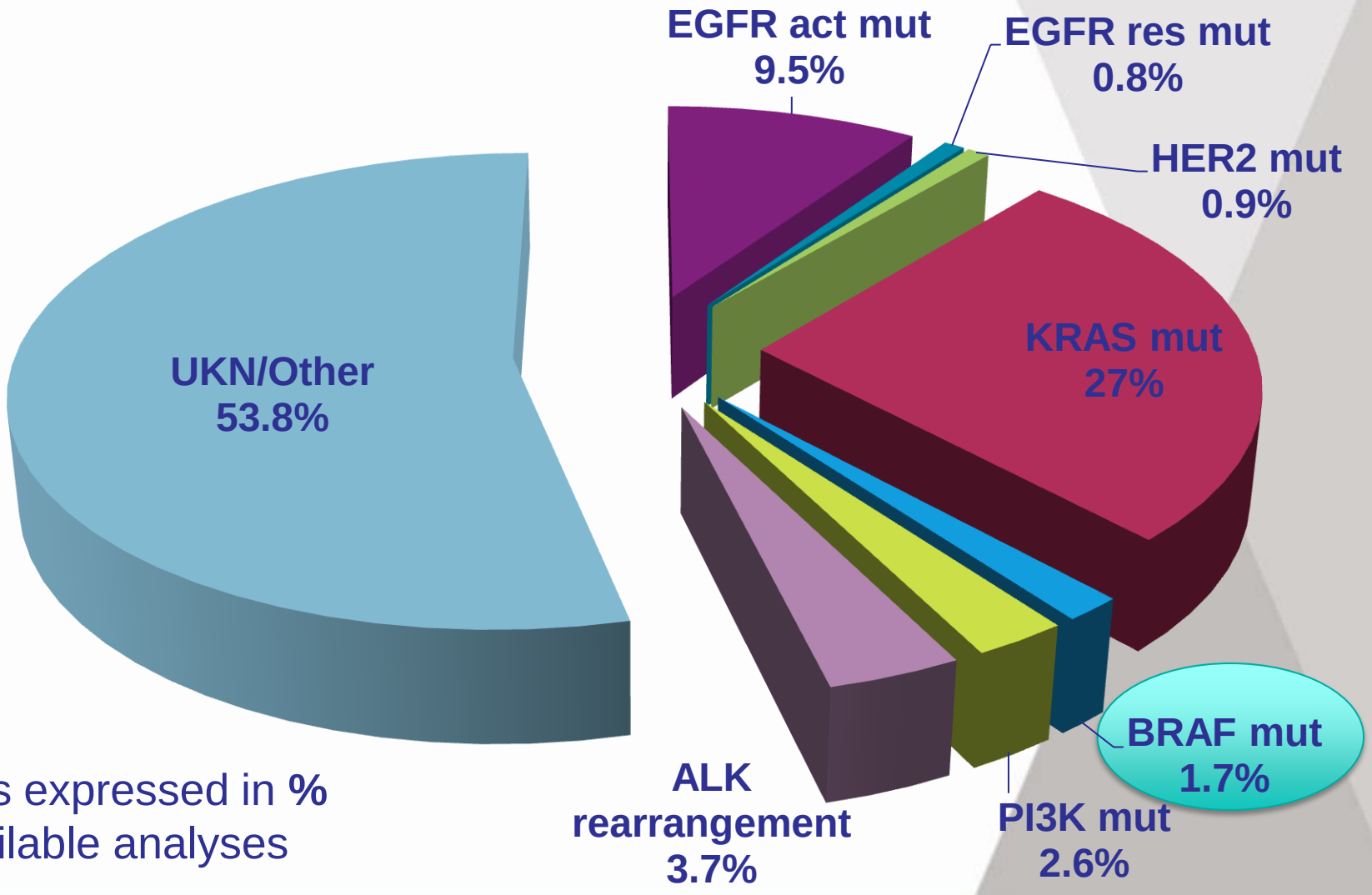
« Druggable » genomic alterations

- BRAF

Frequency of BRAF mutations In various cancer

Tumor Type	Percentage of Patients With *BRAF* Mutations
Melanoma	30-70
Papillary thyroid cancer	40-70
Cisplatin-refractory testicular cancer	25
Cholangiocarcinoma	10-20
Colorectal cancer	5-20
Ovarian cancer	5-10
Prostate cancer	5-10
Glioblastoma, NSCLC, HNSCC, breast cancer, and pancreatic cancer	1-5

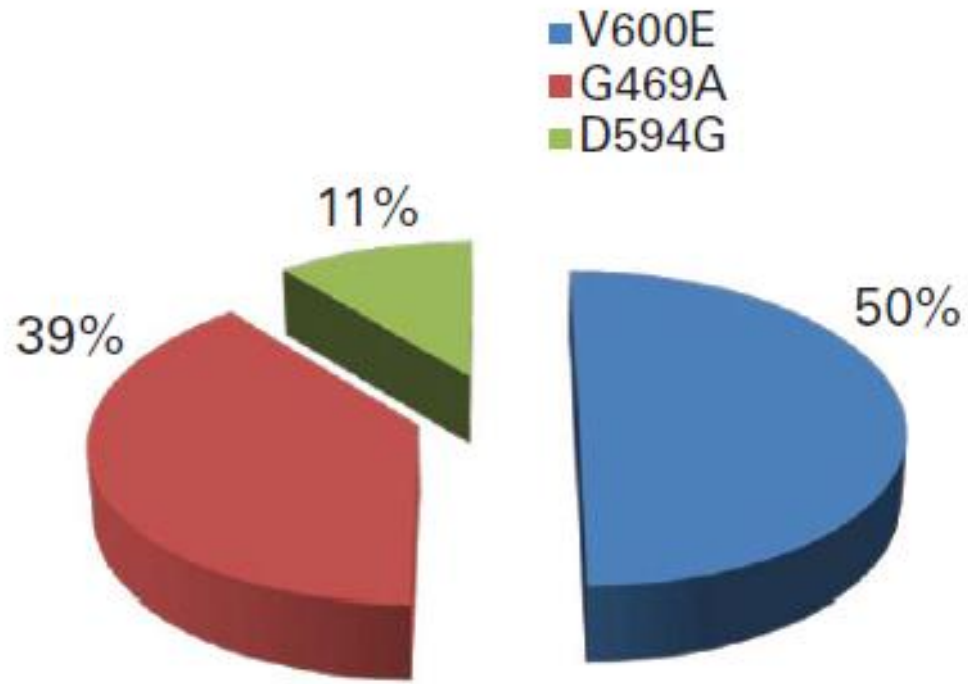
Biomarqueurs France (n=9911)



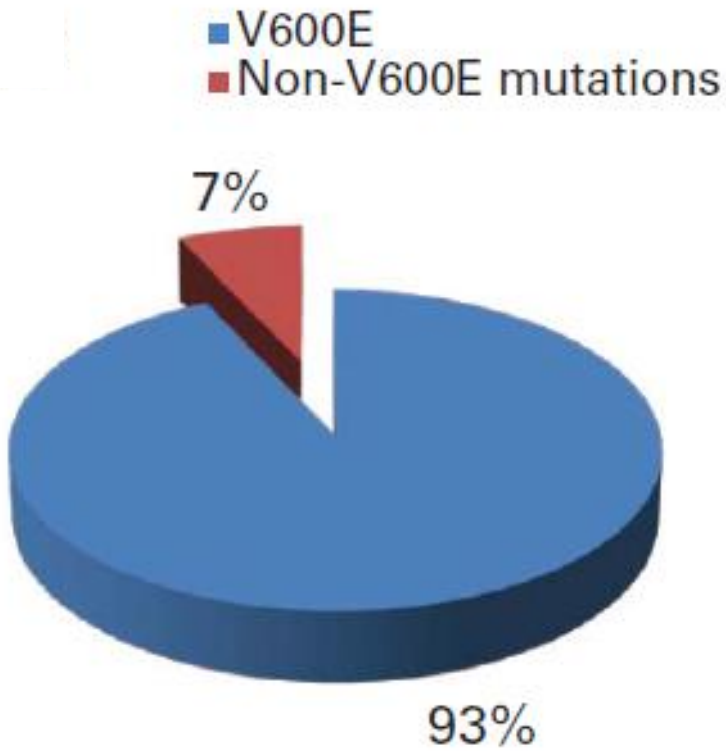
Results expressed in **%**
on available analyses

BRAF mutation in NSCLC vs Melanoma

NSCLC



Melanoma



Paul K. Paik et al, JCO 2011

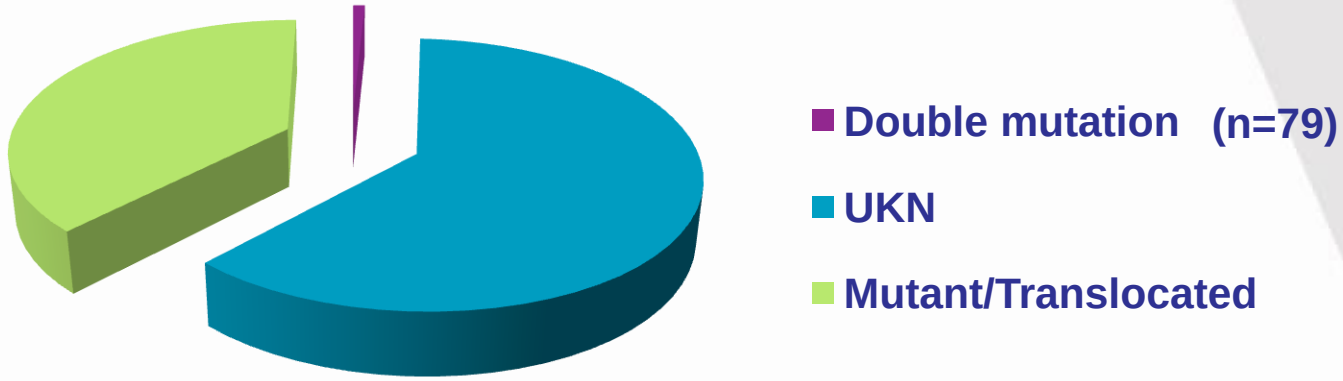
Genomic mutation in BRAF Gene

BRAF Mutation	Change		Histologic Type		*P*
	Nucleotide	Aminoacid	ADC	SCC	
Exon					.001
15	T1799A	V600E	21	—	
	A1781G	D594G	2	—	
	T1790G	L597R	2	—	
	C1789G	L597V	1	—	
	T1790A	L597Q	1	—	
	G1798T	V600L	1	—	
	A1801G	K601E	1	—	
	A1803T	K601N	1	—	
	T1810A	W604R	—	1	
	G1817C	G606A	1	—	
	G1817T	G606V	1	—	
11	G1397T	G466V	2	—	
	G1406C	G469A	1	—	
	G1406T	G469V	1	—	
Total					.001
No.			36	1	
%			4.9	0.3	

Retrospective series of 1,046 NSCLCs (739 adenocarcinomas and 307 SCC)

Antonio Marchetti et al, JCO 2011

Double mutation
Biomarqueurs France (n=9911)



	EGFR	ALK	KRAS	BRAF	PI3K	HER2
EGFR	-					
ALK	3	-				
KRAS	5	10	-			
BRAF	2	1	6	-		
PI3K	16	1	33	1	-	
HER2				1		-

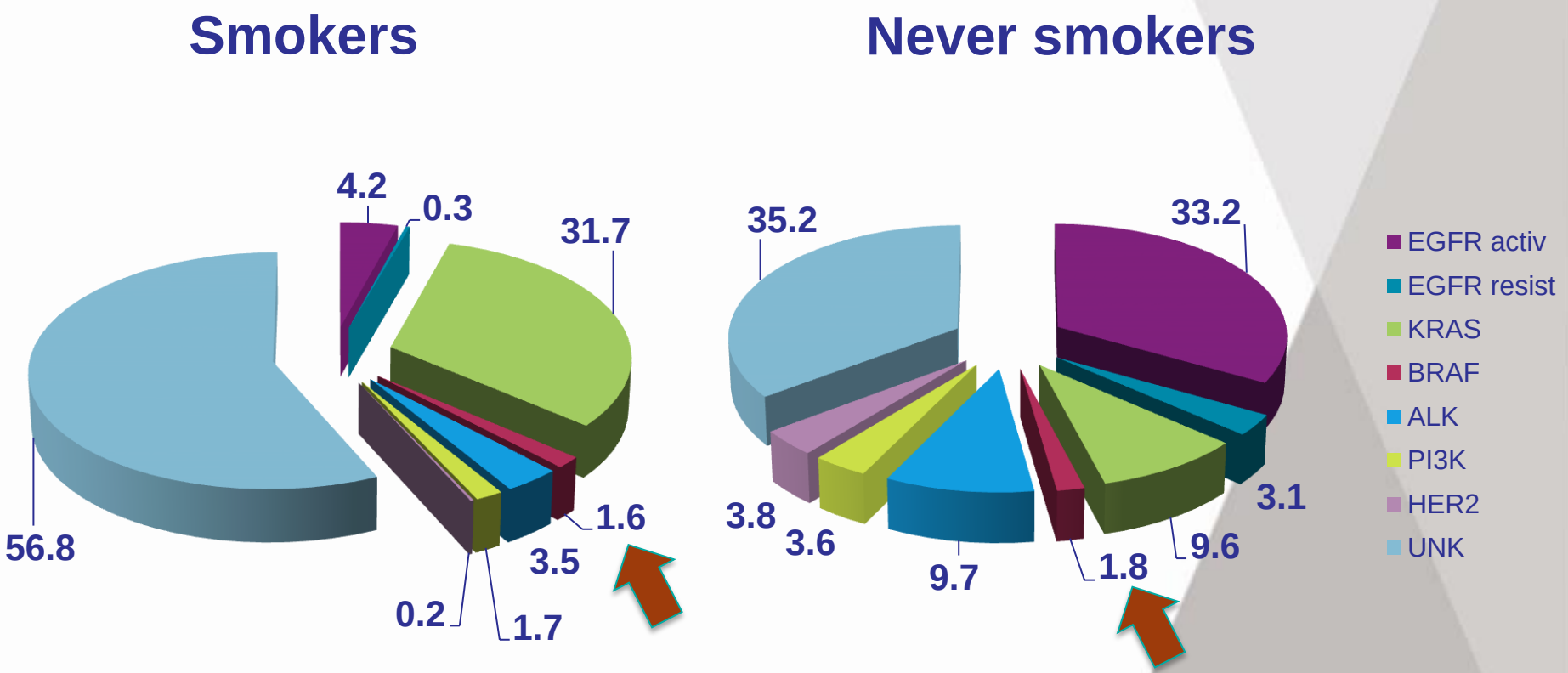
Patient Clinical Characteristics

	Paik et al n = 697	Marchetti et al. N = 739	Brustugun et al. N= 979	Kinno et al. N=2001
BRAF mut. V600E	18 (3%) 50%	21 100%	17 (1.7%) 100%**	26 (1.7%) 31%
Stage I-III* IV	 8 (44%) 10 (56%)	 19 (90%) 2 (10%)	 11 (65%) 6 (35%)	 26 (100%) 0
Female	11 (61%)	16 (76%)	10 (58%)	13 (50%)
Age	64	67.7	71	63
Smoking status never current/former	 0 18 (100%)	 11 (52%) 10 (48%)	 5 (29%) 12 (71%)	 12 (46%) 14 (54%)
Pathology Adenoc. SCC LCC	 18 (100%) N/A N/A		 15 (88%) 0 2 (12%)	 25 (96%) 1 (4%) 0

*IIIA **BRAF V600E/K

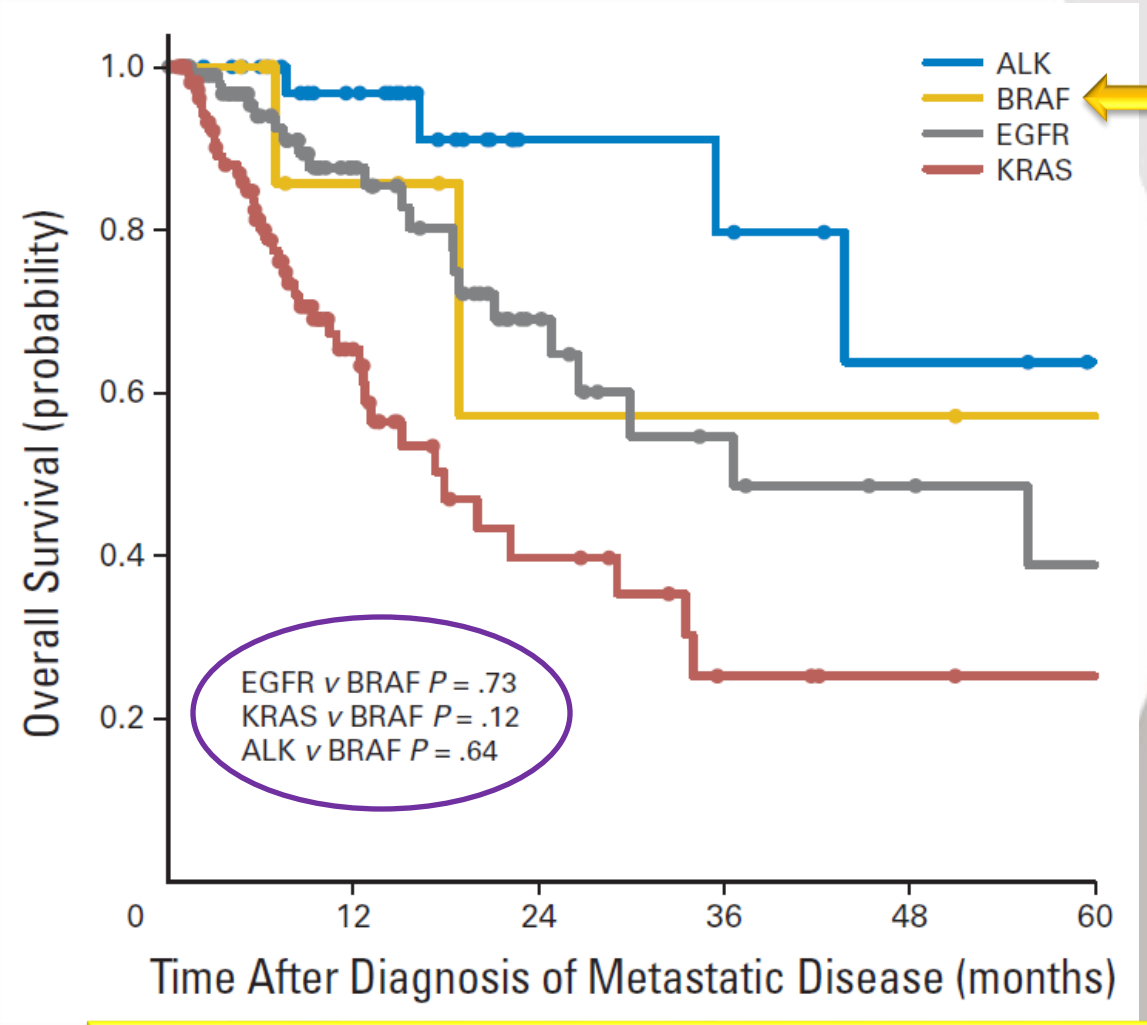
Paik J Clin Oncol 2011, Marchetti J Clin Oncol 2011, Brustugun Lung Cancer 2014, Kinno Ann Oncol 2014

Biomarkers by smoking status (n=9911*)



** Including 2664 with full clinical data available at the time of this analysis.*

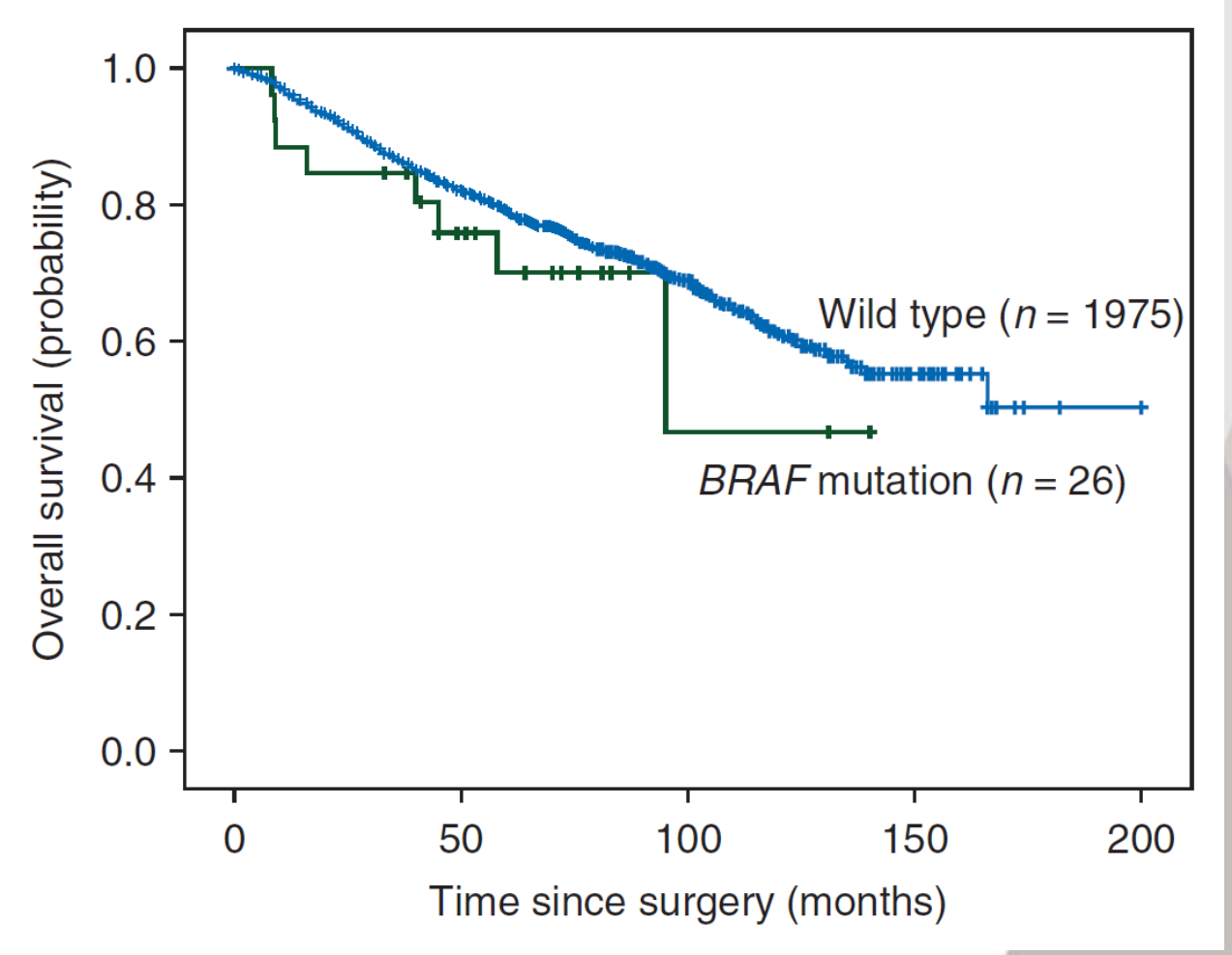
Overall survival in patients with advanced stage (IIIB/IV)



450 patients with stage IIB/IV lung adenocarcinoma

Paul K. Paik et al, JCO 2011

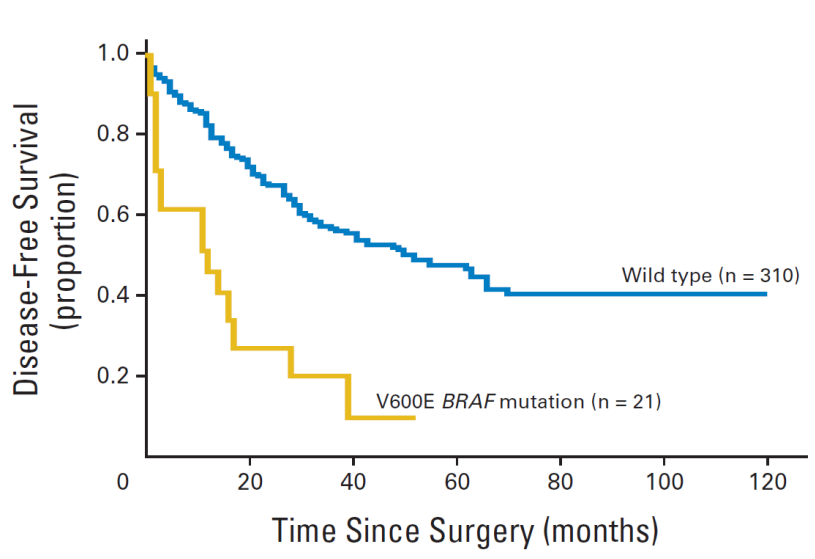
Clinicopathological features of NSCLC with BRAF mutations

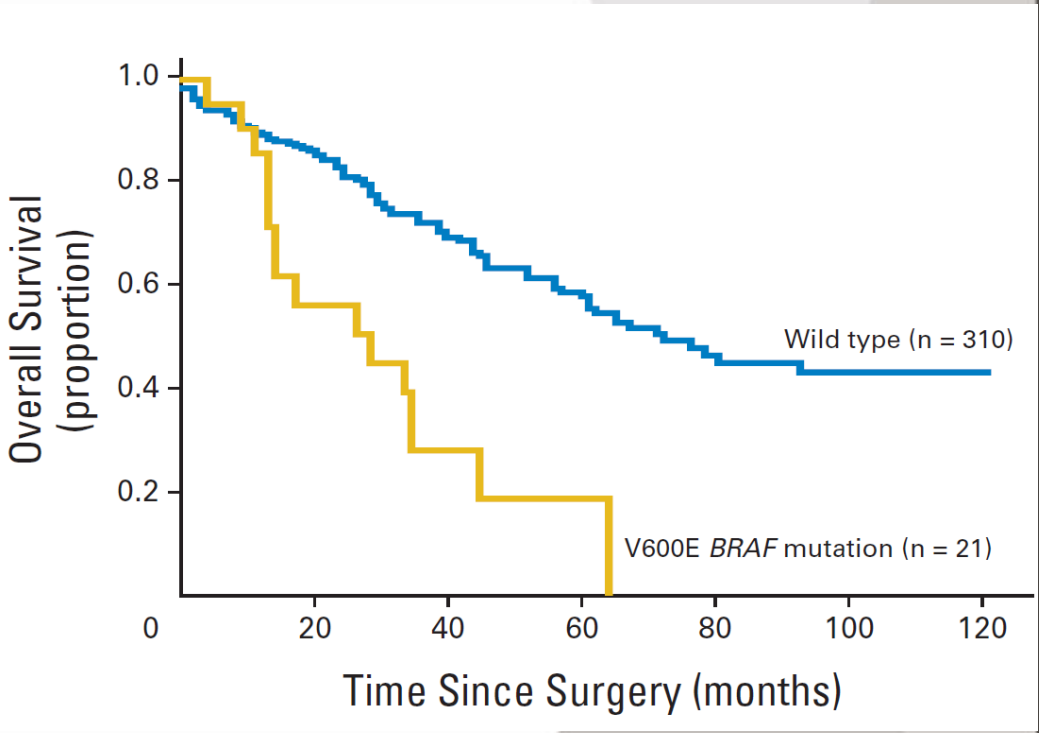


BRAF mutations in 26 (1.3%) of 2001 resected NSCLC

T. Kinno et al, Annals Oncol, 2014

Outcome of Patients BRAF Mutations

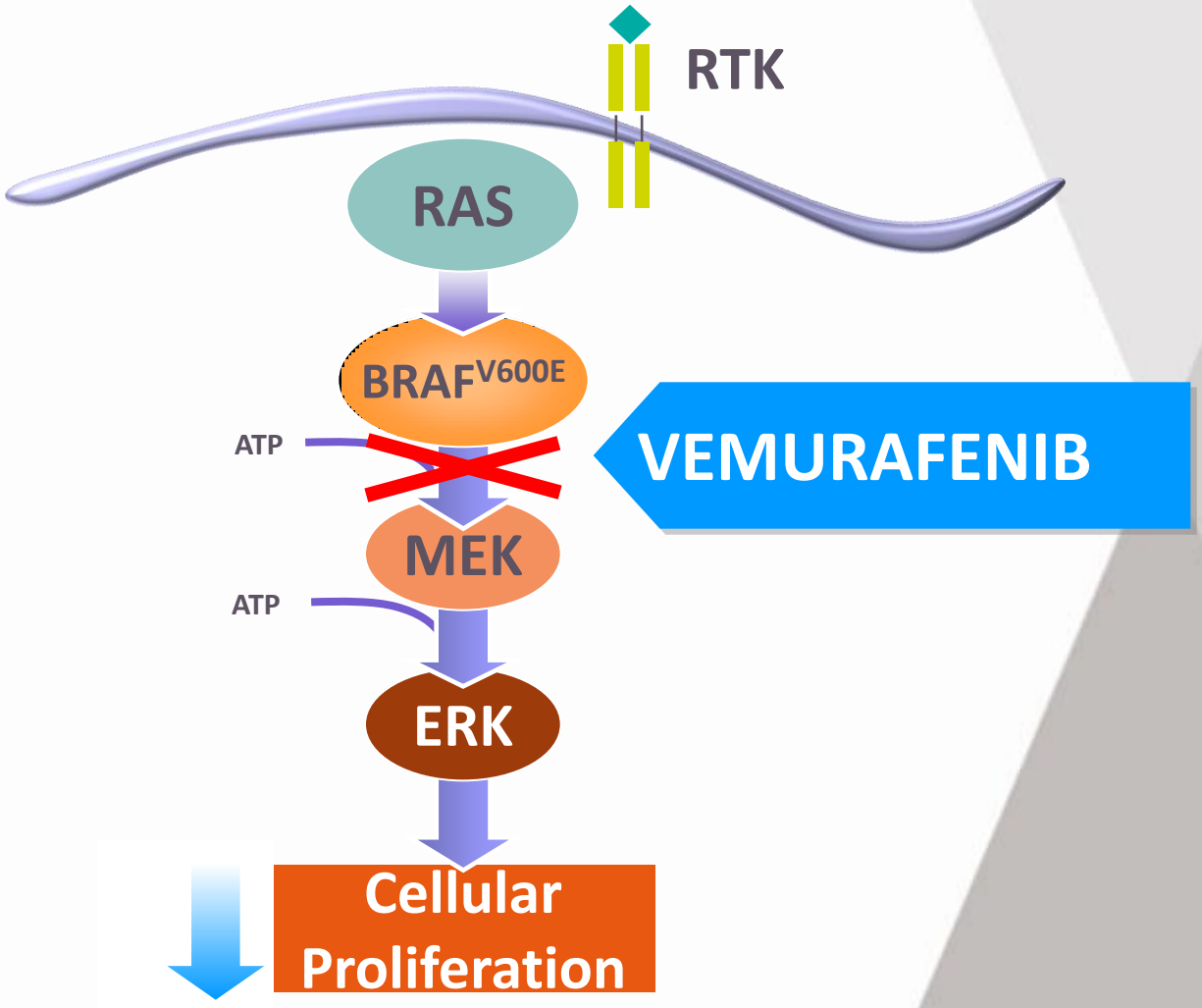




331 lung adenocarcinoma based on presence or absence of V600E *BRAF* mutation - NSCLC Pulmonary surgery

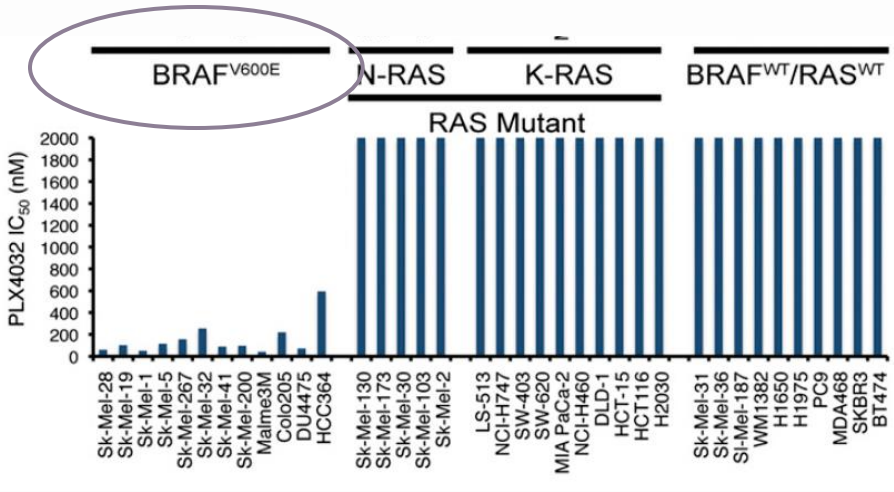
Antonio Marchetti et al, JCO 2011

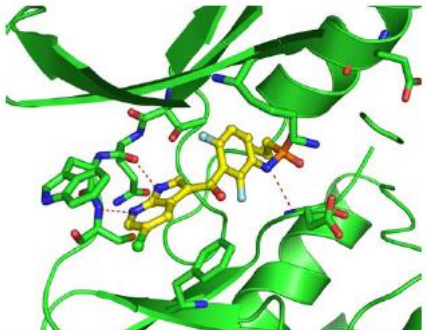
$BRAF^{V600E}$ Kinase



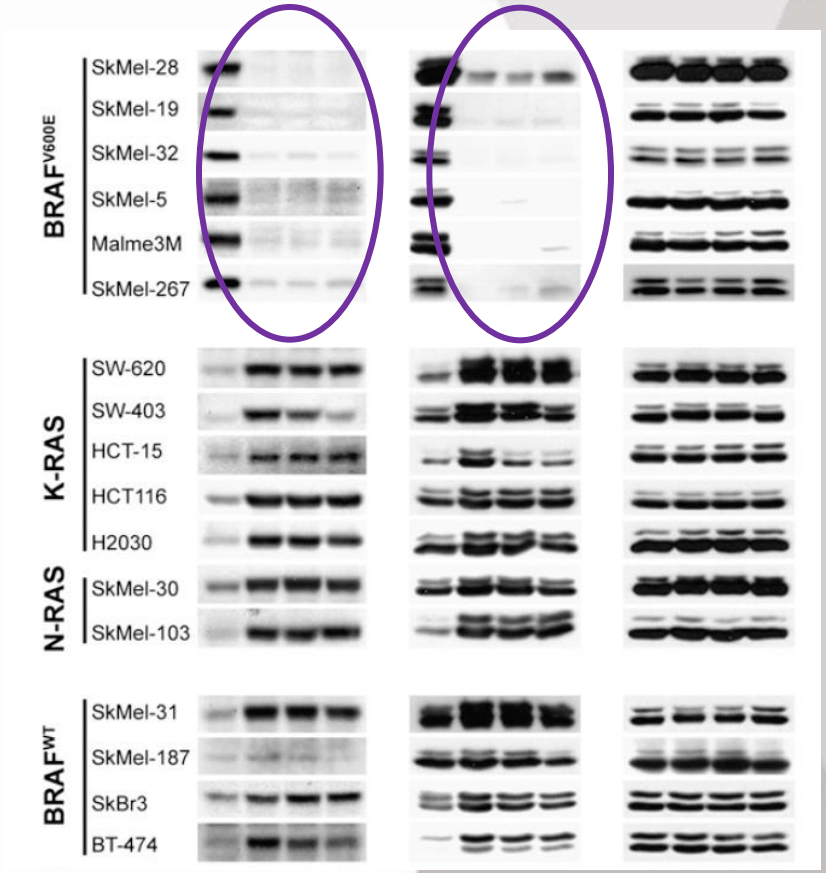
RAF inhibitor vemurafenib

Selectively inhibits growth of BRAFV600E-mutant cell lines



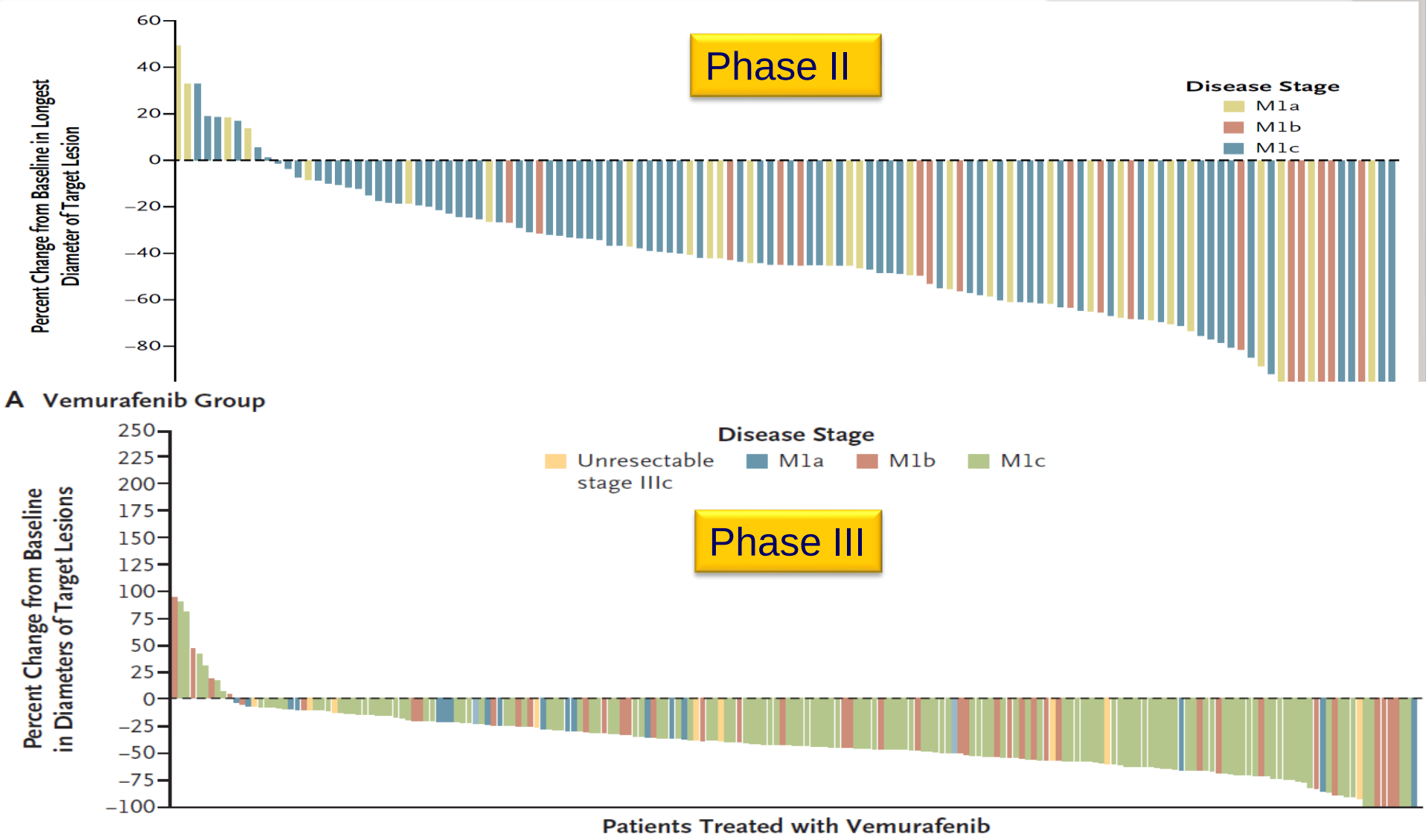


Inhibits ERK phosphorylation only in BRAFV600E-mutant cell lines



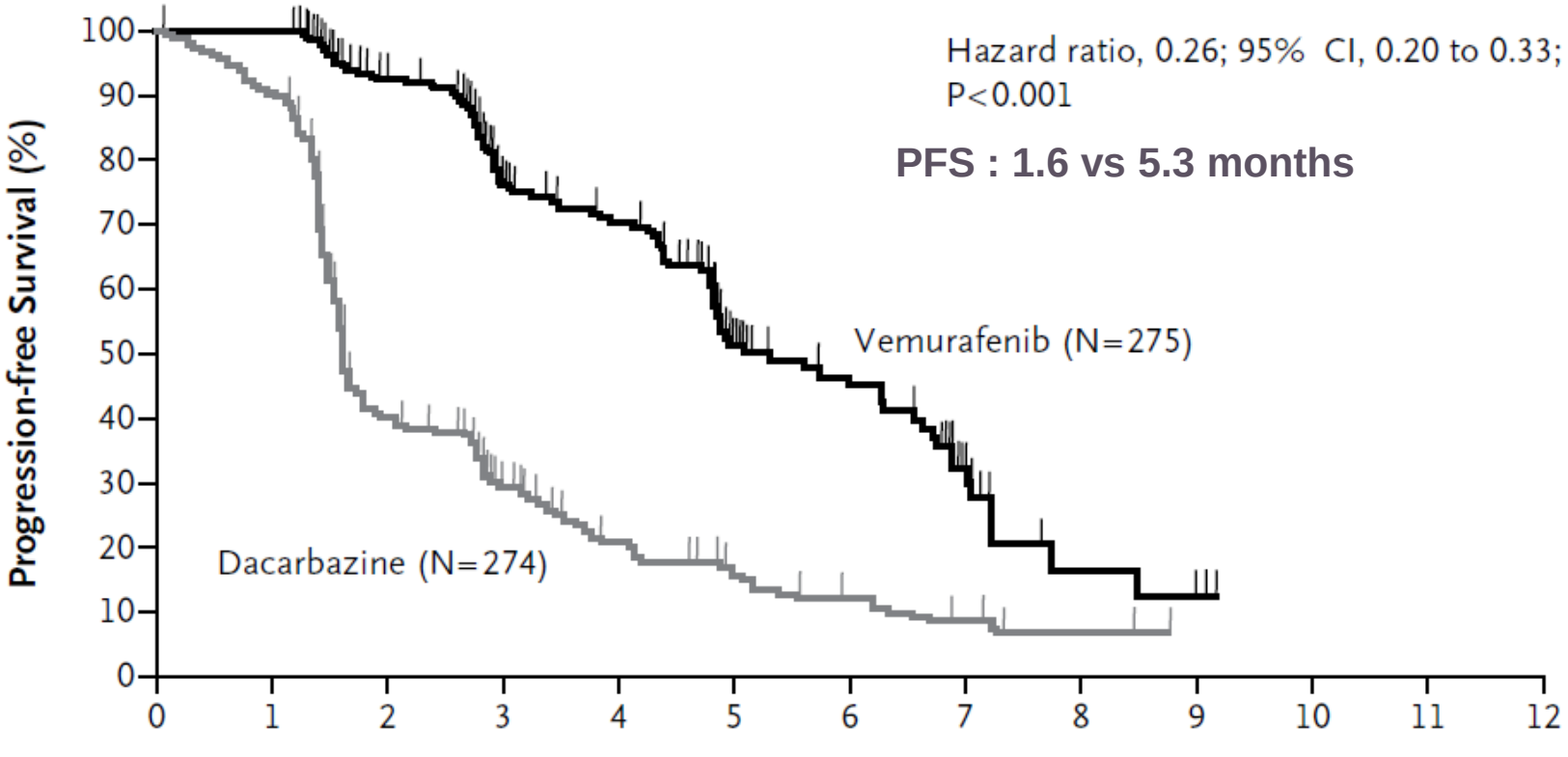
Eric W. Josepha et al, PNAS 2010

High response in patients with metastatic V600E BRAFmut melanoma



Paul B. Chapman et al, NEJM 2011 Sosman J et al, NEJM 2012

Vemurafenib V600E BRAFmut Melanoma



No. at Risk

Dacarbazine	274	213	85	48	28	16	10	6	3	0	0	0	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3	0	0	0

Dabrafenib inhibits BRAF V600E Kinase

Dabrafenib

Mode of Action

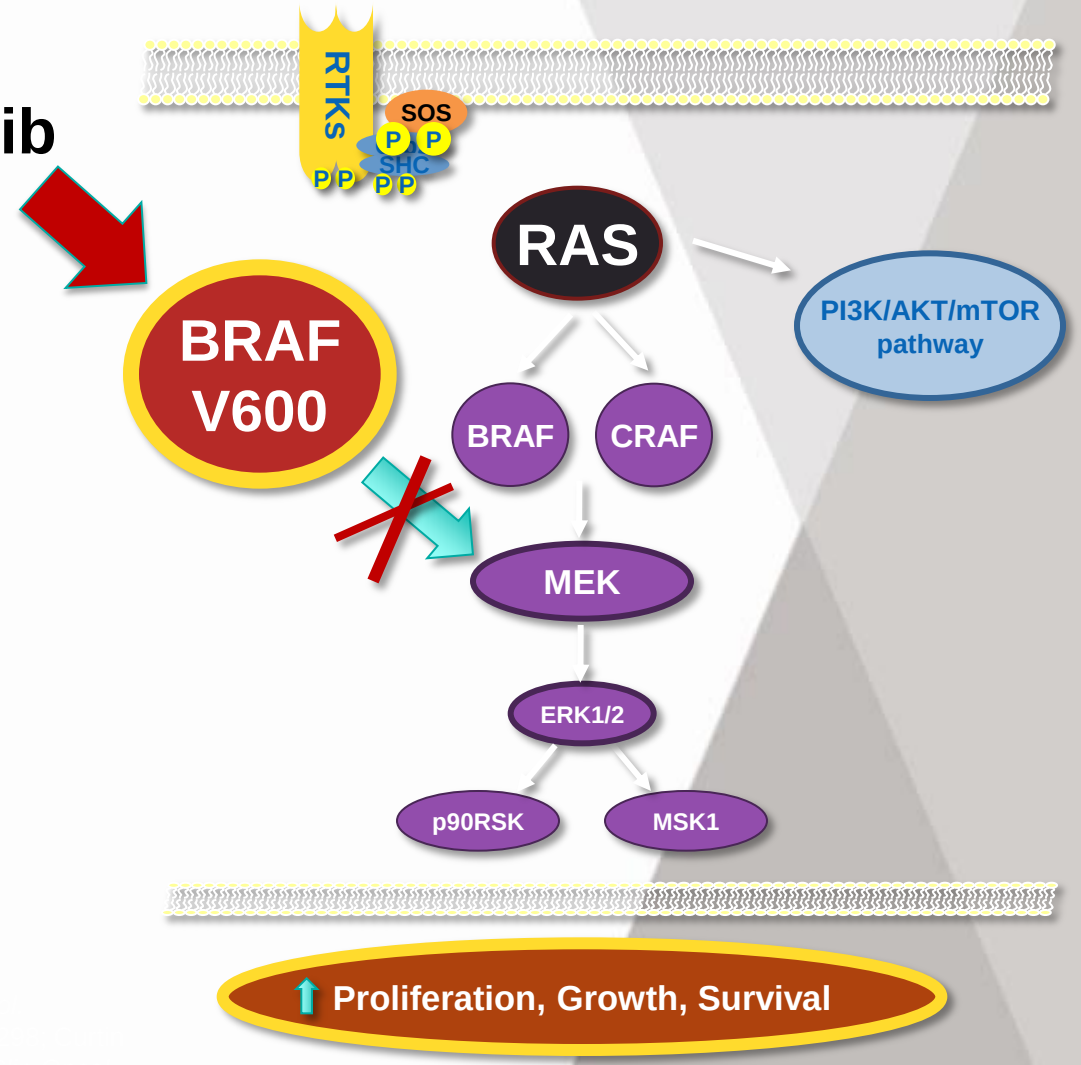
- Reversible, small molecule BRAF inhibitor
- ATP competitive

Molecular Activity:

- BRAF V600E: IC_{50} 0.65 nM
- BRAF WT: IC_{50} 3.2 nM

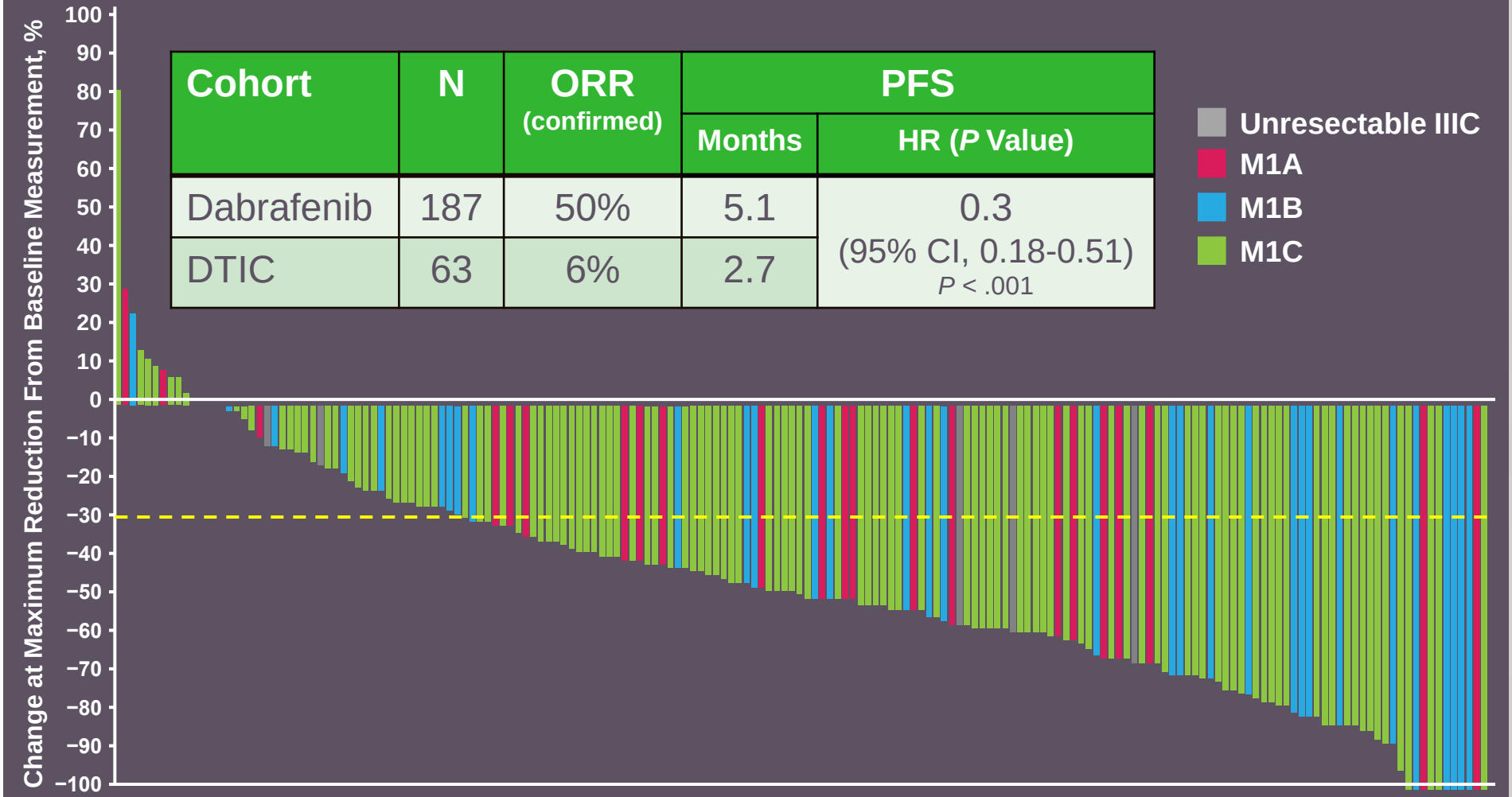
Selectivity:

- IC_{50} of 10-100 nM against 8 of 282 human kinases



Dabrafenib in BRAF V600E–Mutant Melanoma
Phase 3 Study BREAK-3

Cohort	N	ORR (confirmed)	PFS	
			Months	HR (*P* Value)
Dabrafenib	187	50%	5.1	0.3 (95% CI, 0.18-0.51) *P* < .001
DTIC	63	6%	2.7	

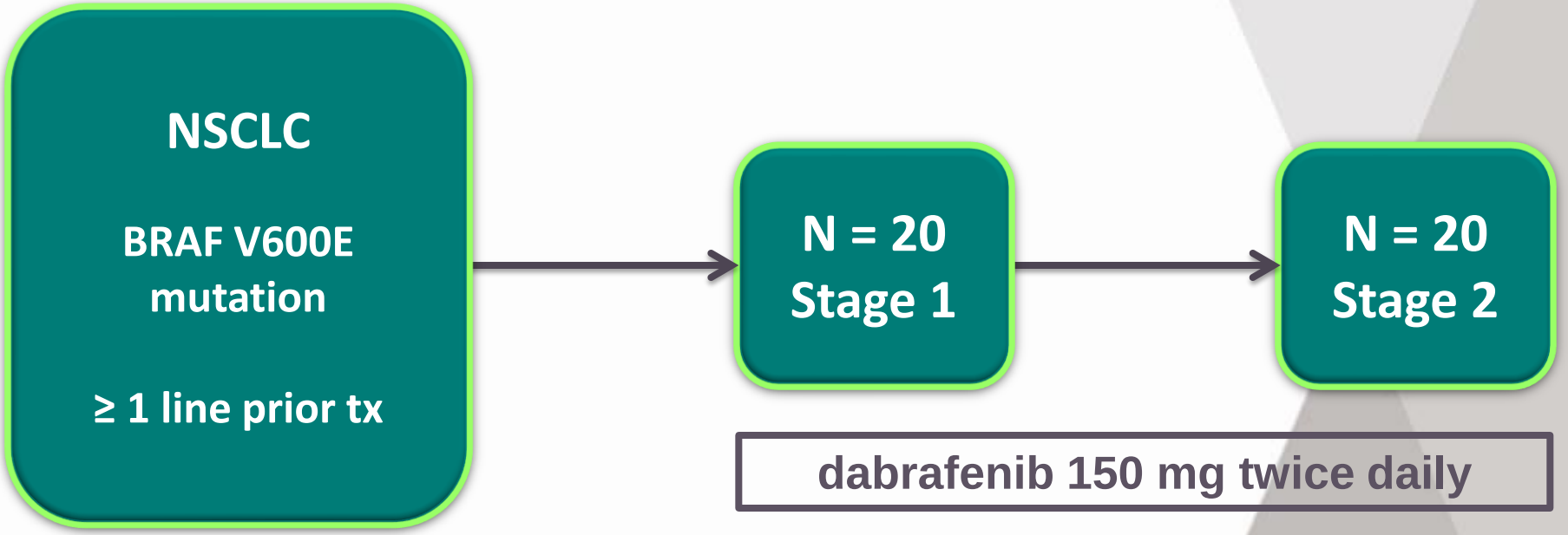


DTIC, dacarbazine; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

Hauschild A, et al. *Lancet.* 2012;380:358-365.

BRF113928: Study Design

- **Single arm, phase 2, open label**



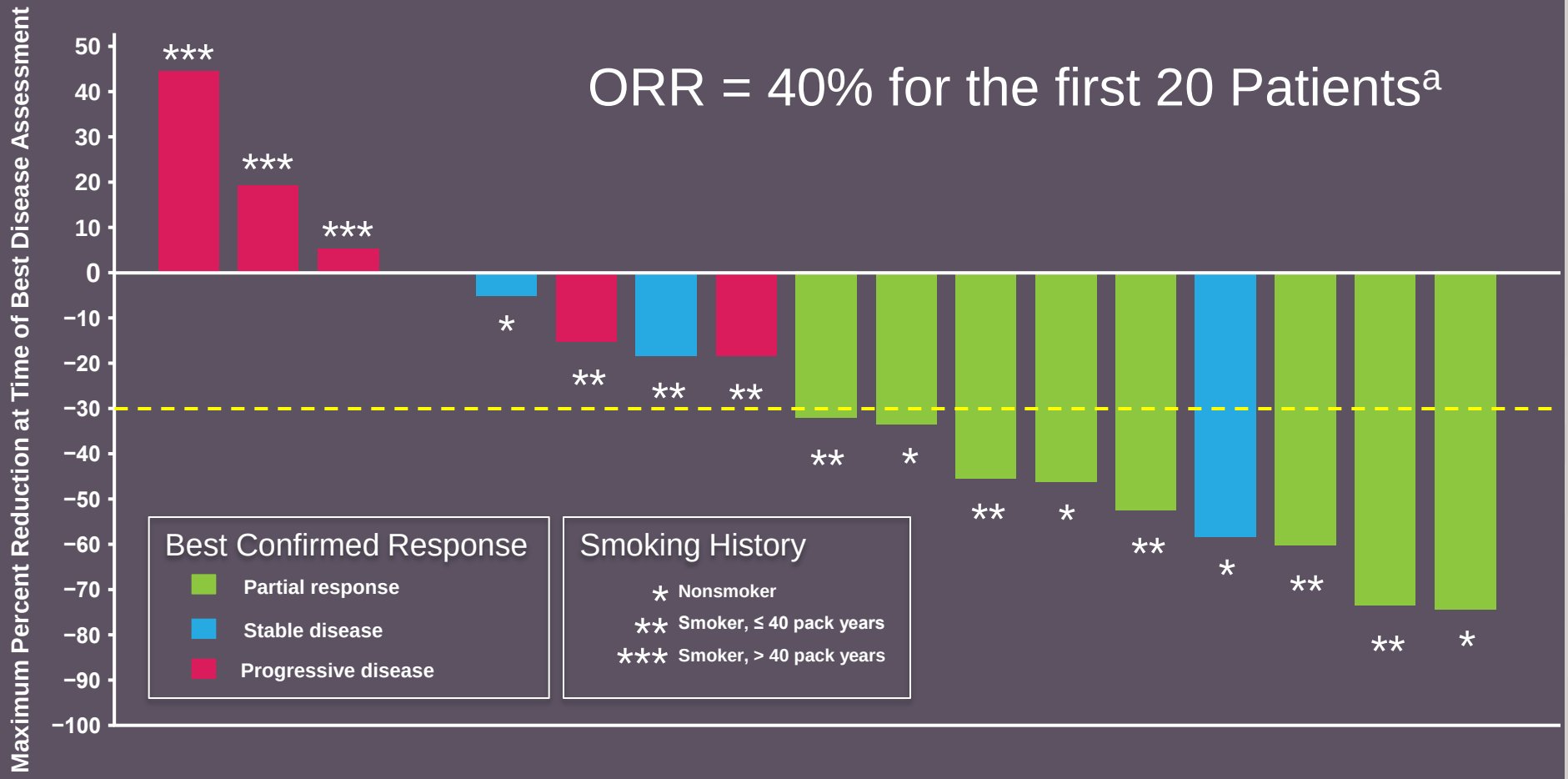
Primary objective: Investigator-assessed ORR

Secondary objectives: PFS, duration of response, overall survival (OS), safety, tolerability, and population pharmacokinetics

Patient Population (N = 25)

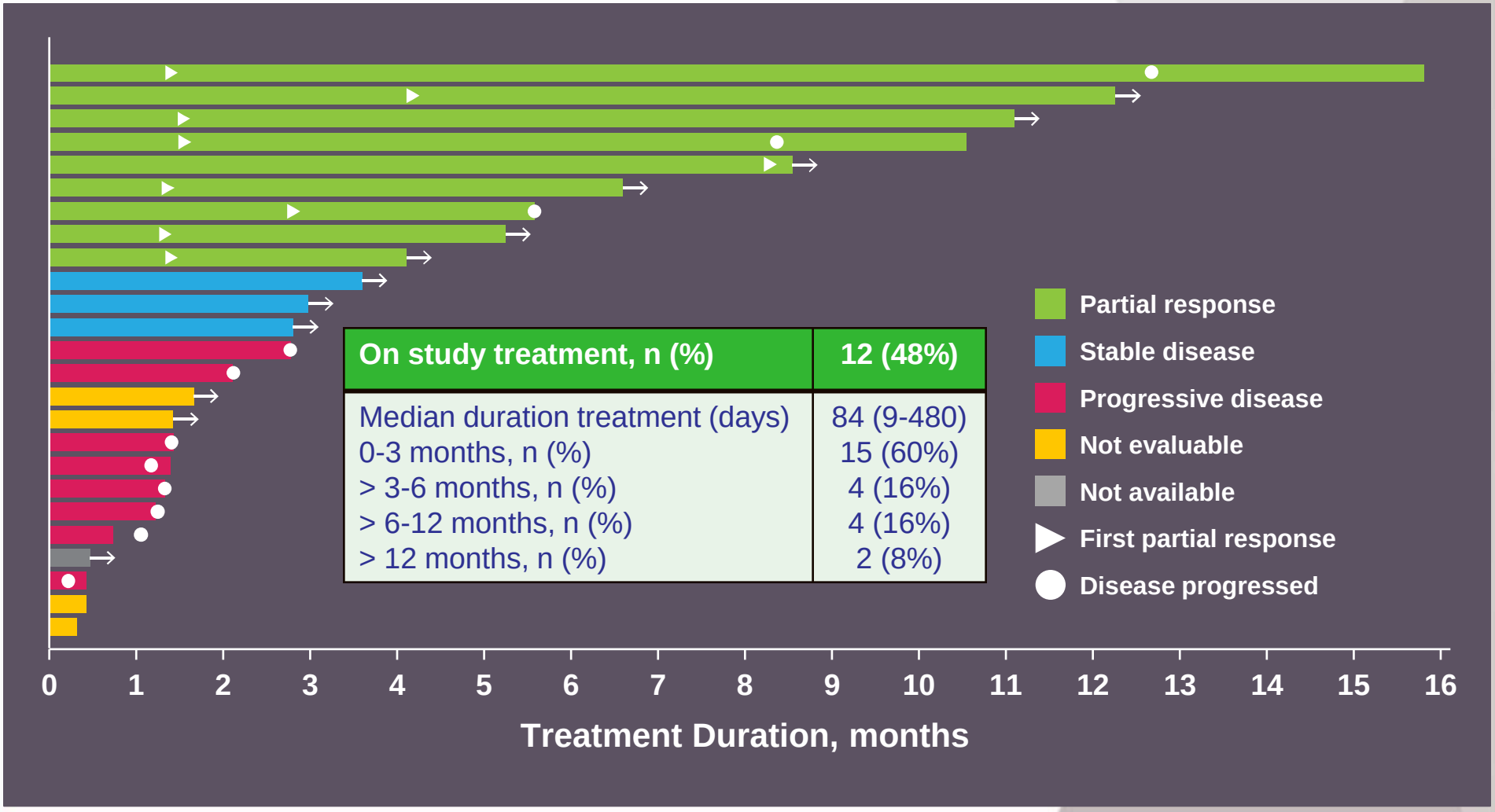
Age, years	Median (min-max)	66 (28-77)
Sex, (%)	Female/male	9 (36%)/16 (64%)
ECOG PS at baseline , (%)	0	5 (20%)
	1	16 (64%)
	2	4 (16%)
Smoking history, (%)	Nonsmoker	8 (32%)
	Smoker, ≤ 40 pack years[a]	12 (48%)
	Smoker, > 40 pack years[a]	5 (20%)
Histology at initial diagnosis, (%)	Adenocarcinoma	25 (100%)
Number of prior systemic regimens for metastatic disease, (%)	1	17 (68%)
	2	4 (16%)
	≥ 3	4 (16%)
Time since initial diagnosis (months)	Median (min-max)	12 (1-71)
Time since initiation of first-line treatment for metastatic disease (months)	Median (min-max)	8.9 (2-50)

Maximum Reduction of Sum of Lesion Diameters by Best Confirmed



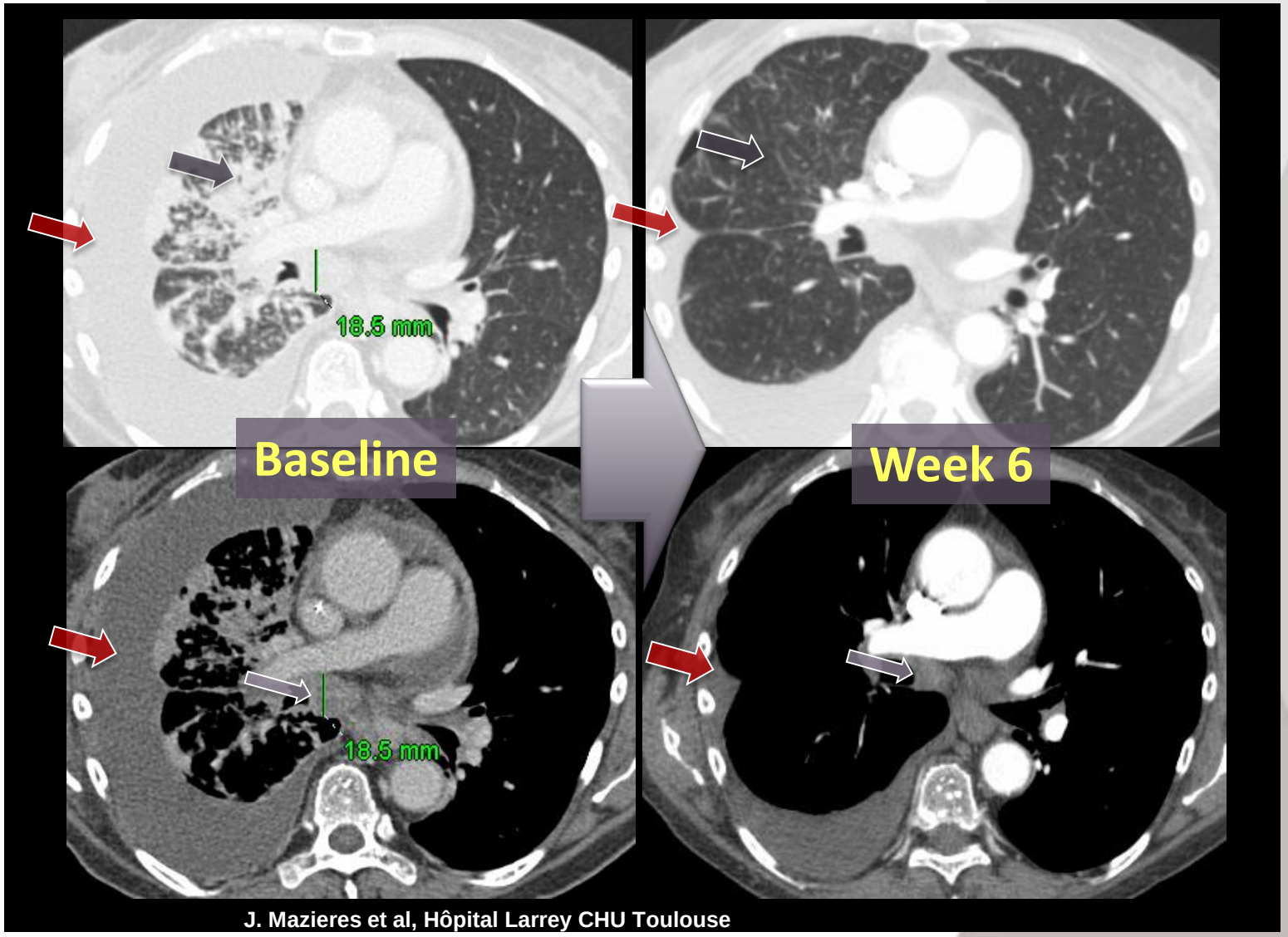
[a] 3 patients are not in the plot: 1 patient had PD on day 6 due to new lesion, target lesions were not assessed postbaseline; and 2 patients discontinued study treatment due to serious adverse events (SAEs) prior to postbaseline disease assessment.

Duration on Treatment by Response (N = 25)



Dabrafenib Activity in BRAF V600E NSCLC

Case Study – 69 year old white female, 3rd line, former smoker, < 1 pack year. From ECOG PS2 to PS0. Still under treatment.



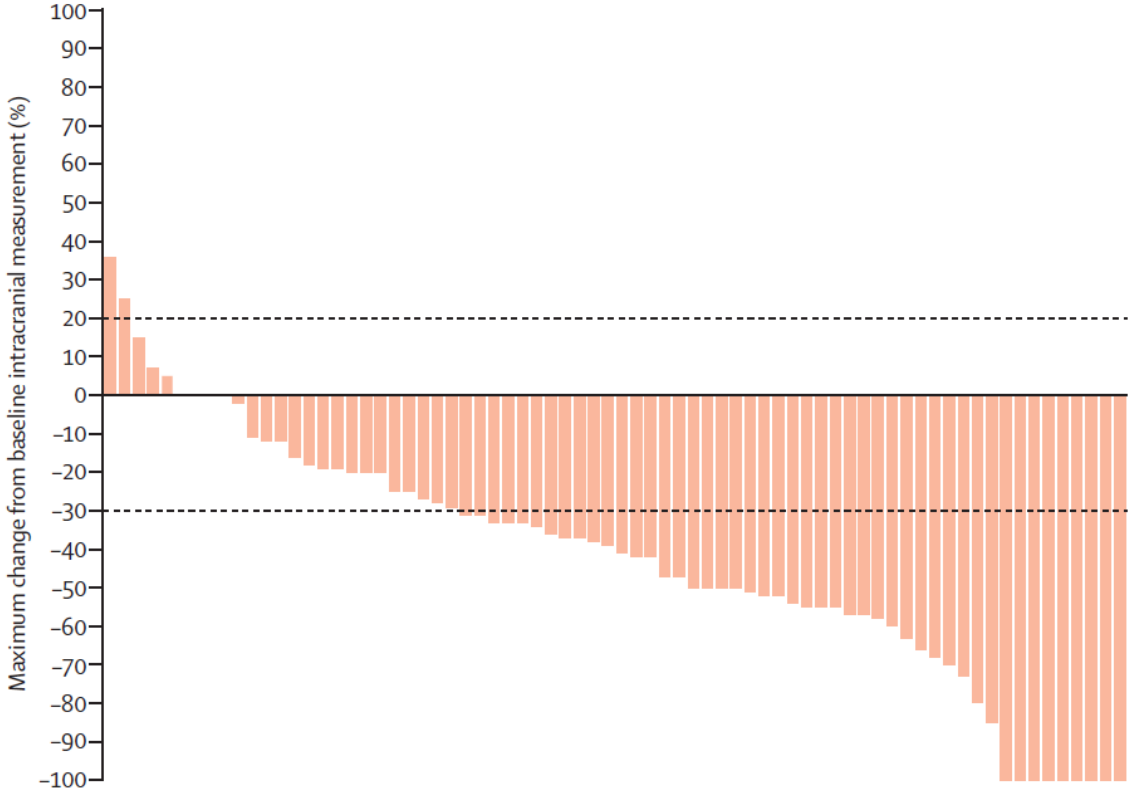
Most Common Adverse Events (≥ 10%)

	Adverse Event	All, n (%)	Grade 3, n (%)
General	Fatigue	10 (40%)	0
	Decreased appetite	8 (32%)	1 (4%)
	Asthenia	6 (24%)	1 (4%)
	Pyrexia	4 (16%)	1 (4%)
	Arthralgia	4 (16%)	0
	Back pain	4 (16%)	1 (4%)
	Headache	4 (16%)	0
Skin	Rash	6 (24%)	0
	Dry skin	5 (20%)	0
	PPES	4 (16%)	0
	Actinic keratosis	3 (12%)	0
	Mucosal inflammation	3 (12%)	0
	Papule	3 (12%)	0
Digestive	Nausea	6 (24%)	1 (4%)
	Diarrhea	5 (20%)	1 (4%)
	Vomiting	5 (20%)	1 (4%)
Hematologic	Anemia	6 (24%)	1 (4%)
	Hypophosphatemia	3 (12%)	2 (8%)

Serious Adverse Events

Serious Adverse Event	Number of Patients (%)
Any	10 (40%)
Squamous cell carcinoma*	2 (8%)
Back pain	1 (4%)
Blister (hypersensitivity)*	1 (4%)
Chest pain	1 (4%)
Chills*	1 (4%)
Decreased appetite	1 (4%)
Hemorrhage intracranial (fatal)*	1 (4%)
Inflammation*	1 (4%)
Malnutrition	1 (4%)
Nausea*	1 (4%)
Pericardial effusion	1 (4%)
Pyrexia*	1 (4%)
Vomiting*	1 (4%)

Dabrafenib in Melanoma Val600E or Val600K brain metastatic patients : phase 2 trial



	Cohort A	Cohort B
Val600Glu BRAF mutant	74	65
Overall intracranial response (CR+PR)	29 (39·2%, 28·0–51·2%)	20 (30·8%, 19·9–43·4%)
Intracranial disease control (CR+PR+SD)*	60 (81·1%, 70·3–89·3%)	58 (89·2%, 79·1–95·6%)
Intracranial CR	2 (3%)	0
Intracranial PR	27 (36%)	20 (31%)
Intracranial SD	31 (42%)	38 (58%)
Intracranial PD	9 (12%)	5 (8%)
Not assessable	5 (7%)†	2 (3%)‡
Overall response (CR+PR)§	28 (37·8%, 26·8–49·9%)	20 (30·8%, 19·9–43·5%)
Overall disease control (CR+PR+SD)	59 (79·7%, 68·8–88·2%)	54 (83·1%, 71·7–91·2%)
6-month survival estimate (%)	61% (46·7–73·2%)	61% (46·3–72·7%)

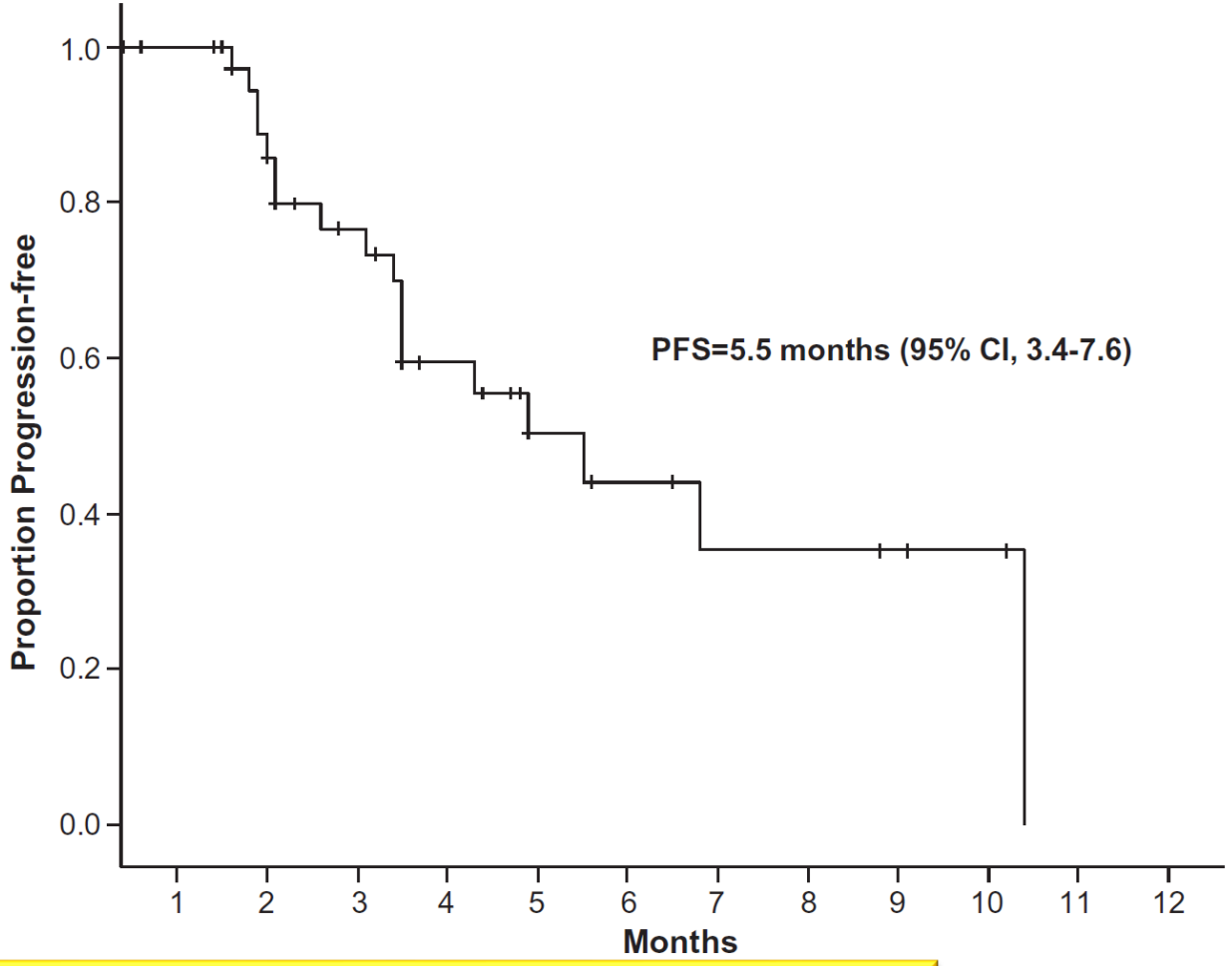
cohort A had not received previous local treatment for brain metastases
cohort B had progressivebrain metastases after previous local treatments.

Georgina V Long et al, Lancet Oncol 2012

BRAF inhibitor activity in V600R metastatic melanoma

Overall response

BRAF V600	18/36 (50%)
BRAF V600E	11/20 (55%)
BRAF V600K	2/10 (20%)
BRAF V600R	5/6 (83%)

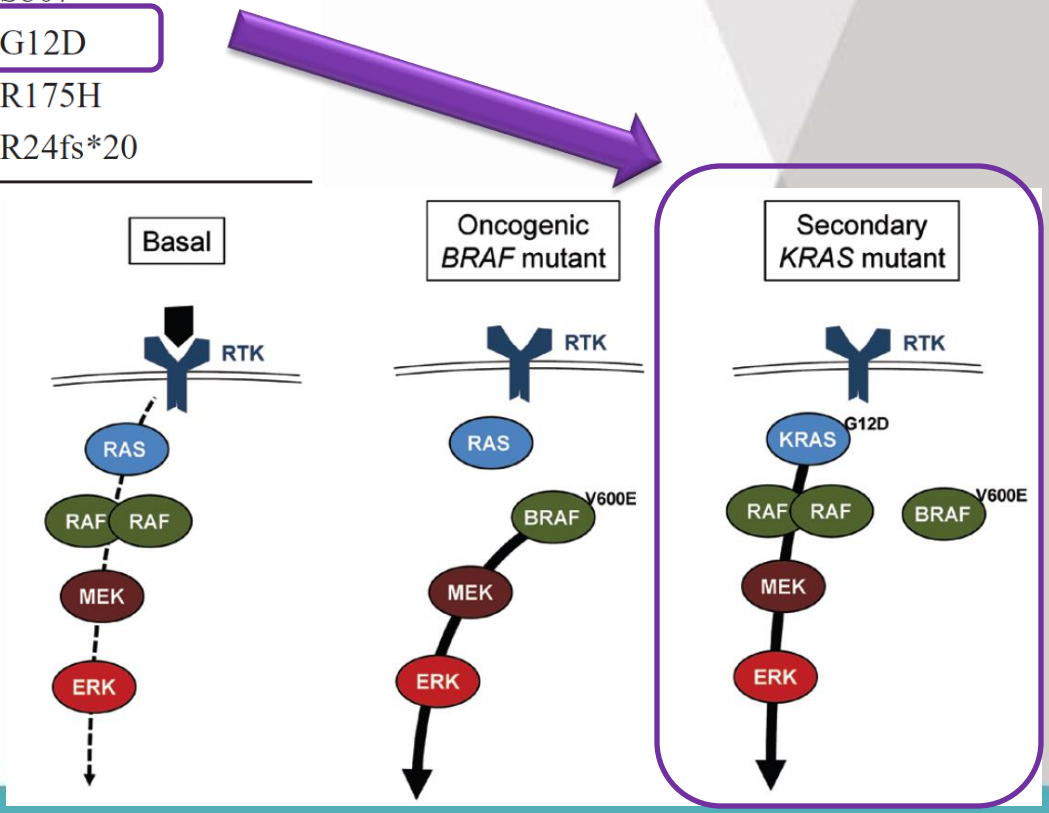


V600 mutated melanoma treated with dabrafenib and vemurafenib

Oliver Klein et al, Eur J Cancer 2013

Acquired Resistance to dabrafenib

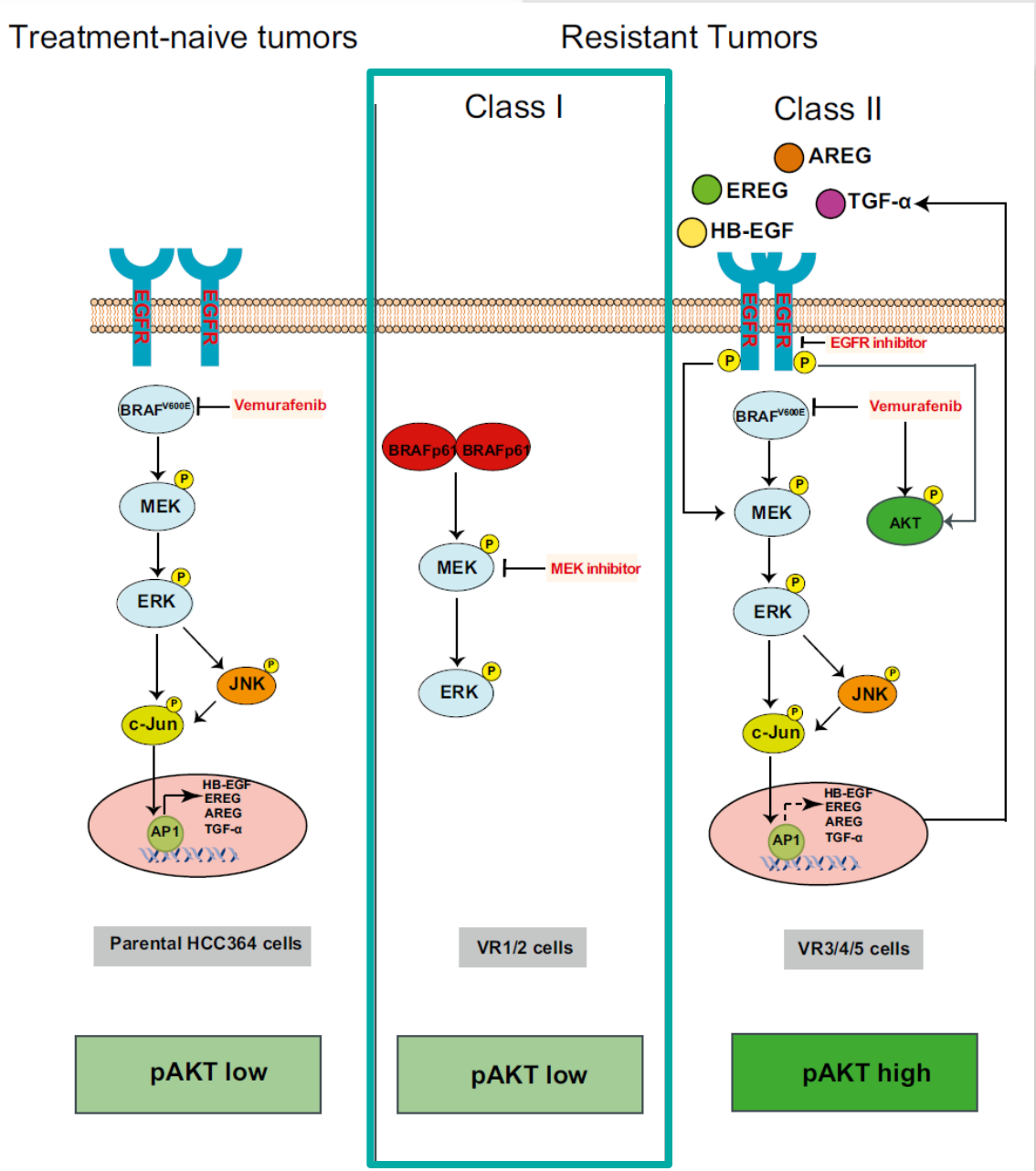
	Mutations	
Gene	**Prestudy[a]**	**Progressive Disease[a]**
BRAF	V600E	V600E
CCND3	Amplification	Amplification
ARID1A	S90fs*11	S90fs*11
RB1	S807*	S807*
KRAS	—	G12D
TP53	—	R175H
CDKN2A	—	R24fs*20



Charles M. Rudin et al, JTO 2013

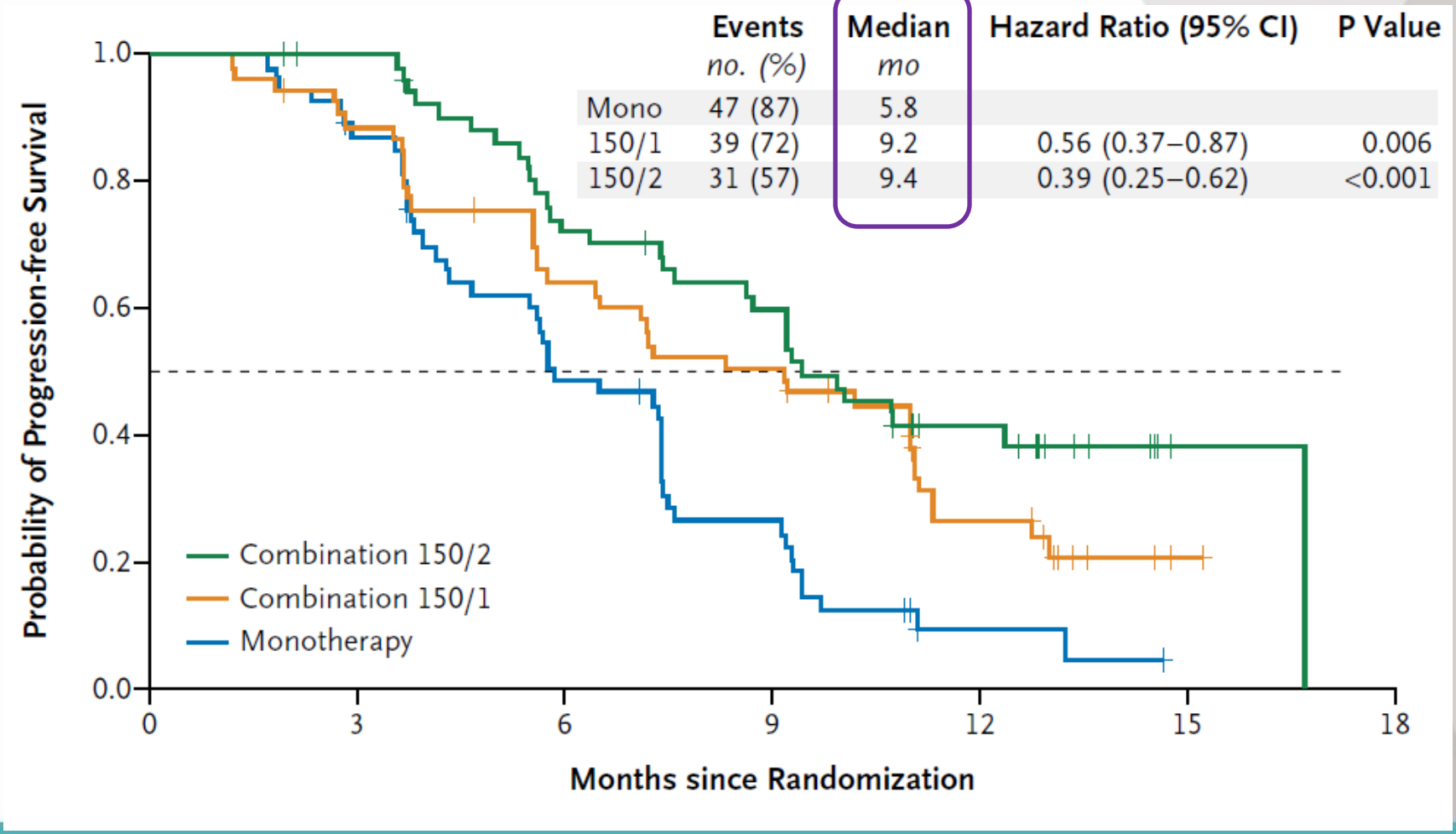
Acquired resistance

- In vitro hypothesis
- **Class I : aberrant BRAFV600E**
- Class II: EGFR loop
- IHC pAKT: potential marker



Combined BRAF and MEK Inhibition in melanoma with BRAF V600 Mutations

Dabrafenib and Trametinib

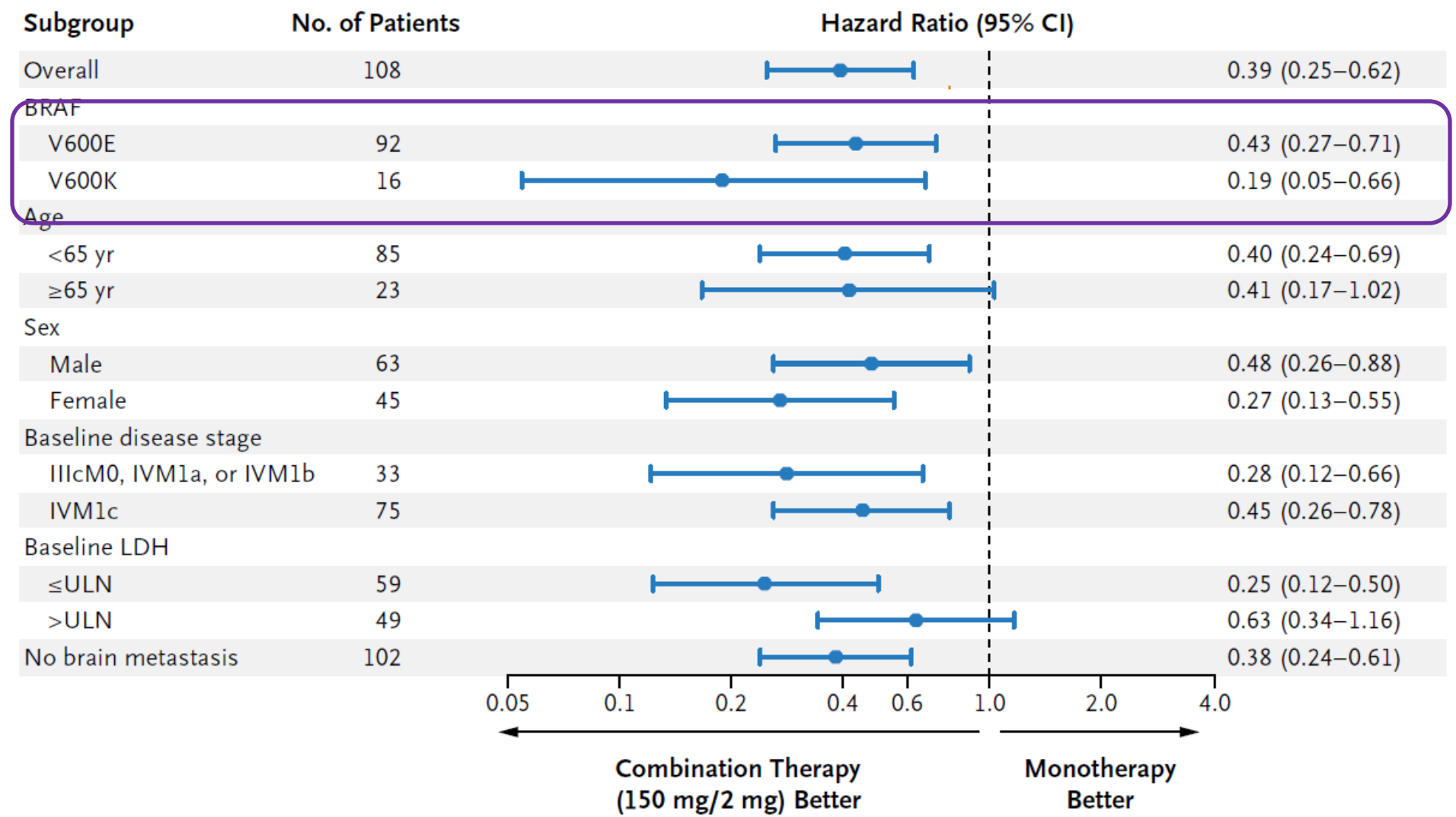


	Events no. (%)	Median mo	Hazard Ratio (95% CI)	P Value
Mono	47 (87)	5.8		
150/1	39 (72)	9.2	0.56 (0.37–0.87)	0.006
150/2	31 (57)	9.4	0.39 (0.25–0.62)	<0.001

Keith T. Flaherty et al, NEJM 2012

Progression-free Survival

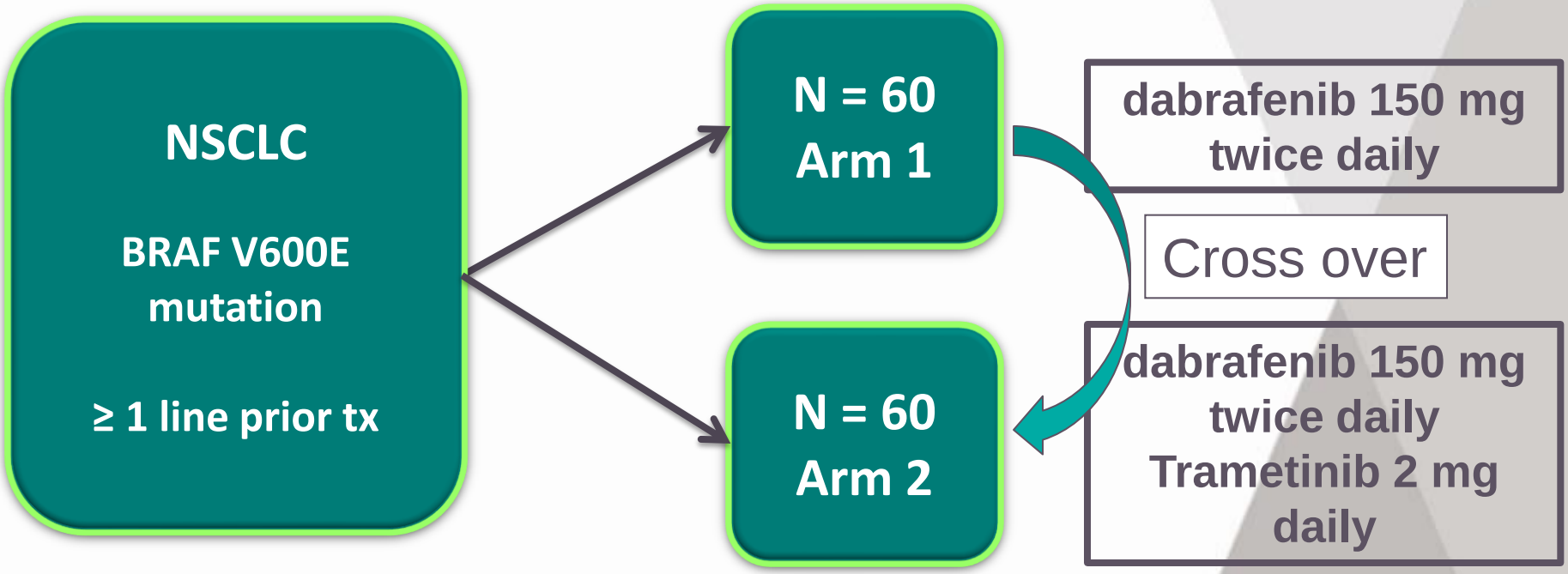
Dabrafenib and Trametinib



Keith T. Flaherty et al, NEJM 2012

BRF113928: New Study Design

- Phase 2, open label

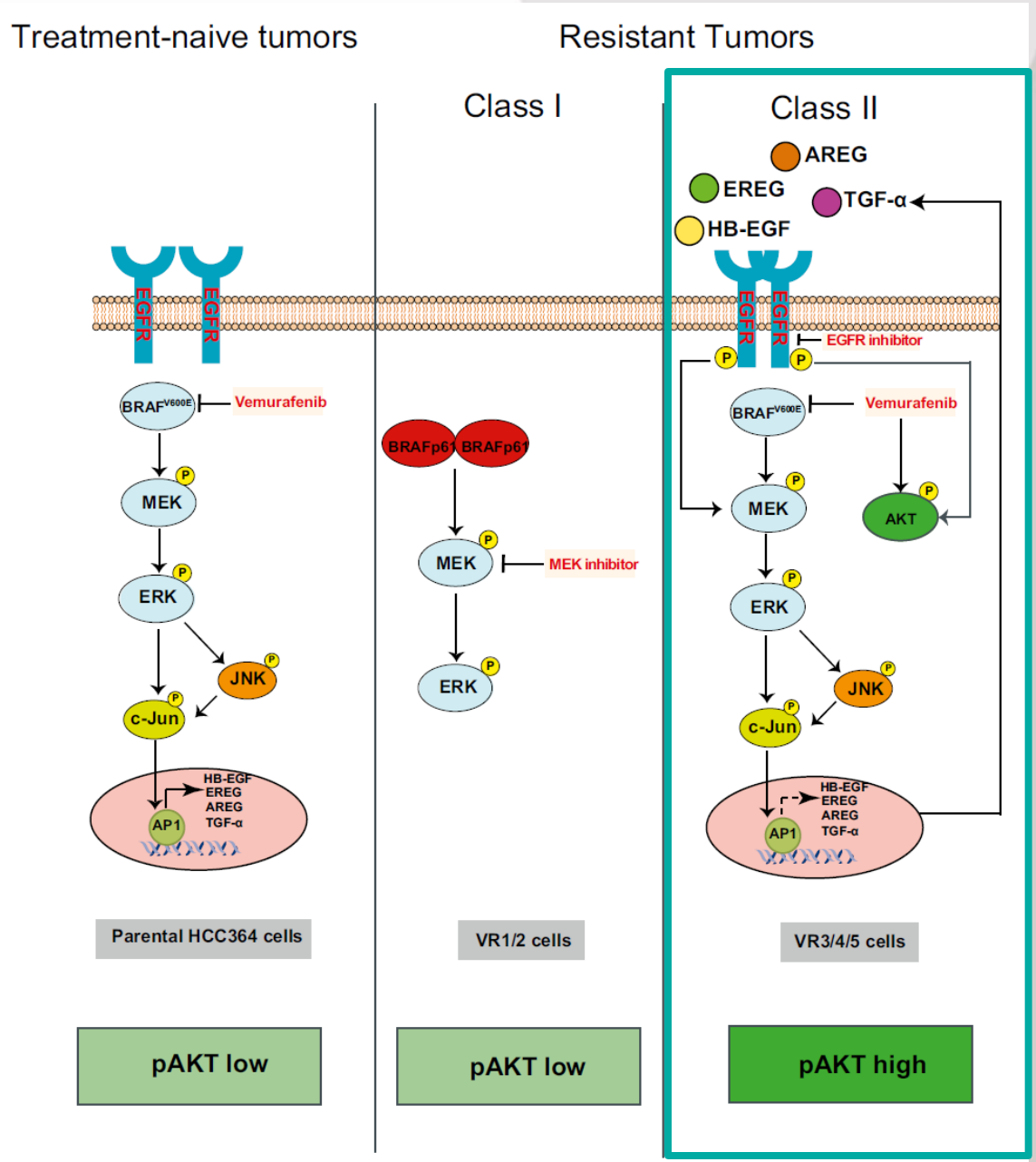


Primary objective: Investigator-assessed ORR

Secondary objectives: PFS, duration of response, overall survival (OS), safety, tolerability, and population pharmacokinetics

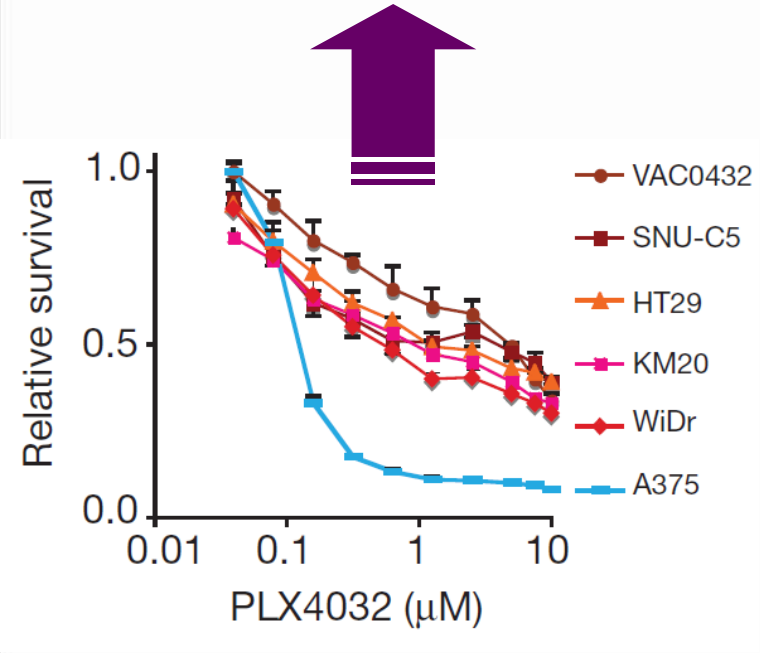
Acquired resistance

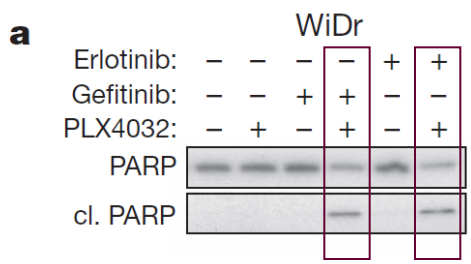
- In vitro hypothesis
- Class I : aberrant BRAFV600E
- Class II: EGFR loop
- IHC pAKT: potential marker

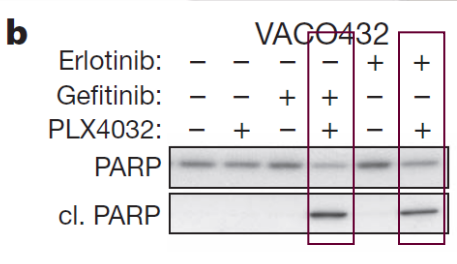


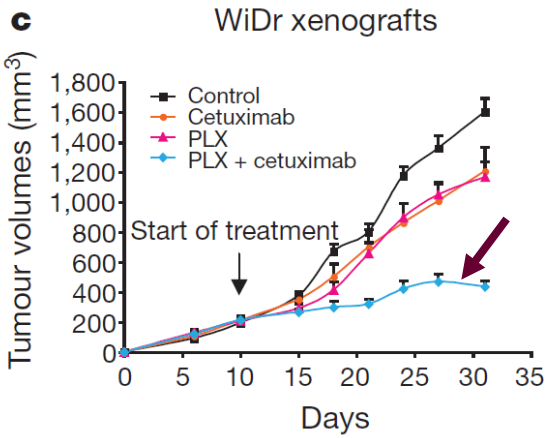
Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

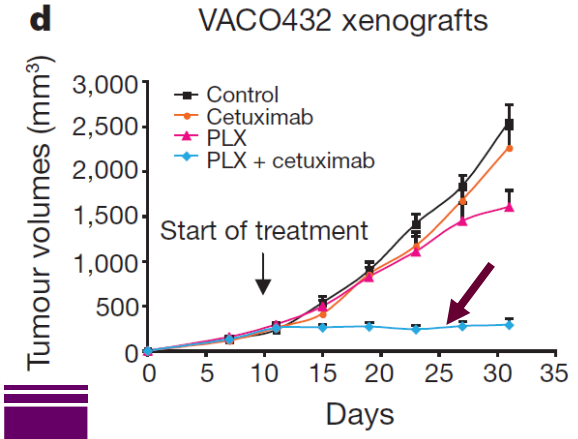
CRC but not melanoma cells harbouring the BRAF(V600E) mutation are resistant to PLX4032 treatment









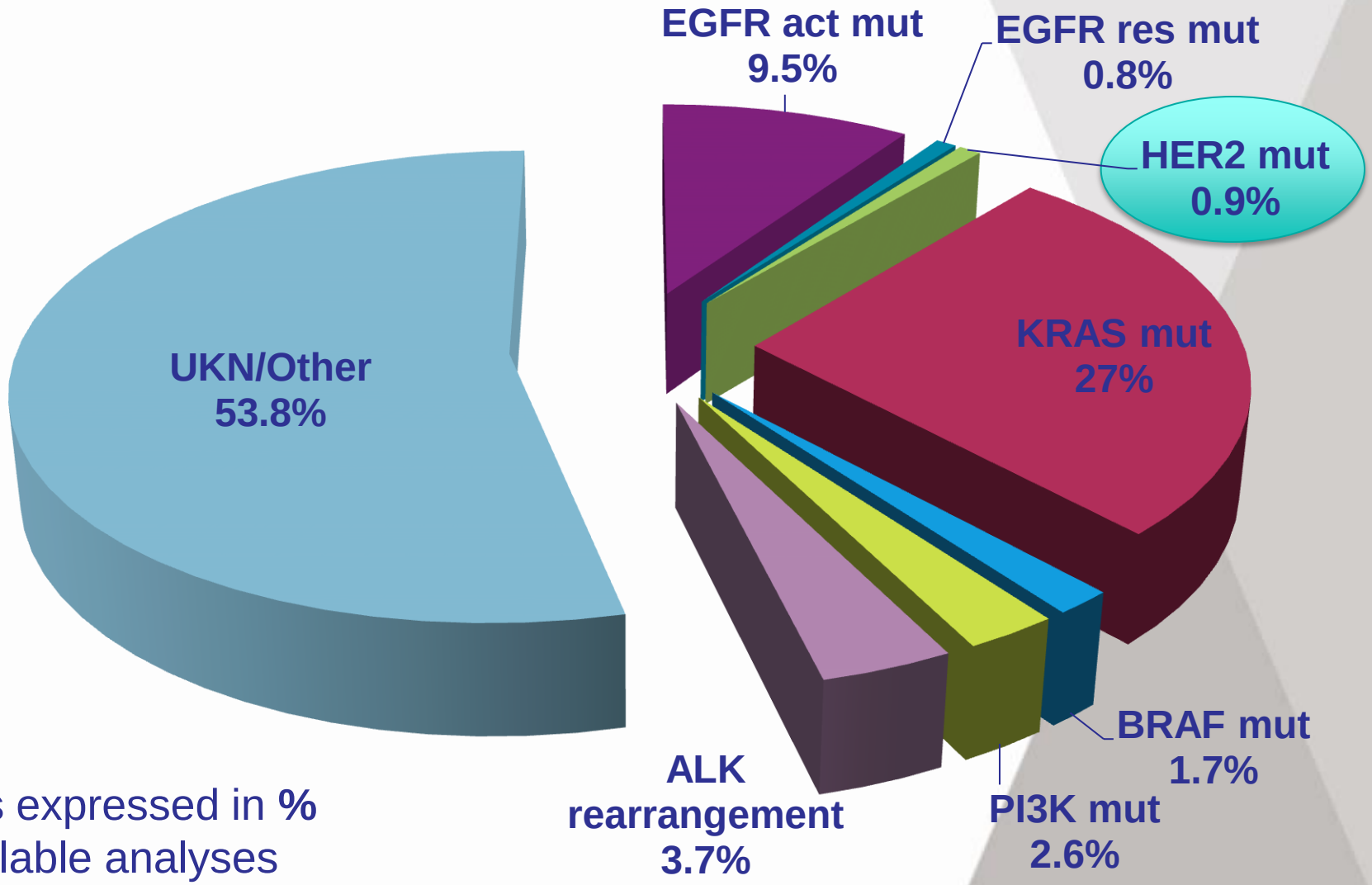


-Feedback activation of EGFR
-Combination of EGFR and BRAF(V600E) inhibitors leads to apoptosis in CRC cells

Anirudh Prahallad et al, nature 2012

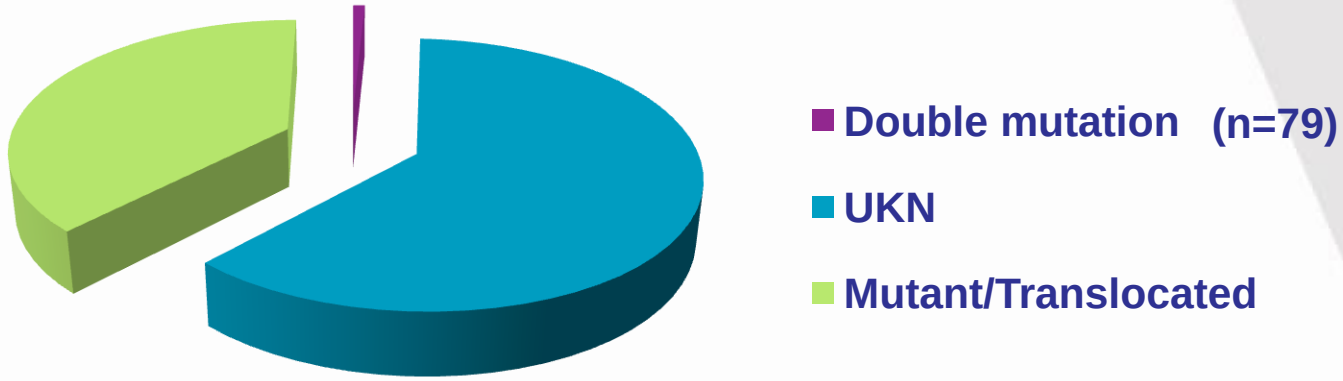
- HER2

Biomarqueurs France (n=9911)



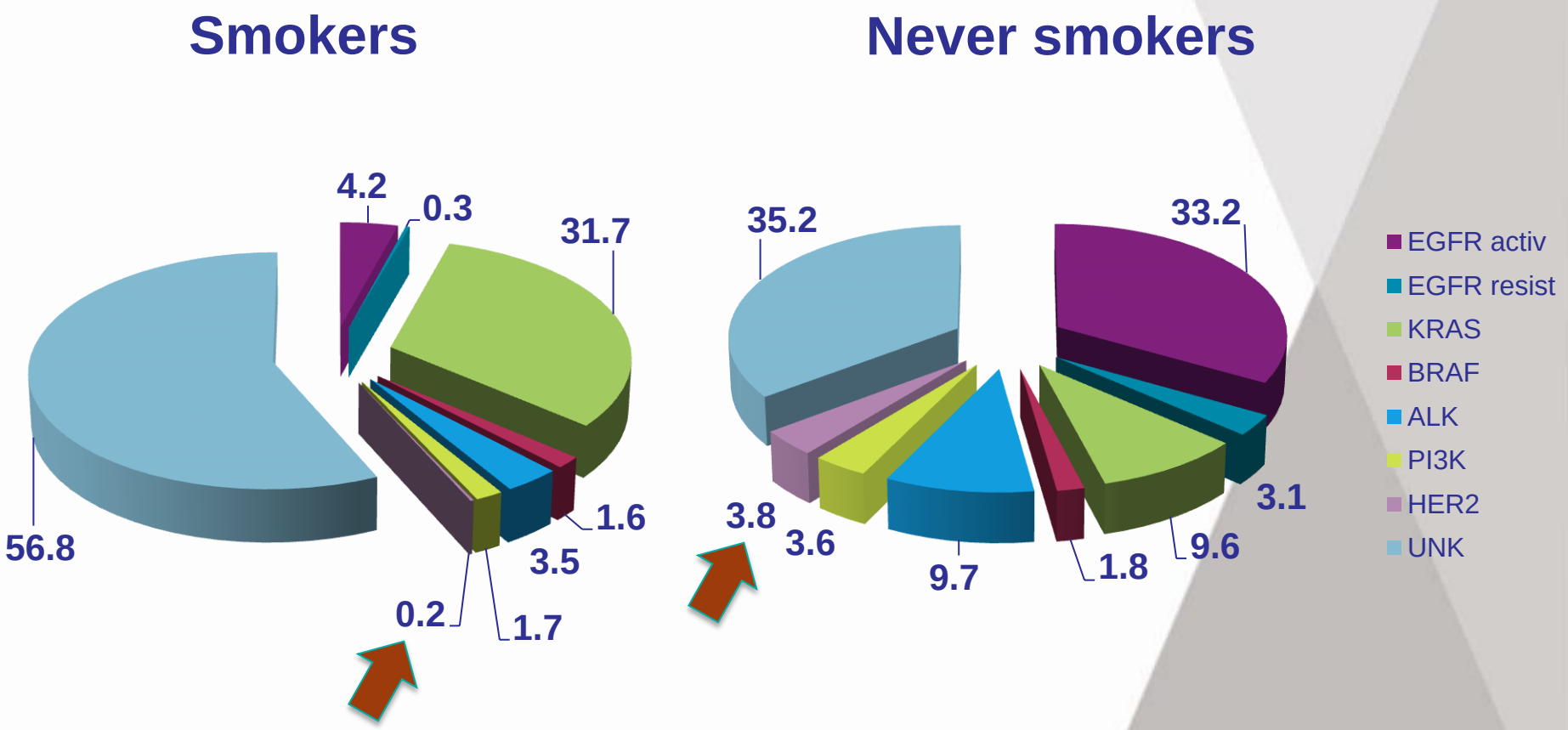
Results expressed in **%**
on available analyses

Double mutation
Biomarqueurs France (n=9911)



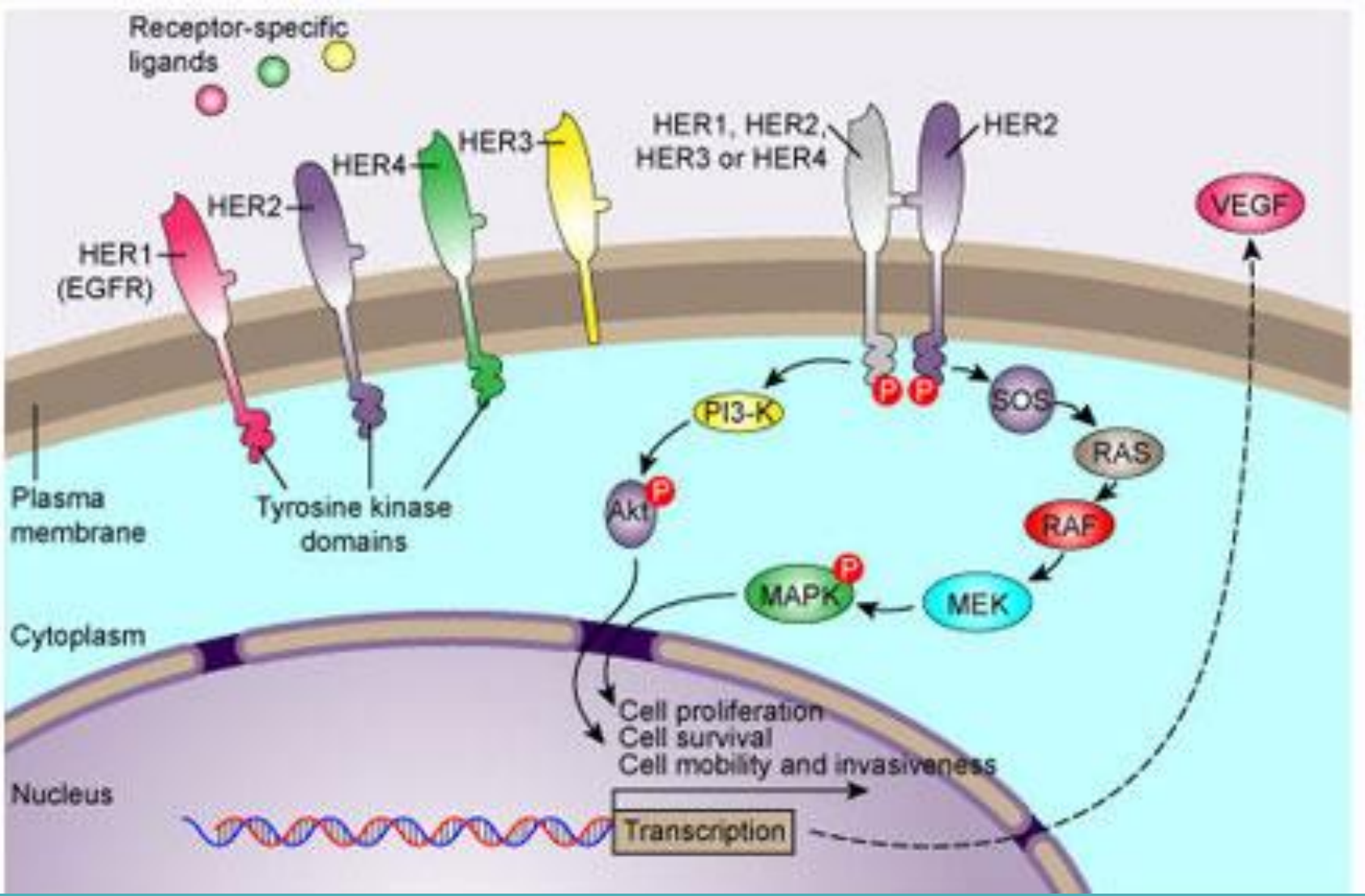
	EGFR	ALK	KRAS	BRAF	PI3K	HER2
EGFR	-					
ALK	3	-				
KRAS	5	10	-			
BRAF	2	1	6	-		
PI3K	16	1	33	1	-	
HER2				1		-

Biomarkers by smoking status (n=9911*)



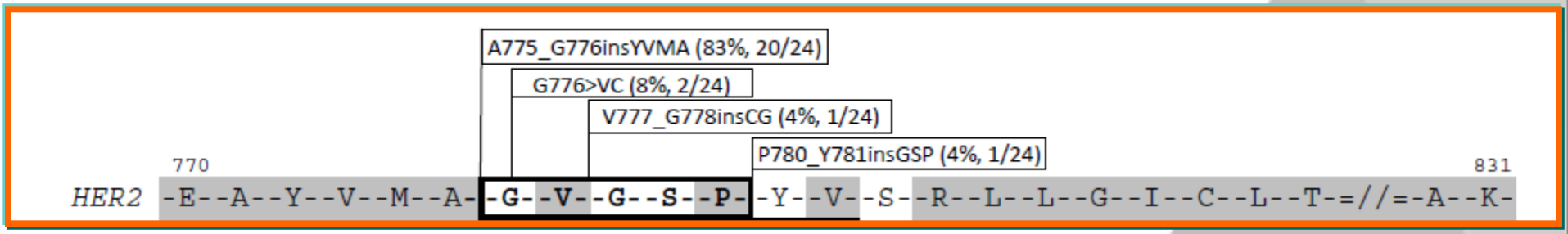
** Including 2664 with full clinical data available at the time of this analysis.*

HER2 : physiopathology



HER2 : physiopathology

- **May HER2 mutations/insertions**
  - Exon 20 insertions (3-12 bp).
    - Between codons 775 and 881 : 83% leading to 4 AA(YVMA) insertion
  - Exon 20 mutations : L755S et G776C 8%.



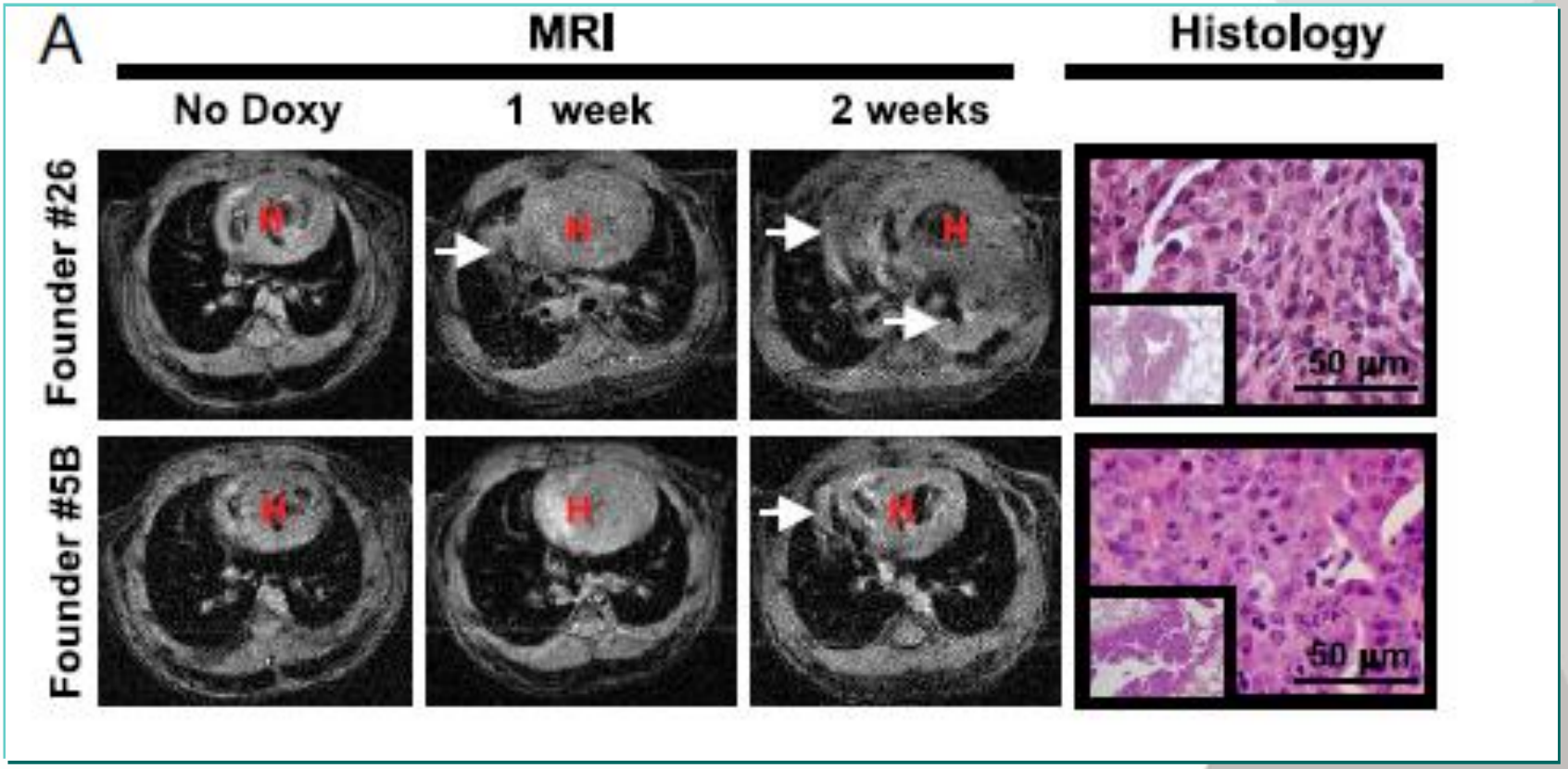
Arcila ME, CCR 2012

- Exon 17 mutations : G660D, V659E.

Courtesy of J.Mazieres

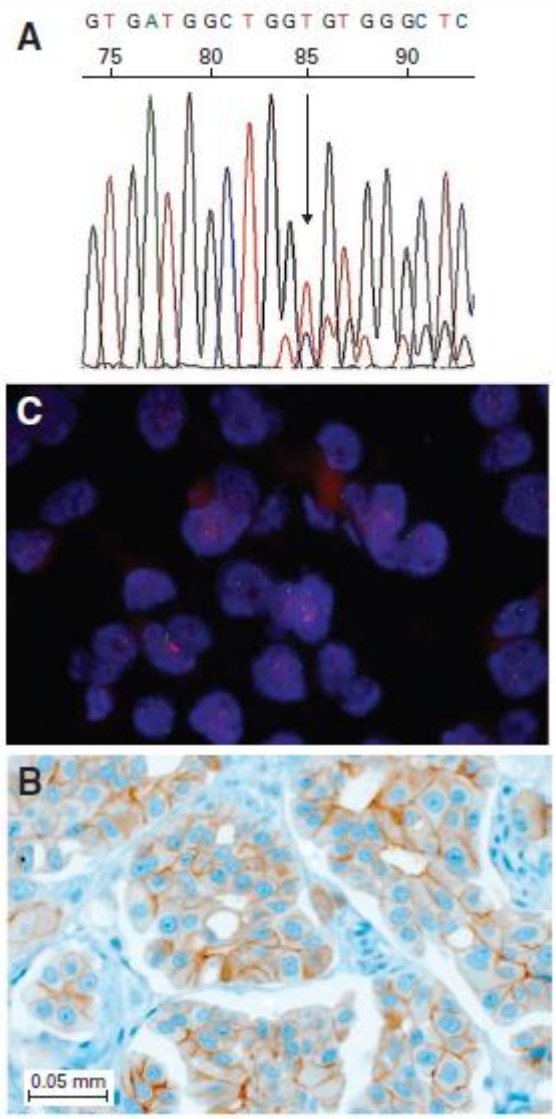
Yamamoto H, JNCI 2014

HER2^{YVMA} drives rapid development of adenosquamous lung tumors in mice that are sensitive to BIBW2992 and rapamycin combination therapy



Perera SA, PNAS 2008

Clinical characteristics

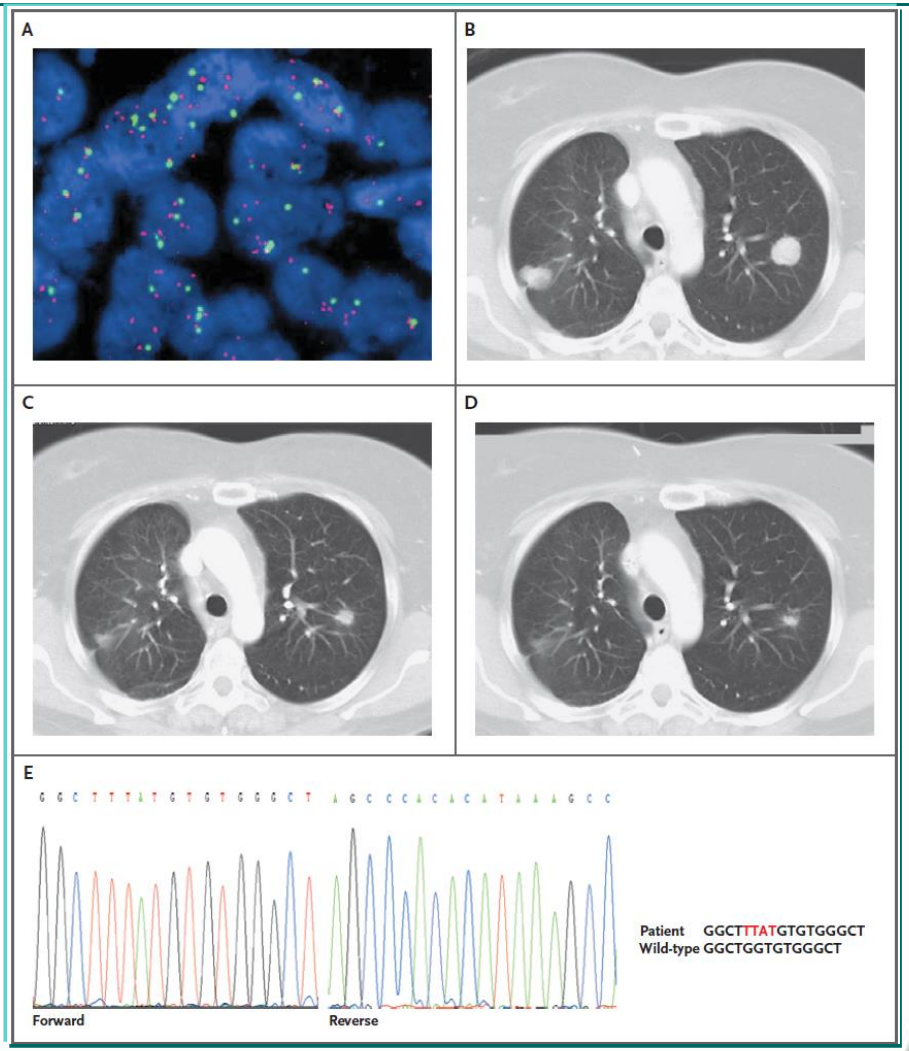


		No	value
Age at diagnosis, years		65	
	Mean		61.1
	SD		11.6
	Median		60.4
		No	%
Gender			
	Women	45	69
	men	20	31
Tobacco			
	never	34	52,3
	former	11	16,9
	current	12	18,5
	unknown	8	12,3
Tumor stage			
	I	11	16,9
	II	3	4,6
	III	15	23.1
	IV	33	50.8
	unknown	3	4,6

Courtesy of J.Mazieres

Mazières J, JCO 2013

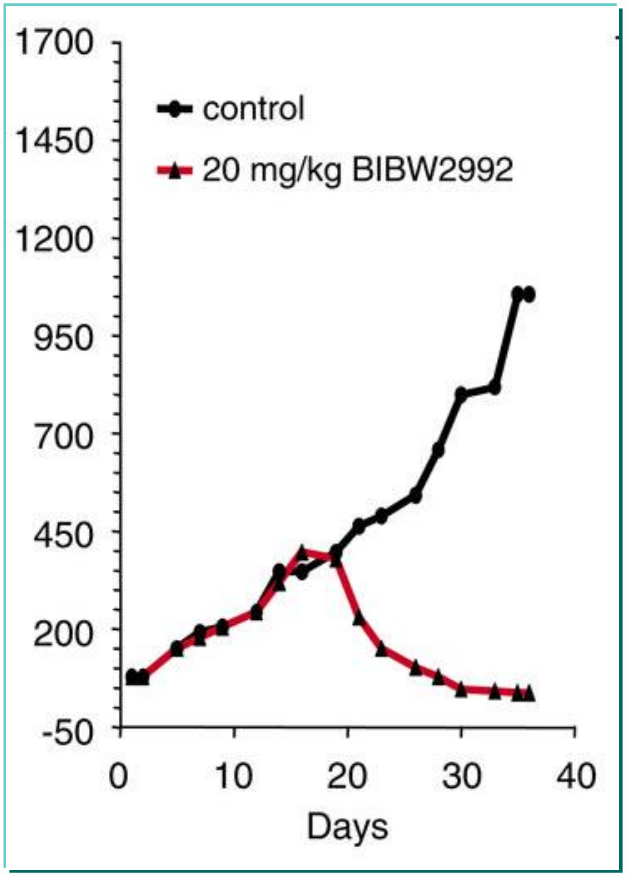
HER2 Mutation and Response to Trastuzumab Therapy in Non–Small-Cell Lung Cancer

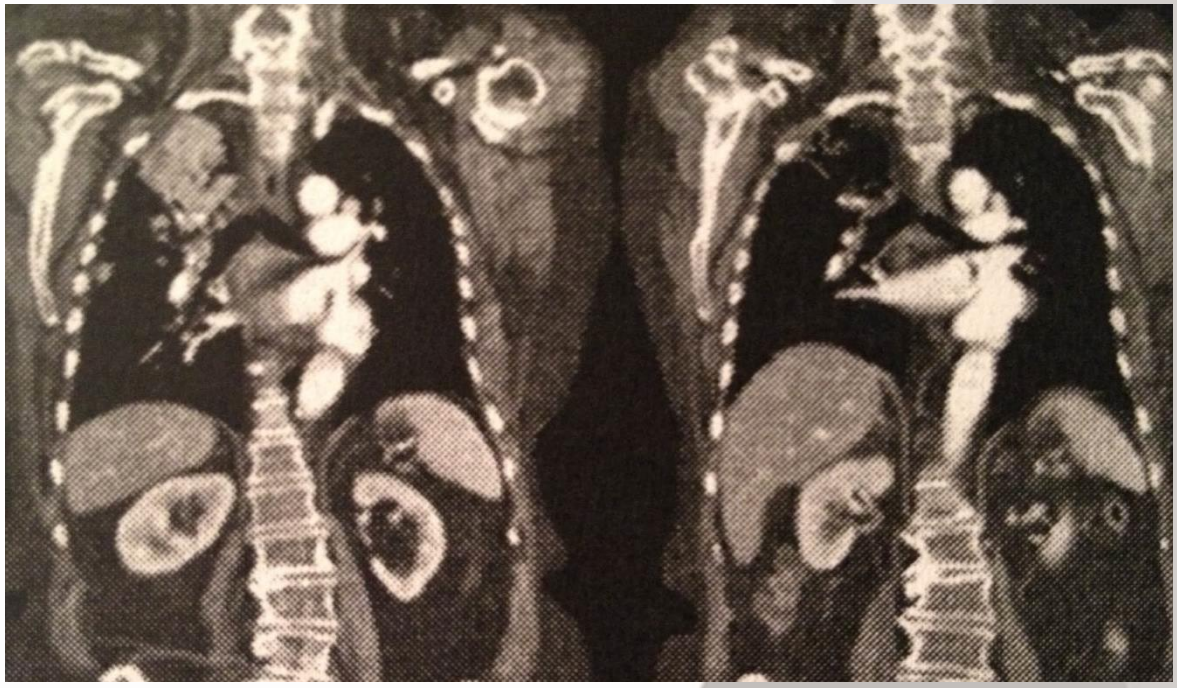


Cappuzzo F, NEJM 2005

HER2 mutation and targeted therapy

- Afatinib efficacy in a in vitro model
- 3 ORR reported





Li, Oncogene 2008

De Greve, Lung Cancer 2012

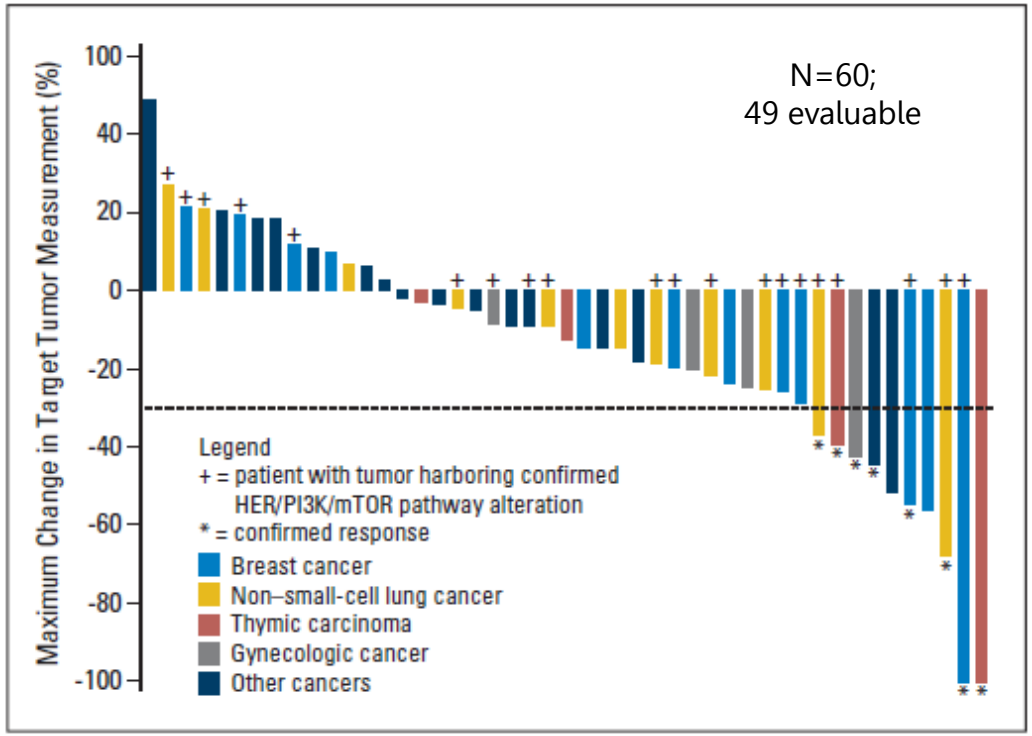
Torisel +Neratinib

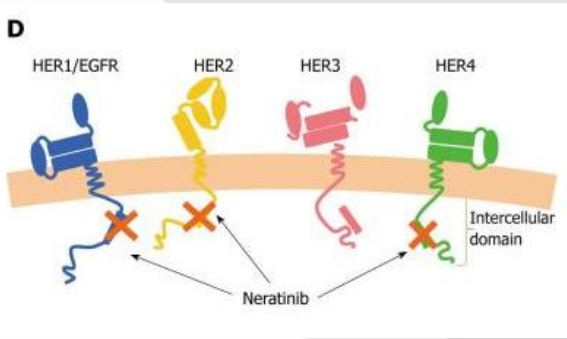
VOLUME 32 · NUMBER 2 · JANUARY 10 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Neratinib in Combination With Temsirolimus in Patients With Human Epidermal Growth Factor Receptor 2–Dependent and Other Solid Tumors

Leena Gandhi, Rastislav Bahleda, Sara M. Tolaney, Eunice L. Kwak, James M. Cleary, Shuchi S. Pandya, Antoine Hollebecque, Richat Abbas, Revathi Ananthakrishnan, Anna Berkenblit, Mizue Krygowski, Yali Liang, Kathleen W. Turnbull, Geoffrey I. Shapiro, and Jean-Charles Soria





HER2-mutated NSCLC
n=6

Gandhi et al, J Clin Oncol 2014; 32(2): 68-75

HER2 mutation

Stage IV patients treated with anti-HER2 therapies

Patient	1st line T	Best disease response	2nd line T	Best disease response	3rd line T	Best disease response	4th line T	Best disease response
1	VIN-HER	PR						
2	CAR-PAC-TRAS	SD						
3	TXT-MASA	PD						
4	VIN-TRAS	PR						
5	CAR-PAC-TRAS	PR						
6	VIN-TRAS	PR						
7	VIN-TRAS	SD						
8	LAP	PD						
9	NVB-HER	PR						
10	LAP	PD	TRAS-VIN	PR	AFA	SD	CAR-TRAS	SD
11	VIN-TRAS	PD						
12	DOC-TRAS	PR						
13	VIN-TRAS	PR	AFA	PR				
14	VIN-TRAS	PR	AFA	SD				
15	VIN-TRAS	SD	PAC-TRAS	SD				
16	TRAS	PR						

SD: Stable Disease, PR: Partial Response, PD: Progressive disease, NE: non evaluated
Conventional treatment: CAR: Carboplatin, PAC: Paclitaxel, VIN: Vinorelbin, DOC: Docetaxel.
HER2 specific treatments: TRAS: Trastuzumab, LAP: Lapatinib, AFA: Afatinib, MASA: masatinib

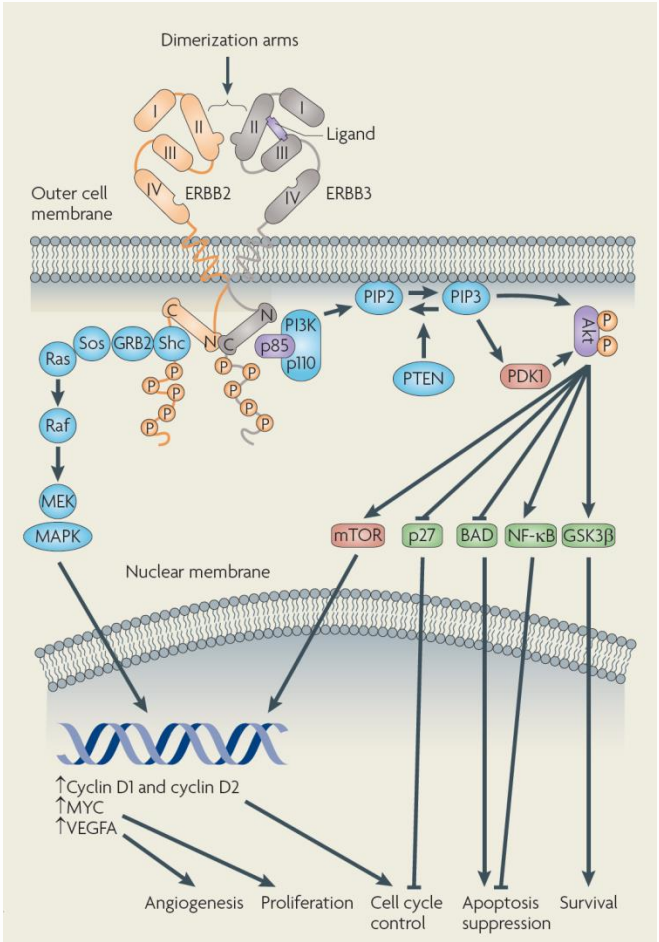
Disease control rate :
96% for trastuzumab (n = 15), 100 % for afatinib (n = 4) .

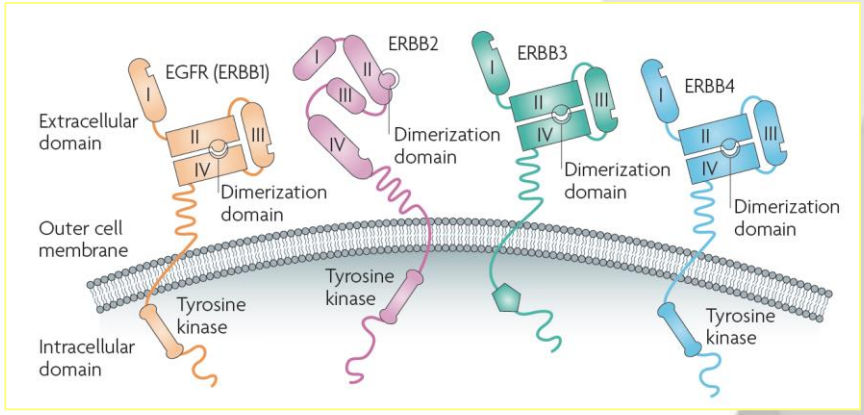
Courtesy of J.Mazieres

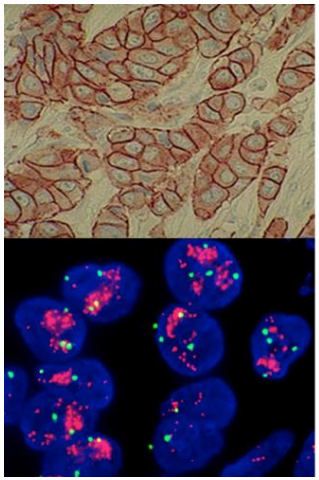
Mazières J, JCO 2013

HER2+ Breast Cancer

Overexpression/amplification 15-20% breast cancers







Shortened Median Survival*	
HER2 positive	3 years
HER2 normal	6-7 years

* Combined metastatic and adjuvant patients

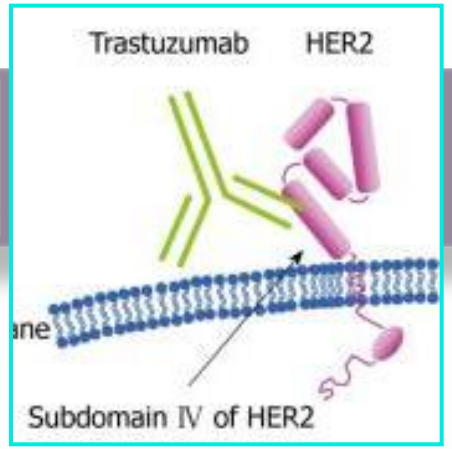
Baselga and Swain, *Nat Rev Cancer* 2009; 9:463

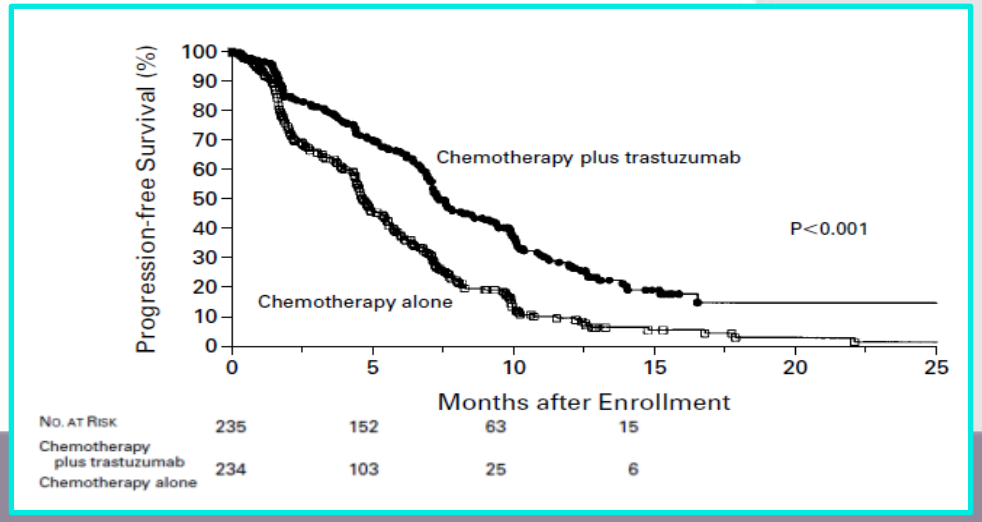
Slamon et al. *Science*. 1987;235:177
Pauletti et al. *J Clin Oncol*. 2000;18:3651

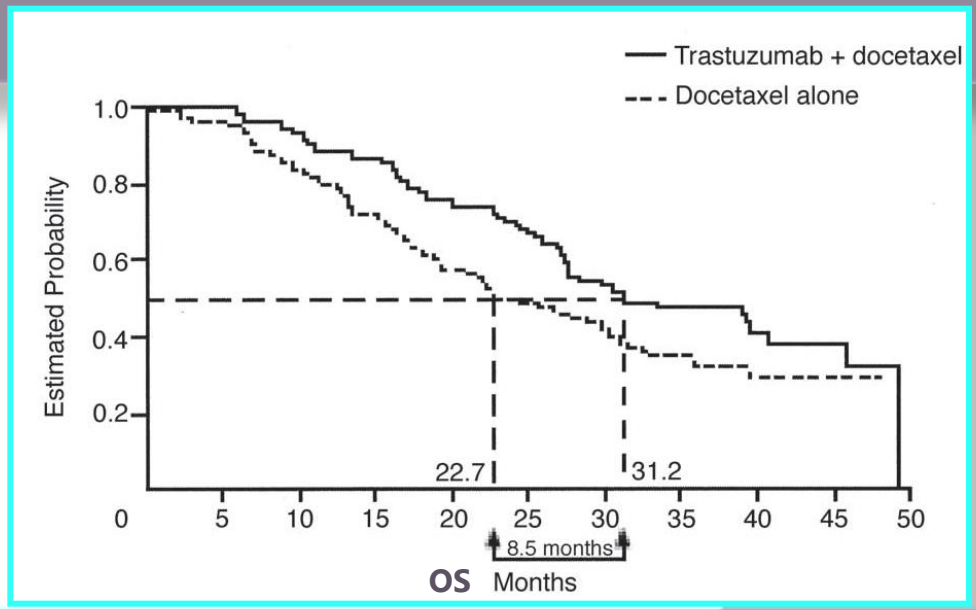
Milestones in HER2+ breast cancer

1998

Trastuzumab





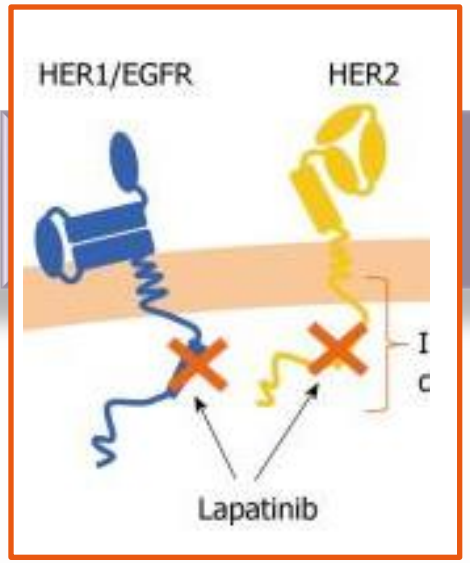


Slamon et al, NEJM 2001;344(11):783-92;
Marty et al, J Clin Oncol 2005; 23(19):4265-74

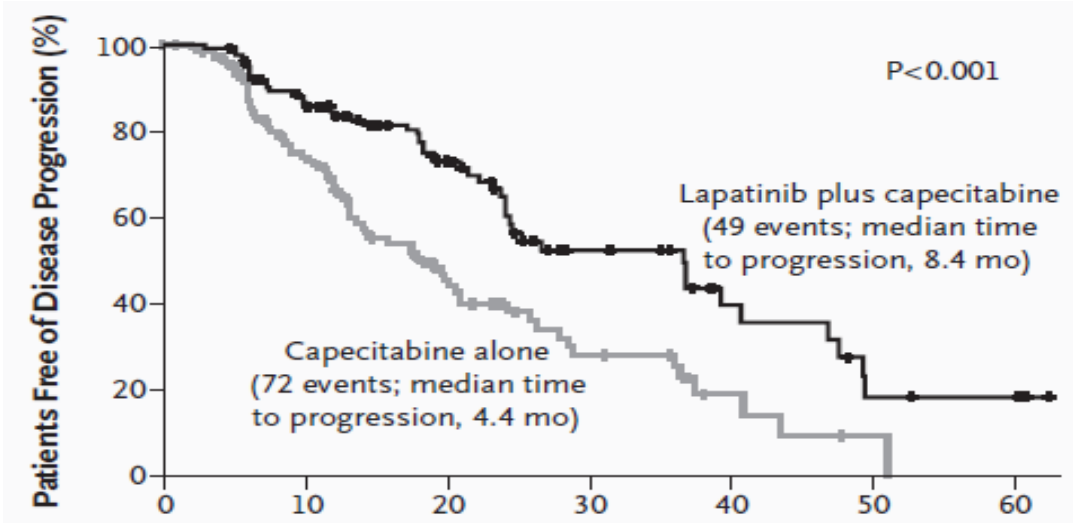
Milestones in HER2+ breast cancer

2007

Lapatinib



TKI



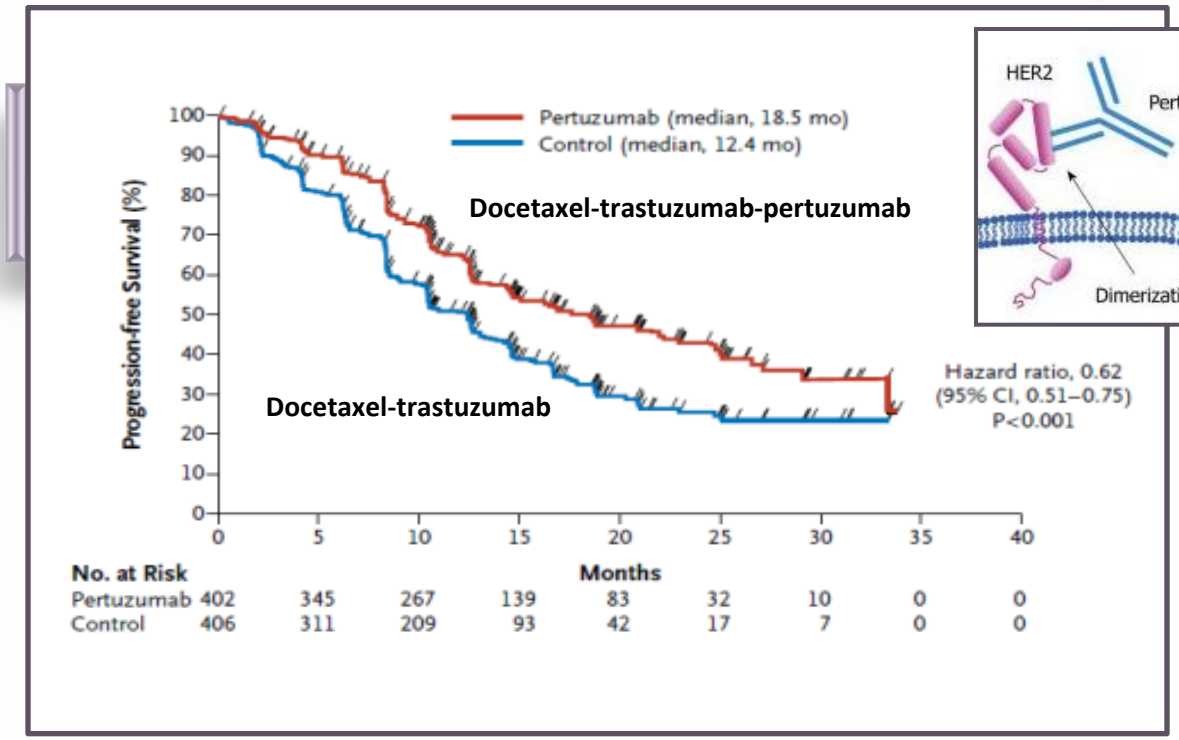
No. at Risk							
Lapatinib plus capecitabine	163	96	52	21	10	4	3
Capecitabine alone	161	78	33	14	4	1	0

Geyer et al, NEJM 2006;355(26):2733-43

Milestones in HER2+ breast cancer

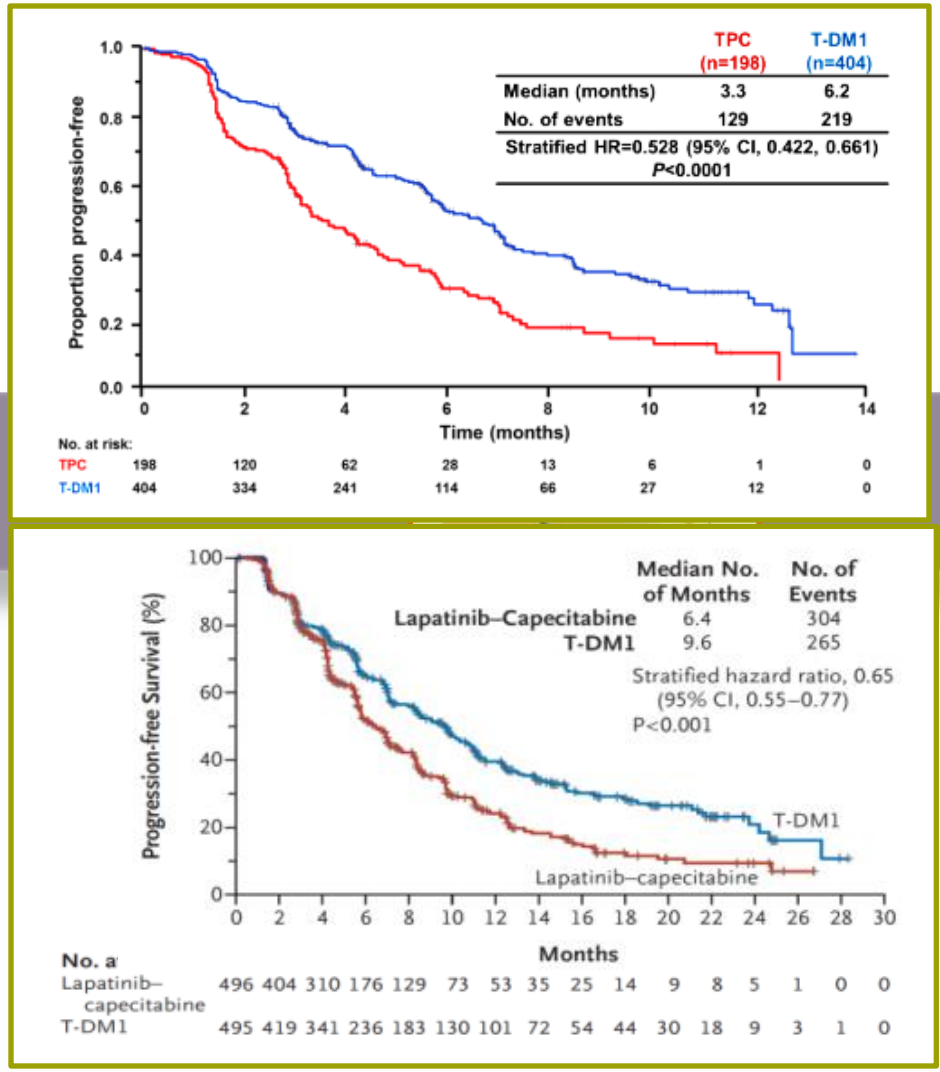
2012

Pertuzumab



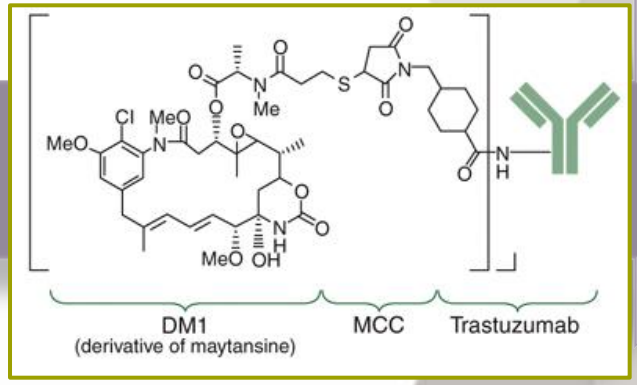
Baselga et al, NEJM 2012;366(2):109-19

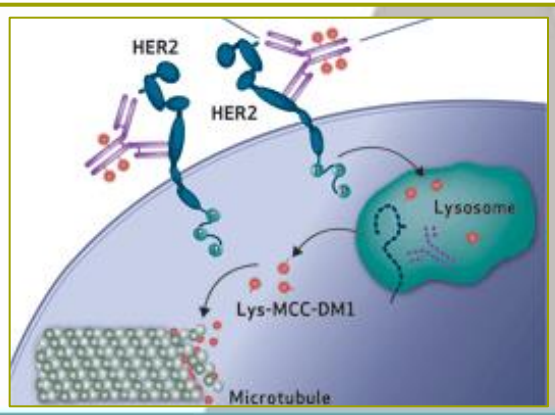
Milestones in HER2+ breast cancer



2013

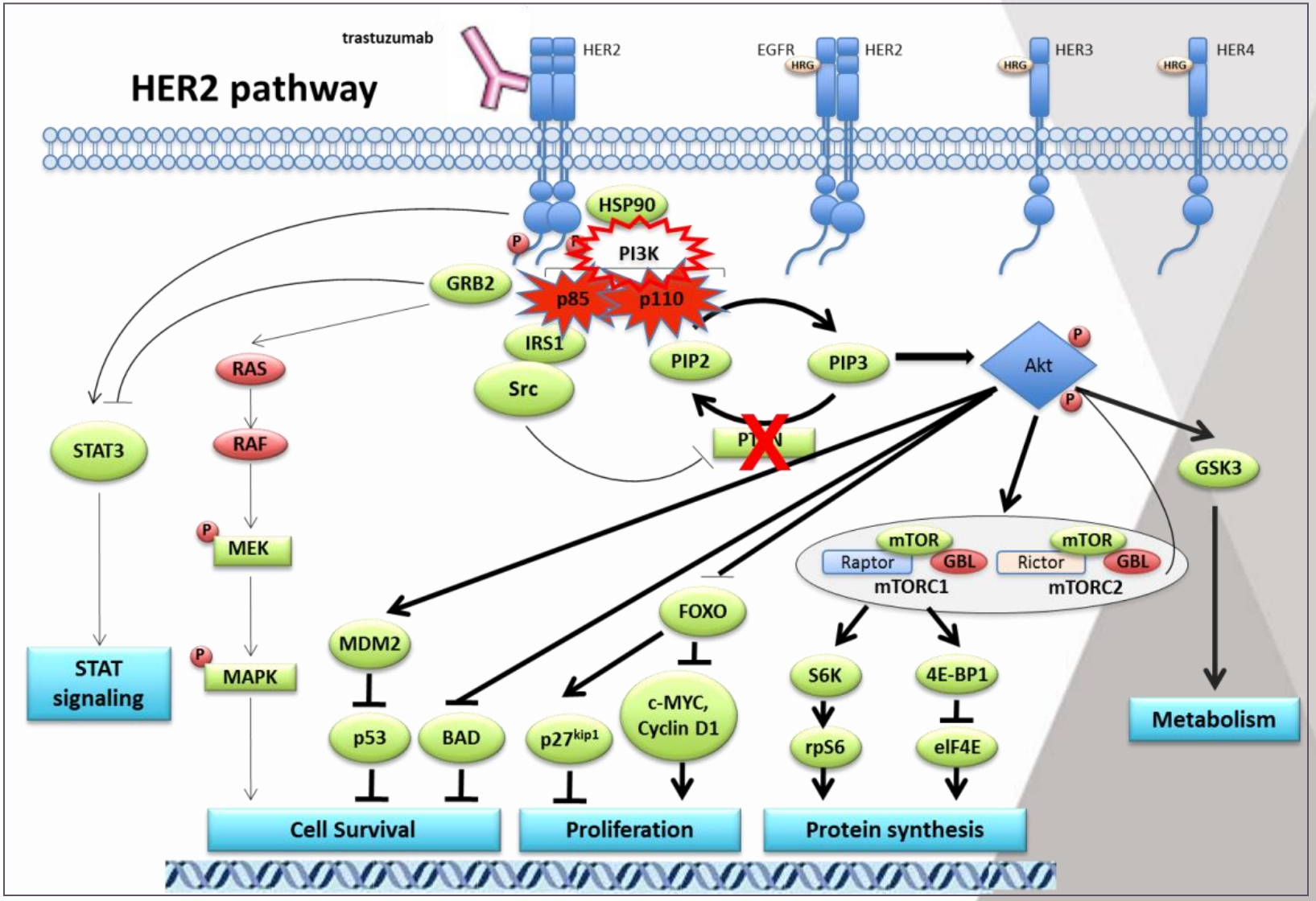
TDM1





Verma et al, NEJM;367(19):1783-91;
Wildiers, H. *et al*. Eur. Cancer Congress 2013 LBA15 (2013)

Trastuzumab resistance



Torisel +Neratinib

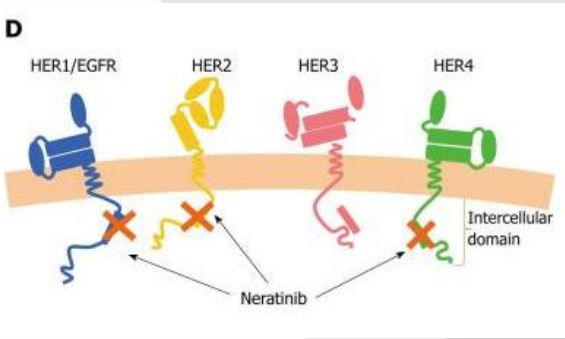
VOLUME 32 · NUMBER 2 · JANUARY 10 2014

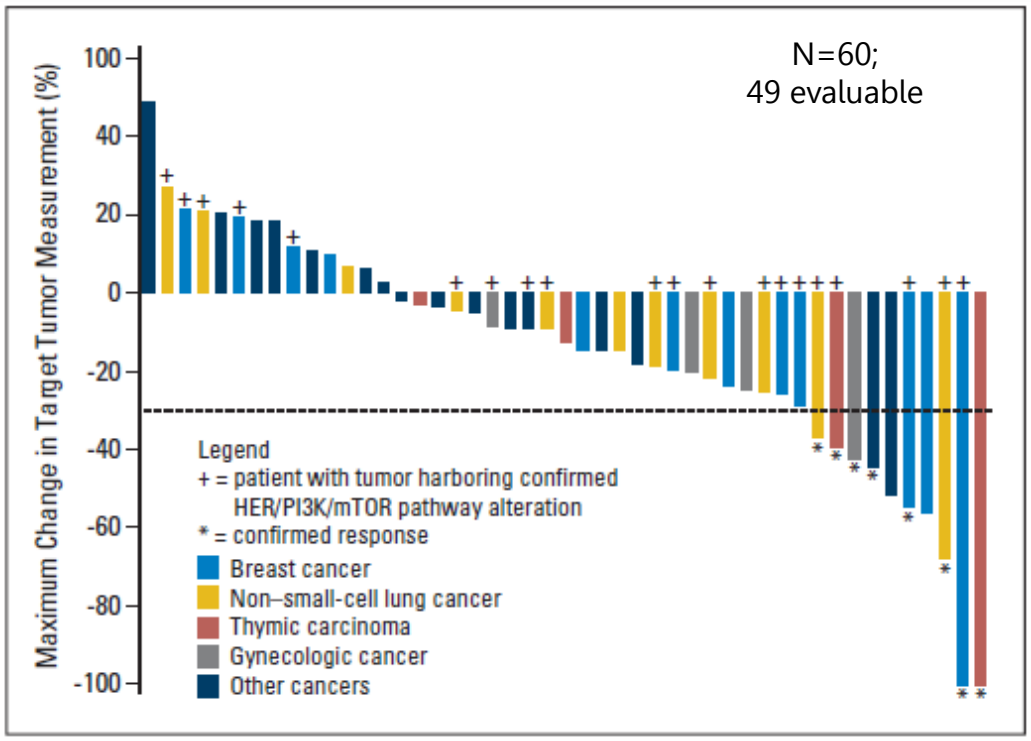
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Study of Neratinib in Combination With Temsirolimus in Patients With Human Epidermal Growth Factor Receptor 2–Dependent and Other Solid Tumors

Leena Gandhi, Rastislav Bahleda, Sara M. Tolaney, Eunice L. Kwak, James M. Cleary, Shuchi S. Pandya, Antoine Hollebecque, Richat Abbas, Revathi Ananthakrishnan, Anna Berkenblit, Mizue Krygowski, Yali Liang, Kathleen W. Turnbull, Geoffrey I. Shapiro, and Jean-Charles Soria





Gandhi et al, J Clin Oncol 2014; 32(2): 68-75

Trastuzumab+paclitaxel+everolimus

VOLUME 28 · NUMBER 34 · DECEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

Phase I Study of Everolimus Plus Weekly Paclitaxel and Trastuzumab in Patients With Metastatic Breast Cancer Pretreated With Trastuzumab

Fabrice Andre, Mario Campone, Ruth O'Regan, Corinne Manlius, Cristian Massacesi, Tarek Sahmoud, Pabak Mukhopadhyay, Jean-Charles Soria, Michael Naughton, and Sara A. Hurvitz

Study/Patient Population	Treatments	N	Outcome
NCT00426556 • **HER-2⁺ mBC** • **Disease progression on/after trastuzumab** • **Prior taxane: ~97%**	Everolimus, trastuzumab, paclitaxel	33	• ORR: 44% • 82% with ≥SD

André et al, J Clin Oncol 2010;28(34):5110-5

Breast Cancer Res Treat (2013) 141:437–446
DOI 10.1007/s10549-013-2689-5

CLINICAL TRIAL

A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing advanced breast cancer that progressed during prior trastuzumab and taxane therapy

Sara A. Hurvitz · Florence Dalenc · Mario Campone · Ruth M. O'Regan · Vivianne C. Tjan-Heijnen · Joseph Gligorov · Antonio Llombart · Haresh Jhangiani · Hamid R. Mirshahidi · Elizabeth Tan-Chiu · Sara Miao · Mona El-Hashimy · Jeremie Lincy · Tetiana Taran · Jean-Charles Soria · Tarek Sahmoud · Fabrice André

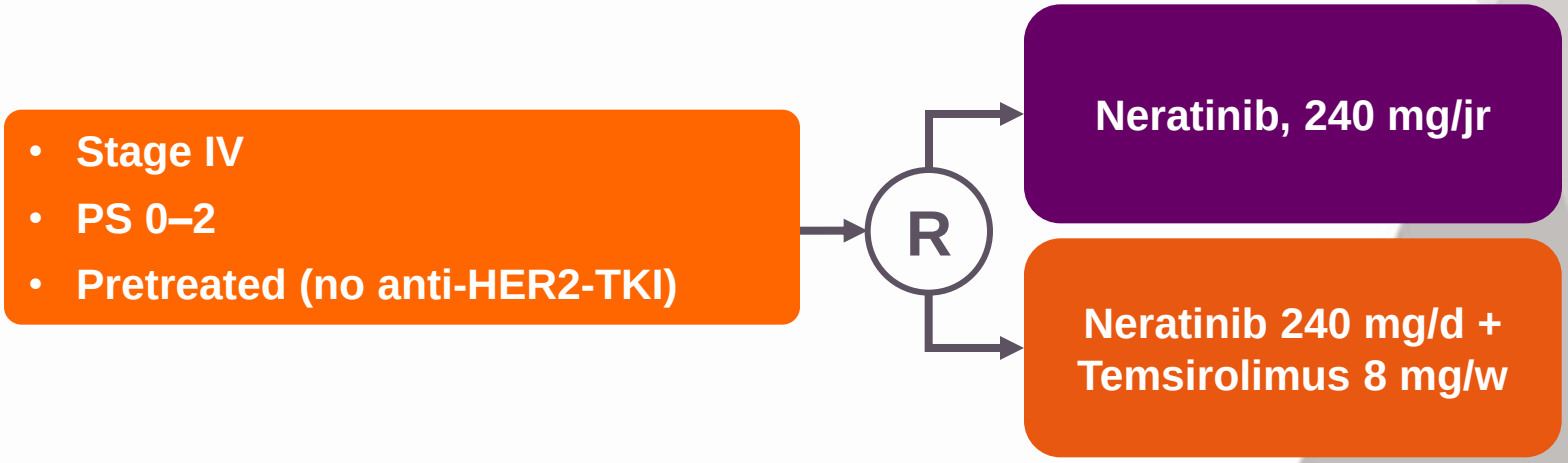
Study/Patient Population	Treatments	N	Outcome
NCT00426556 • **HER-2+ mBC** • **Refractory to trastuzumab AND taxanes**	Everolimus, trastuzumab, paclitaxel	55	Clinical benefit (≥SD for ≥24 wk) in 40% of patients

Hurvitz et al, Breast Cancer Res Treat 2013;141:437-46

HER2 mutated NSCLC

- **Neratinib**
  - HER1/HER2 TKI
  - Ongoing phase II study (France, US)

PUMA-NER4201



- **ETOP trial with afatinib opening soon**

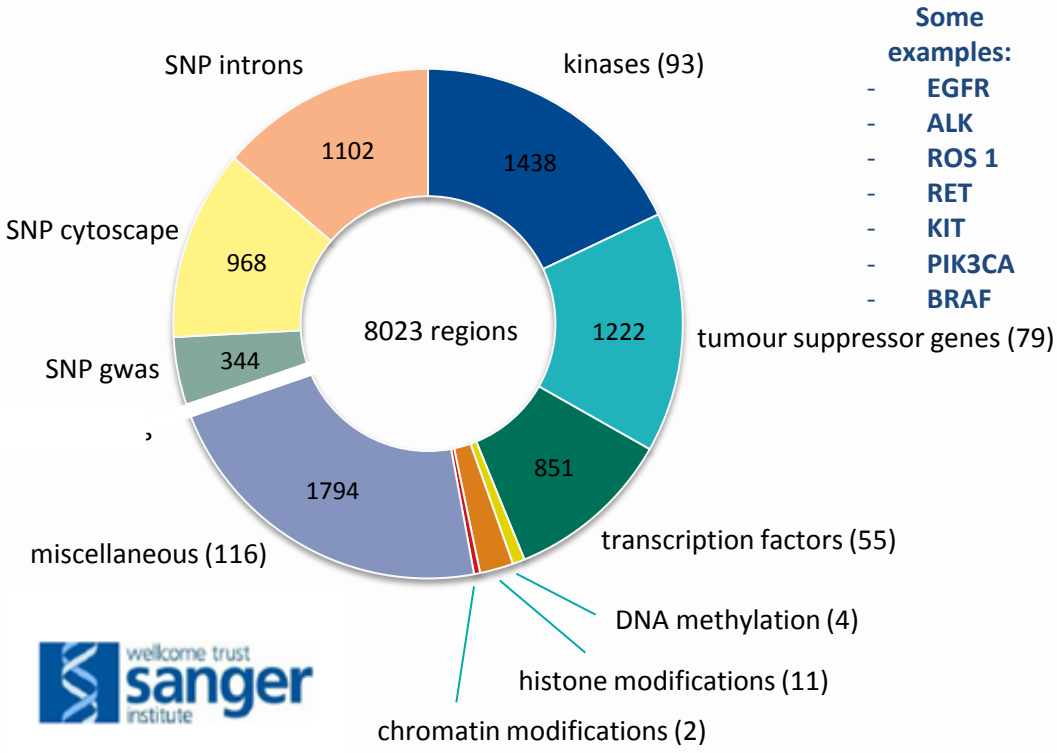
How to run trial in such small population?

EORTC European Organisation for Research and Treatment of Cancer

etop Information | Research

Screening Patients with **Thoracic Malignancy** for Efficient Clinical Trial Access

SPECTAlung



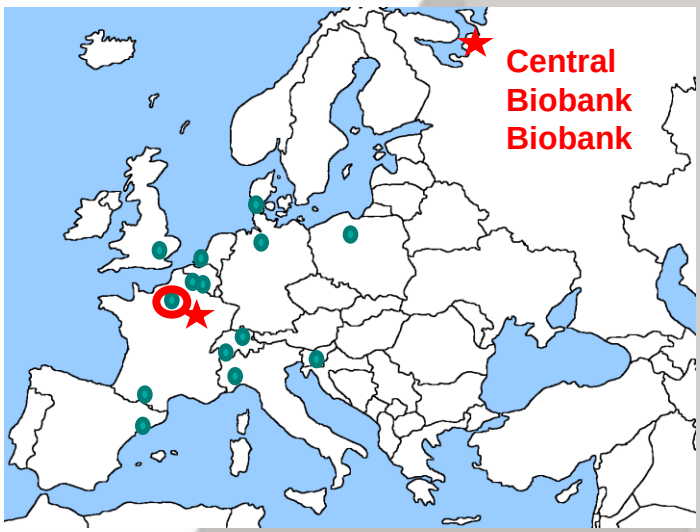
Some examples:

- **EGFR**
- **ALK**
- **ROS 1**
- **RET**
- **KIT**
- **PIK3CA**
- **BRAF**

tumour suppressor genes (79)

wellcome trust sanger institute

Online molecular portrait
Prospective clinical data
500-1000 tumors / yr



Thank you

- David Planchard, Gustave Roussy
- Monica Arnedos, Gustave Roussy
- Julien Mazieres, Toulouse
- EORTC, Jessica Mennis