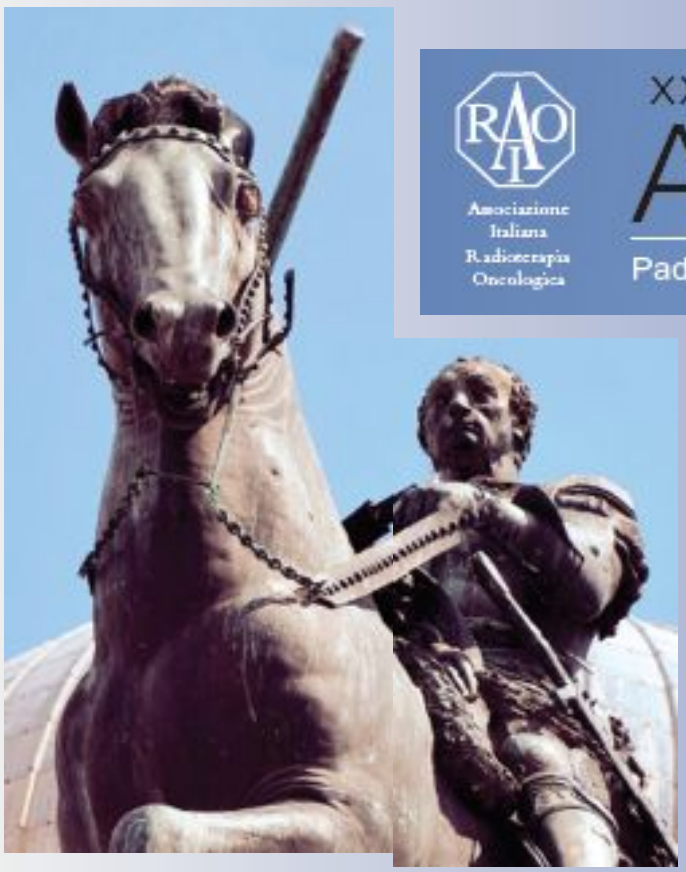


XXIV CONGRESSO NAZIONALE

AIRO2014

Padova, 8-11 novembre

Associazione Italiana Radioterapia Oncologica

MUTAZIONI SENSIBILIZZANTI, NUOVI TARGET E MODERNI TRATTAMENTI ONCOLOGICI

Sara Ramella

Radioterapia Oncologica

Università Campus Bio-Medico di Roma

Associazione Italiana Radioterapia Oncologica

UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

DICHIARAZIONE

Relatore: Sara Ramella

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

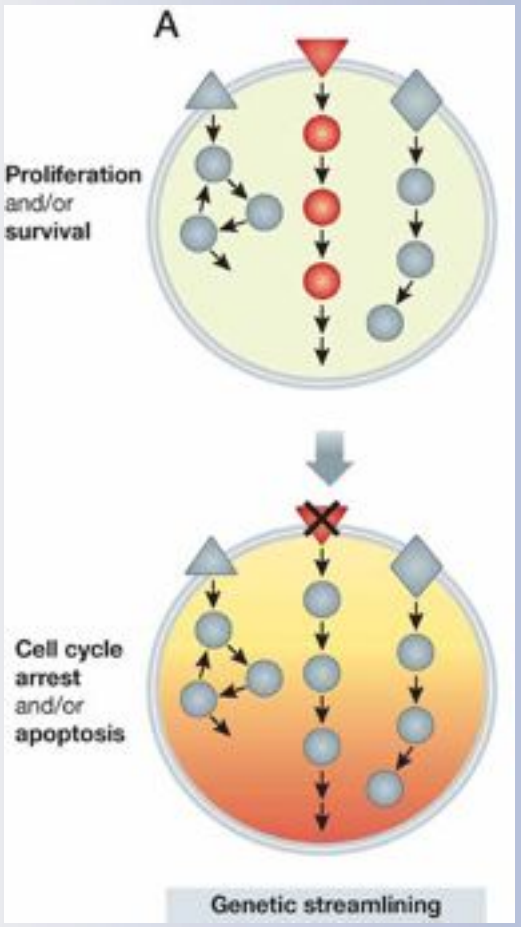
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

ONCOGENE ADDICTION

Some cancers that contain multiple genetic, epigenetic and chromosomal abnormalities ARE DEPENDENT TO ONE OR A FEW GENES for both maintenance of the malignant phenotype and cell survival

Weinstein Science, 2002

Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils

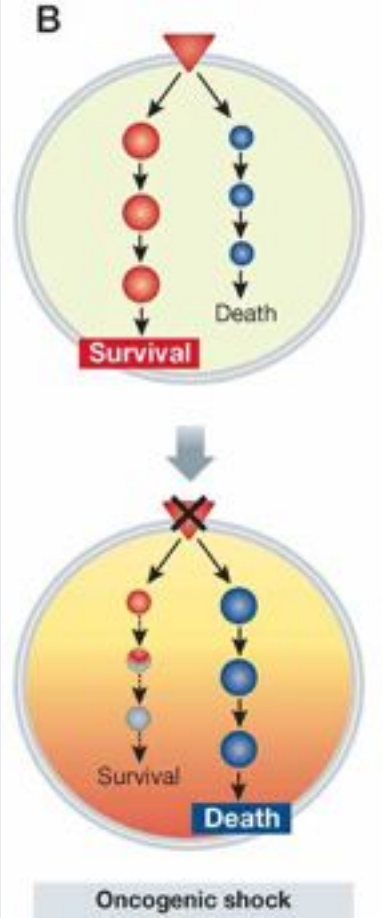


Models of oncogene addiction

A. The 'genetic streamlining' theory postulates that non-essential pathways are inactivated during tumour evolution, so that dominant, addictive pathways are not surrogated by compensatory signals. UPON ABROGATION OF DOMINANT SIGNALS, there is a COLLAPSE in cellular fitness and cells experience cell-cycle arrest or apoptosis

Torti & Trusolino, EMBO Mol Med 2011, 3:623-636

Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils

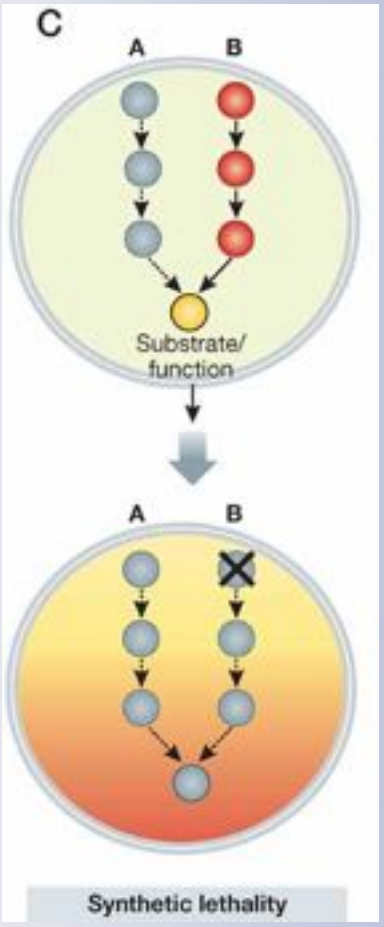


Models of oncogene addiction.

B. In the 'oncogenic shock' model, addictive oncoproteins (*e.g.* RTKs) TRIGGER AT THE SAME TIME PRO-SURVIVAL AND PRO-APOPTOTIC SIGNALS. Under normal conditions, the pro-survival outputs dominate over the pro-apoptotic ones, but following blockade of the addictive receptor, the decline subverts this balance in favour of death-inducing signals

Torti & Trusolino, EMBO Mol Med 2011, 3:623-636

Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils

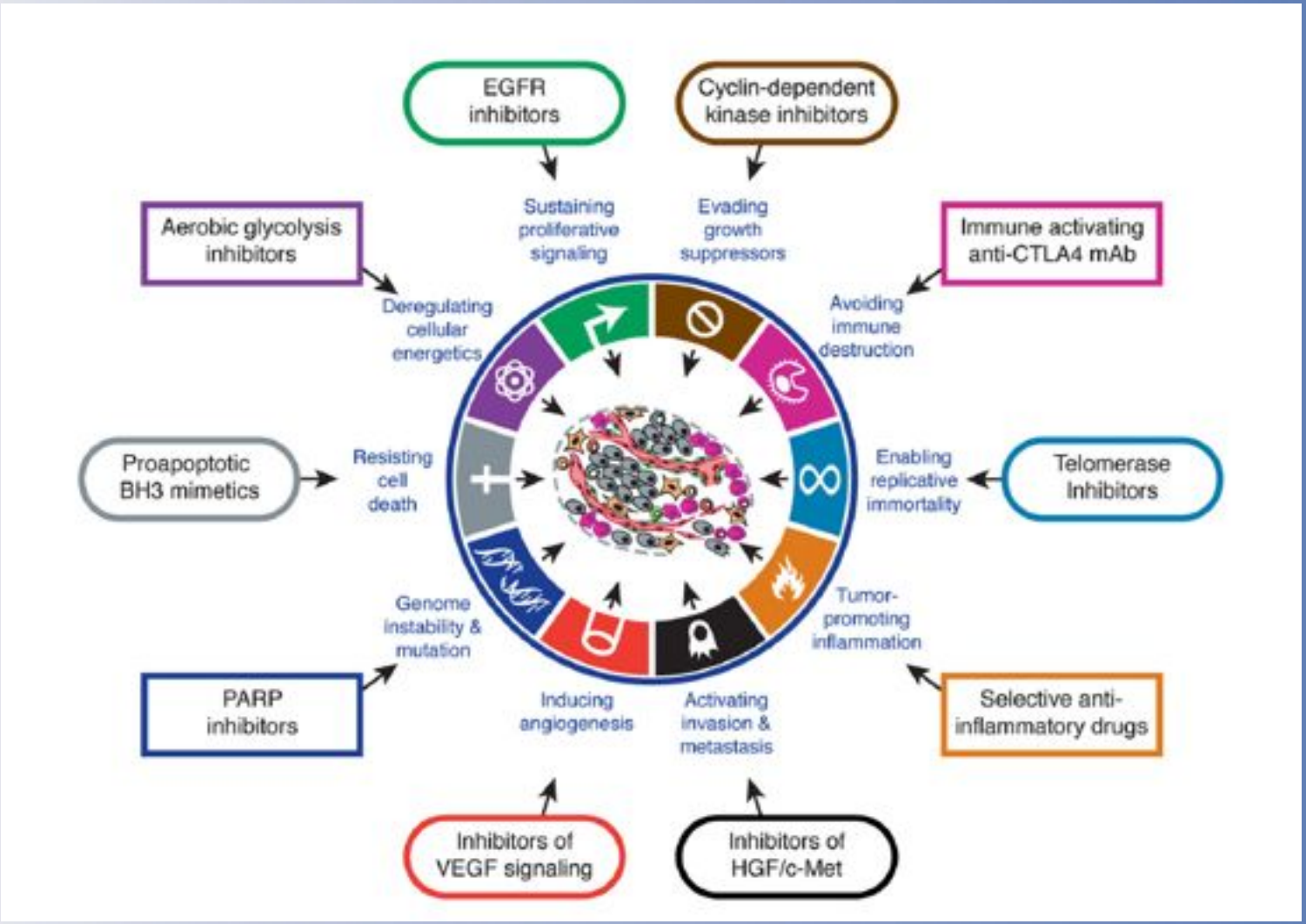


Models of oncogene addiction.

C. Two genes are considered to be in a synthetic lethal relationship when LOSS OF ONE OR THE OTHER IS STILL COMPATIBLE WITH SURVIVAL BUT LOSS OF BOTH IS FATAL. When the integrity of pathway B is disrupted (bottom), the common downstream biochemical function is lost and again cancer cells may experience cell cycle arrest or apoptosis.

Torti & Trusolino, EMBO Mol Med 2011, 3:623-636

Therapeutic targeting of the hallmarks of cancer



Hanahan D, Weinberg RA. Cell 2011;

ONCOGENE ADDICTION IN LUNG CANCER

Original Investigation

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

From 2009 through 2012, 14 sites led by Memorial Sloan Kattering: *1007 patients*

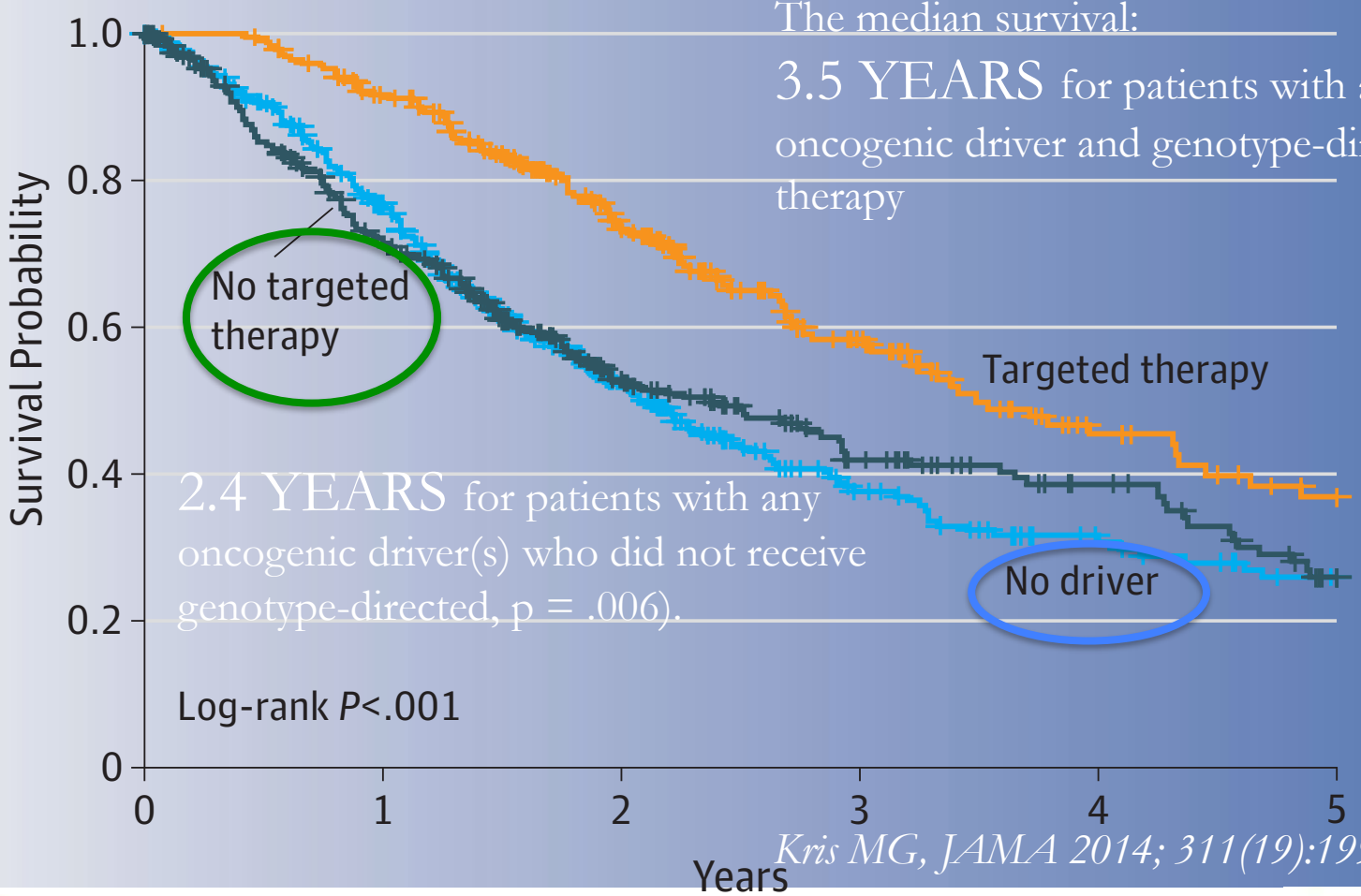
An ONCOGENIC DRIVER was found in **64%**

Results were used to select a TARGETED THERAPY or trial in 275 of 1007 patients (**28%**).

Kris MG, JAMA 2014; 311(19):1998-2006

Original Investigation

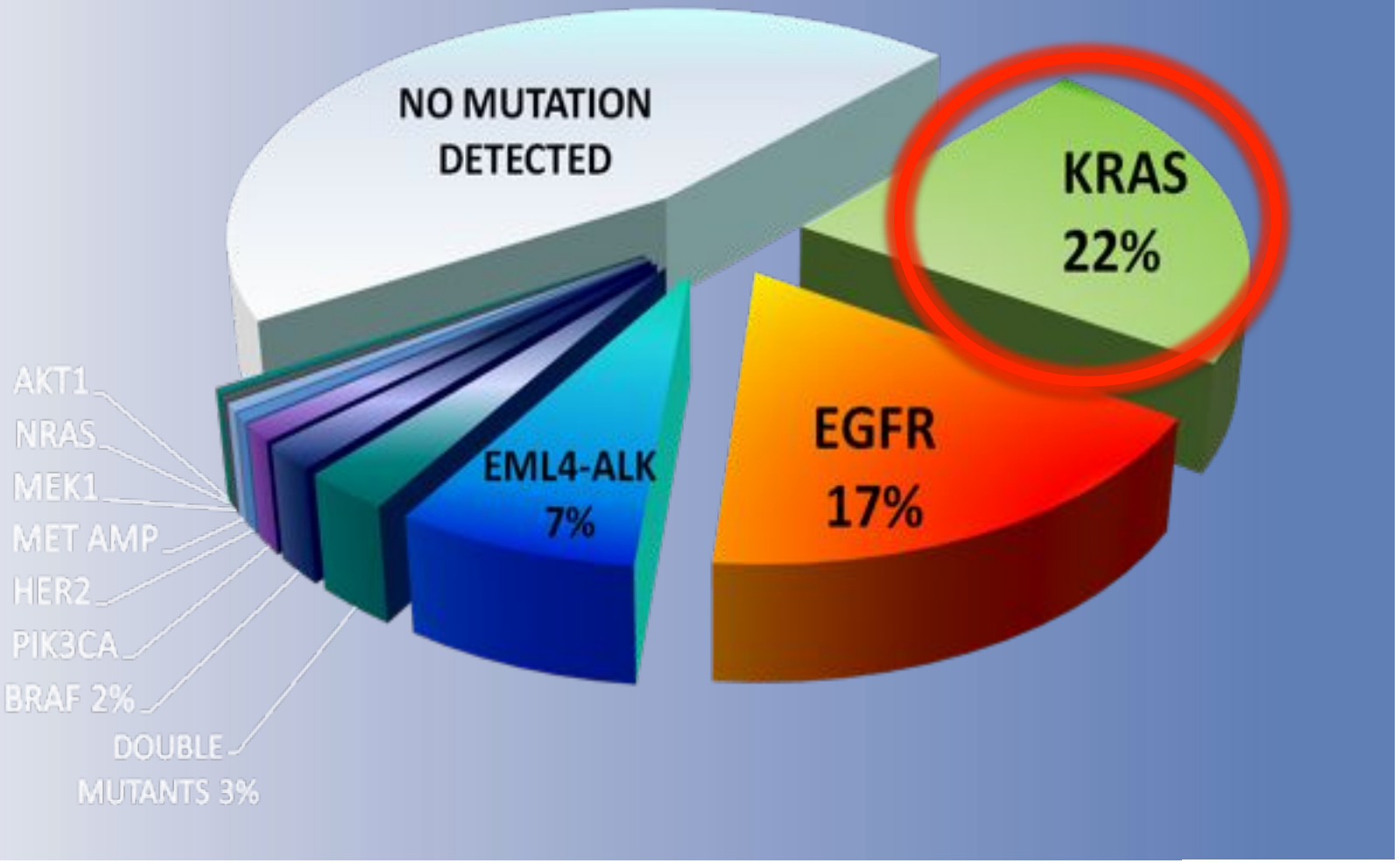
Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs



Kris MG, JAMA 2014; 311(19):1998-2006

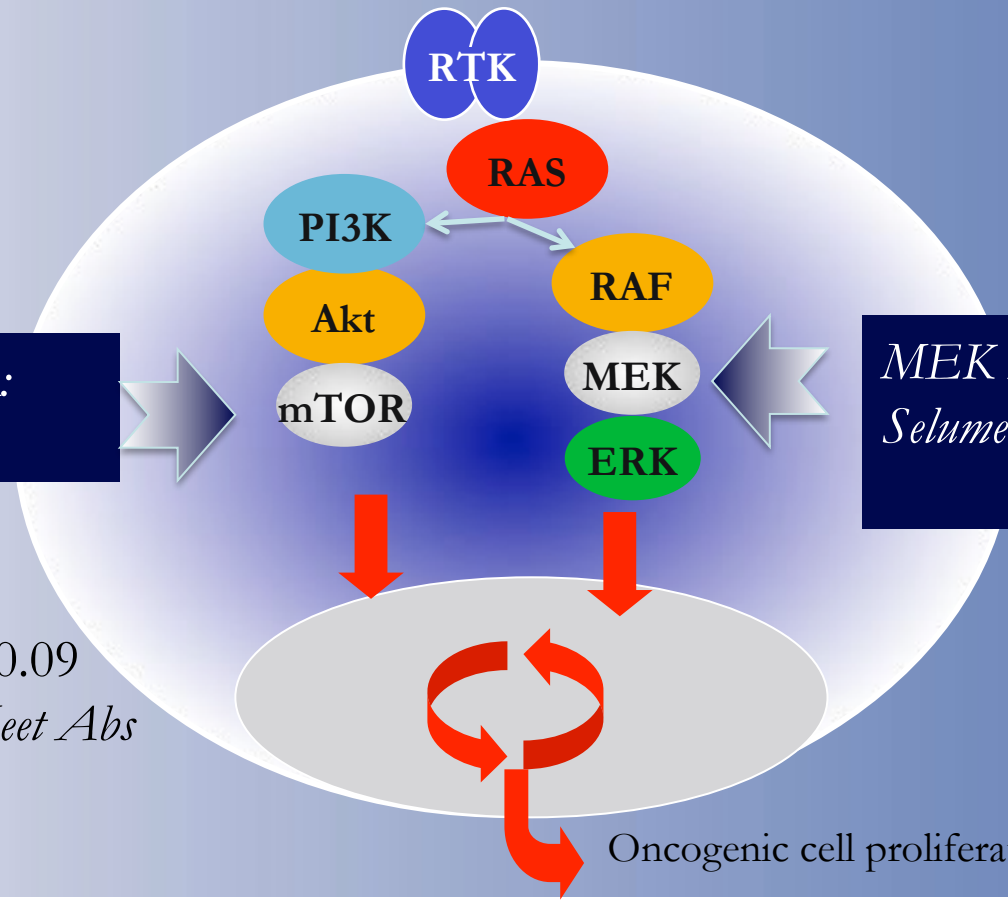
Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



KRAS mutation

KRAS mutation in NSCLC, despite being the most common, remain the most INTRIGUING AND ELUSIVE of therapeutics targets.

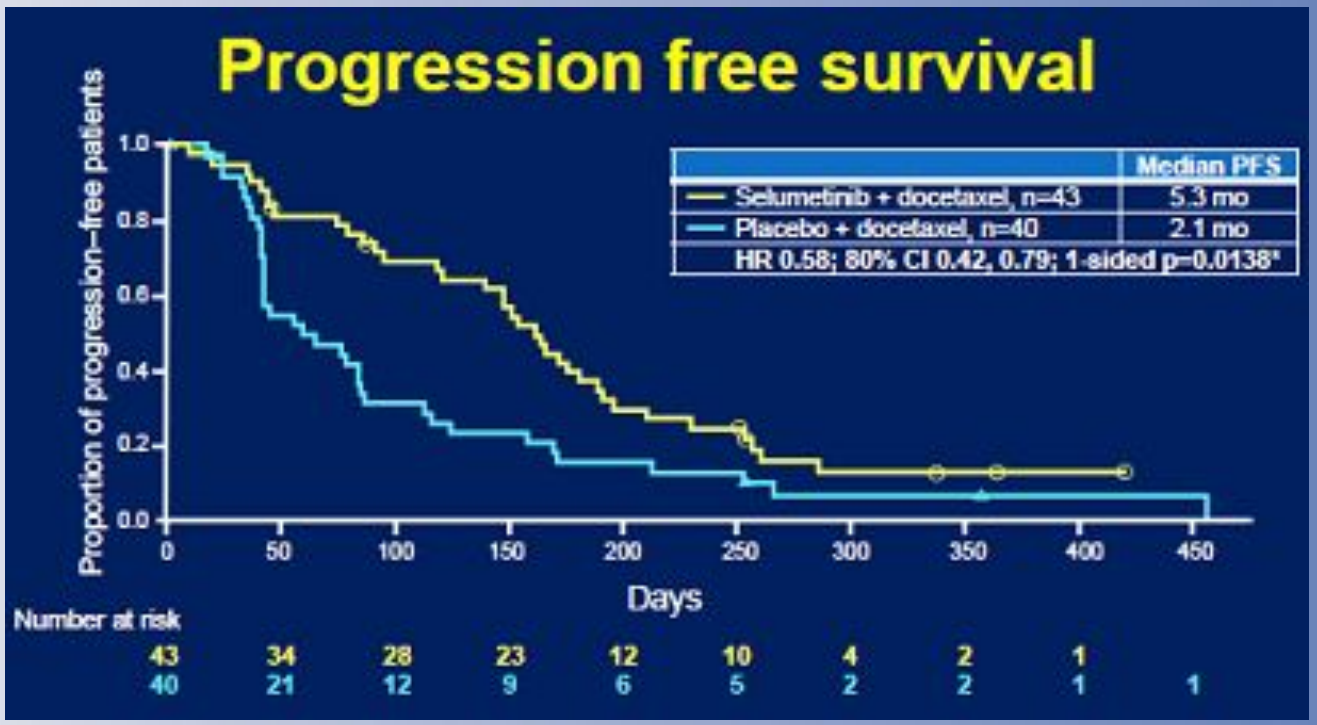


mTOR INHIBITOR:
Ridafolimus

MEK INHIBITOR:
Selumetinib, Trametinib

OS 18 vs 5m, p=0.09
Riely G, ASCO Meet Abs 2012, 30(15):7531

KRAS mutation: *Selumetinib in second line with docetaxel*

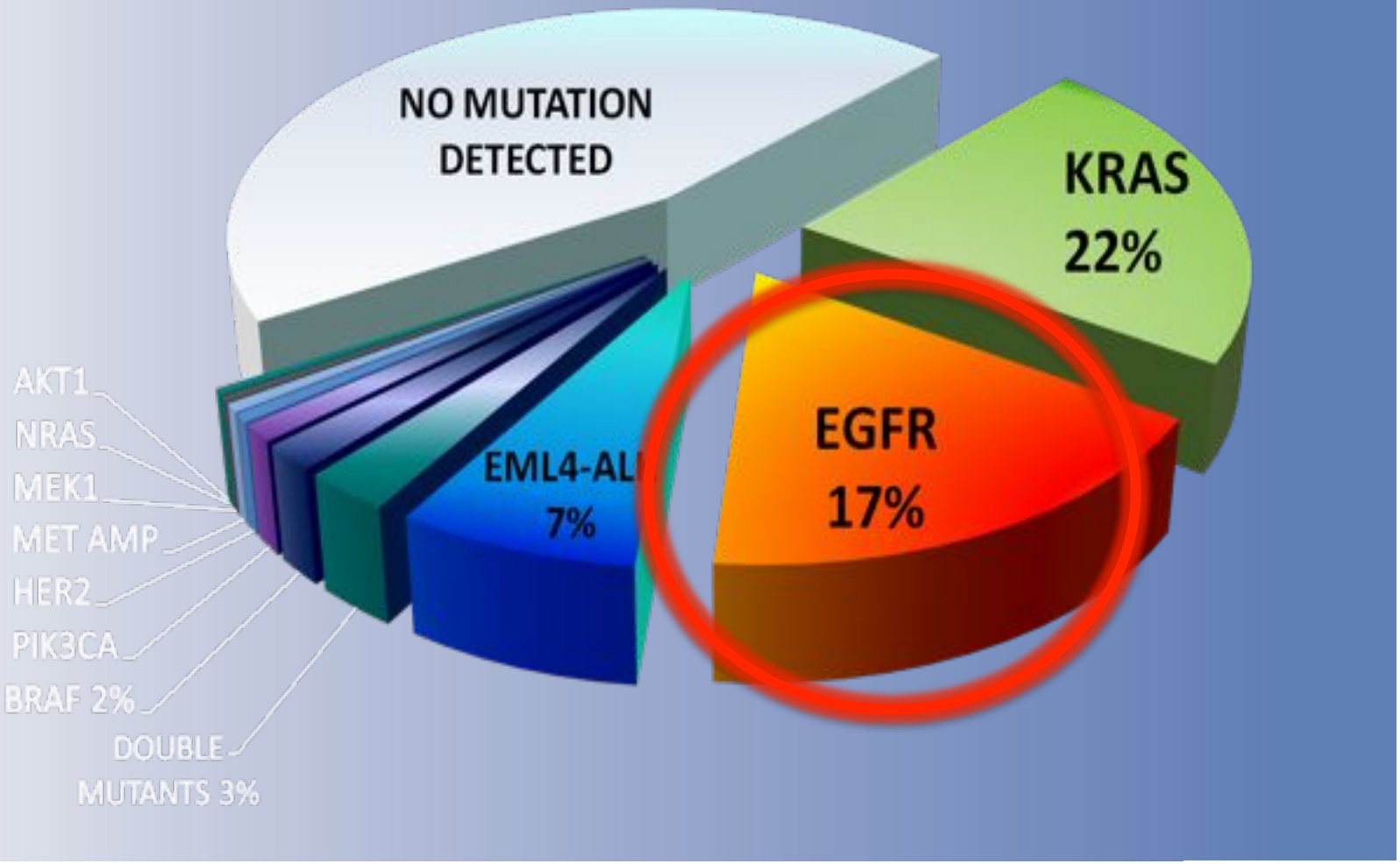


Actually ongoing SELECT-1, a randomized Phase III clinical programme for selumetinib, a selective MEK inhibitor, being investigated as second-line therapy in patients with advanced or metastatic non-small-cell lung cancer (NSCLC) whose tumours are KRAS mutation-positive.

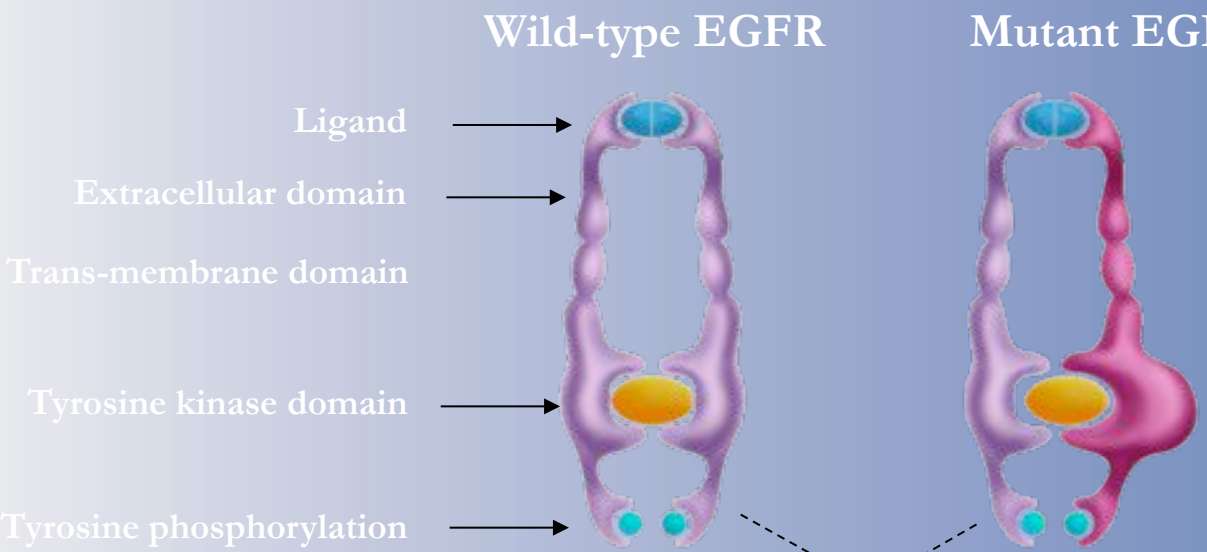
Pasi A. Janne J Clin Oncol 30, 2012 (suppl; abstr 7503)

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations

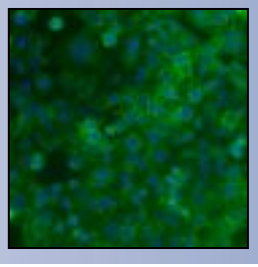


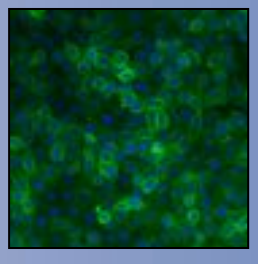
EGFR mutation causes conformational change and increased activation



Ras-Raf-MAPK
Proliferation

Pi3K-AKT
Survival



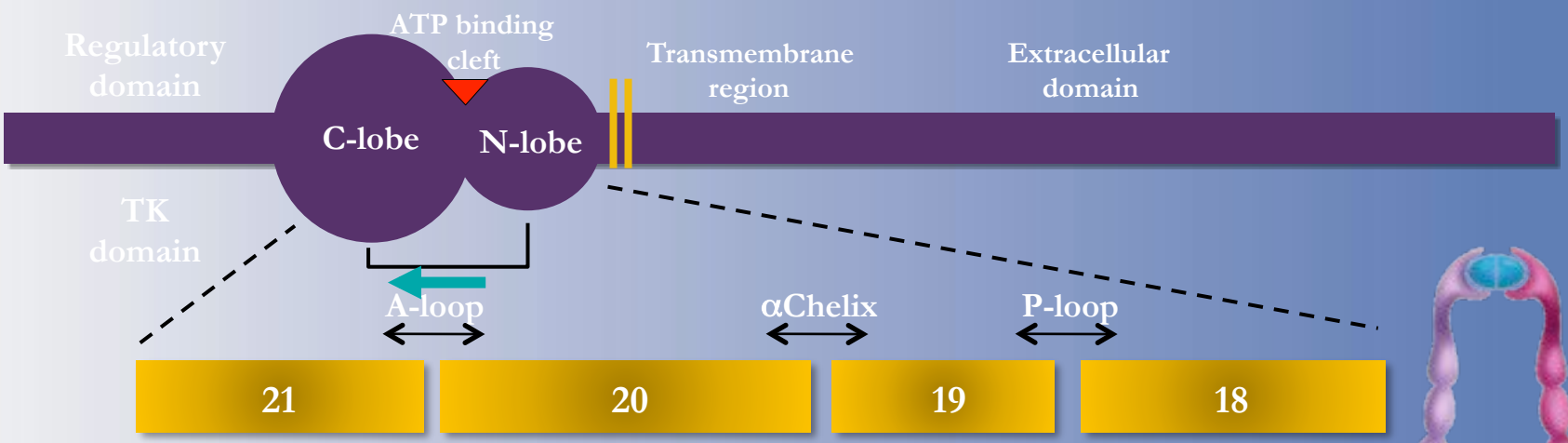


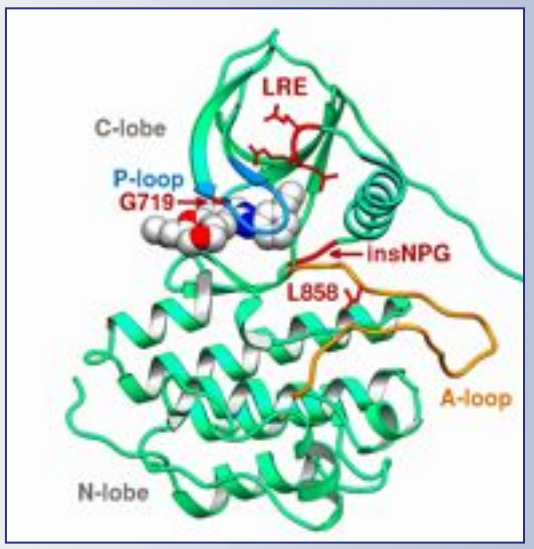
EGFR internalisation
Degradation / recycling

EGFR signals for longer at the cell membrane

Arteaga 2006; Gadzar et al 2004; Hendricks et al 2006; Sordella et al 2004

Common mutation sites in the EGFR gene





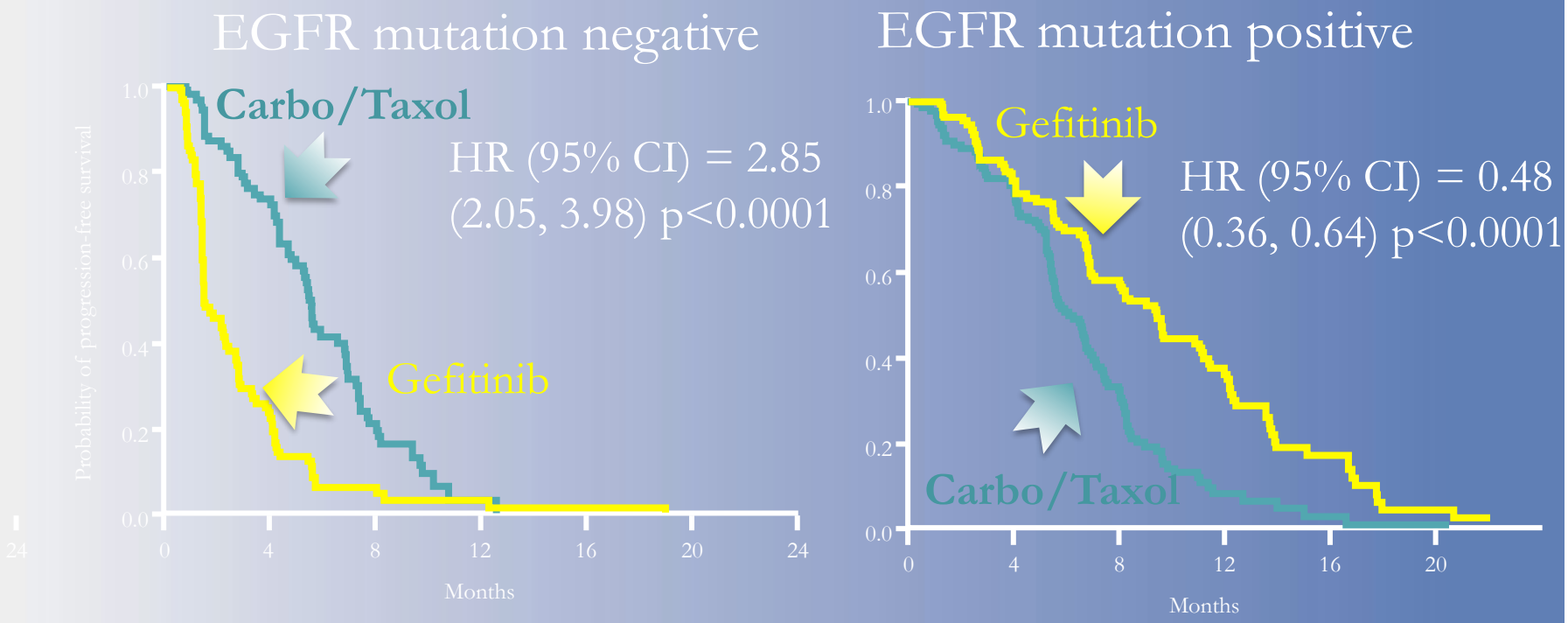
Exon 19
(in frame deletion)

Exon 21
(L858R point mutation)

TKI:
Gefinitib
Erlotinib
Afatinib

Lynch TJ et al. NEJM 2004; 350: 2129-39.
Paez JG et al. Science 2004; 304: 1497-500.

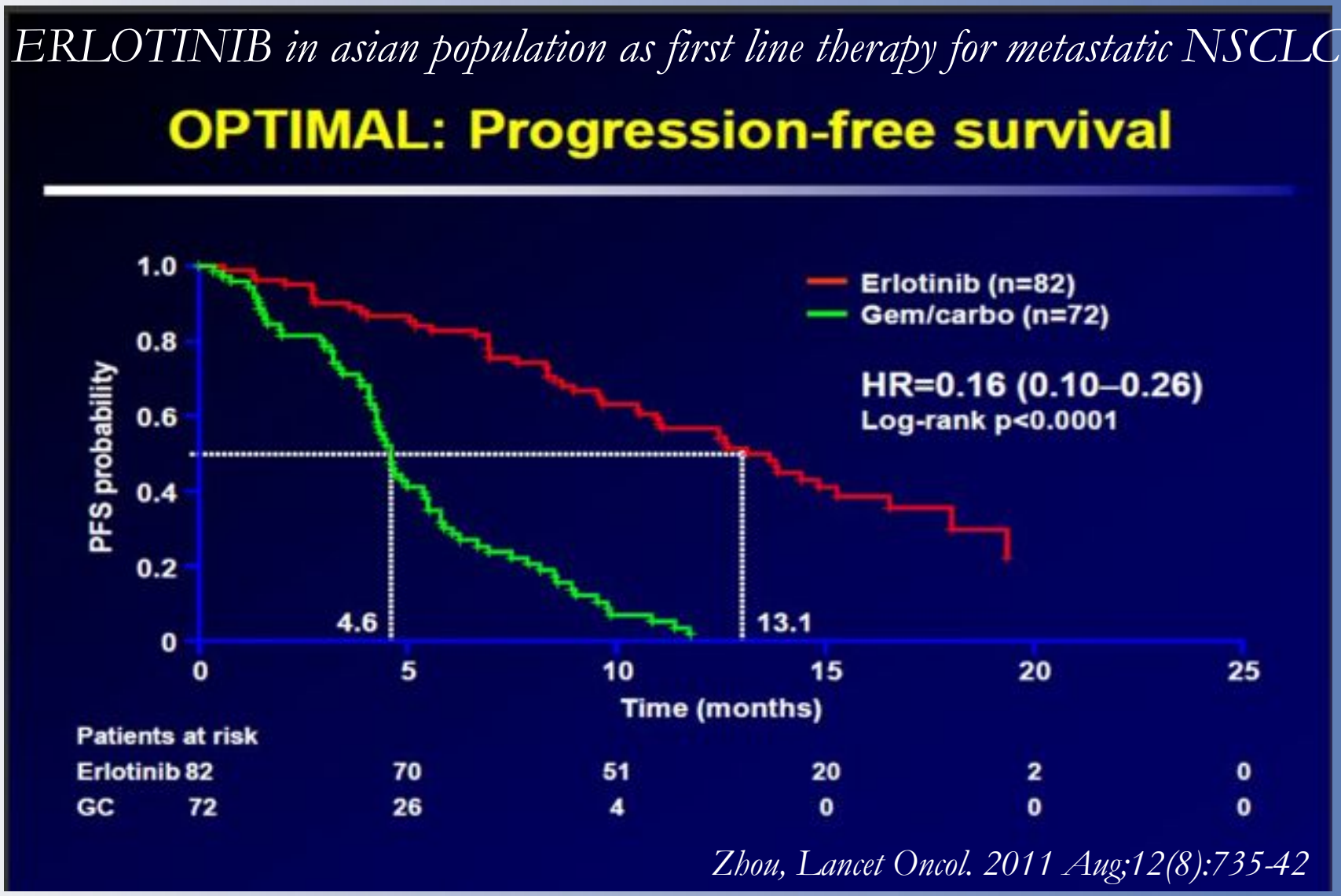
IPASS (*GEFITINIB*): Progression-Free Survival in EGFR Mutated metastatic NSCLC



Treatment by subgroup interaction test, p<0.0001

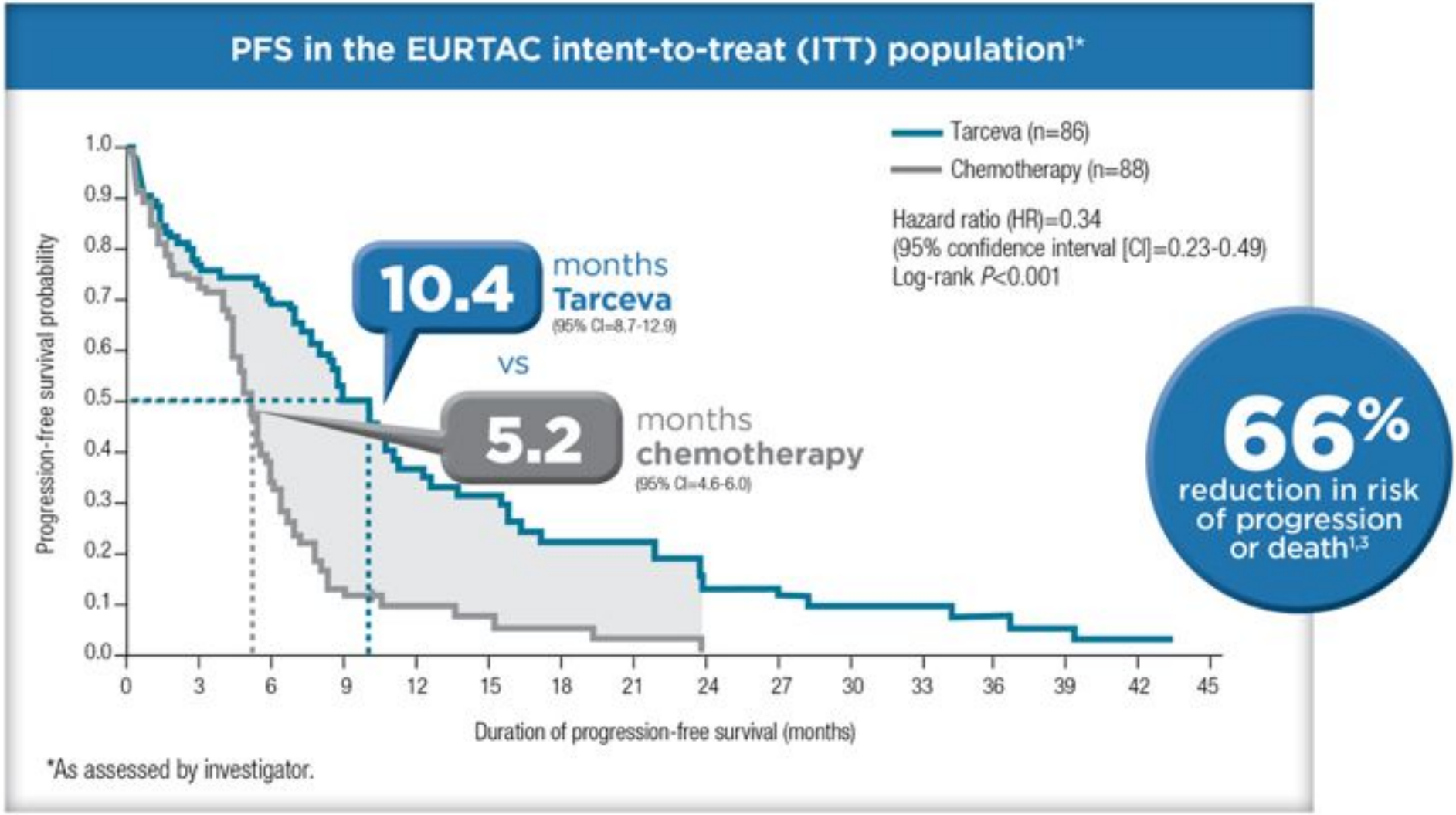
Mok. ESMO. 2008 (abstr LBA2).

ERLOTINIB in asian population as first line therapy for metastatic NSCLC



Zhou, Lancet Oncol. 2011 Aug;12(8):735-42

ERLOTINIB *in caucasian population for metastatic NSCLC*

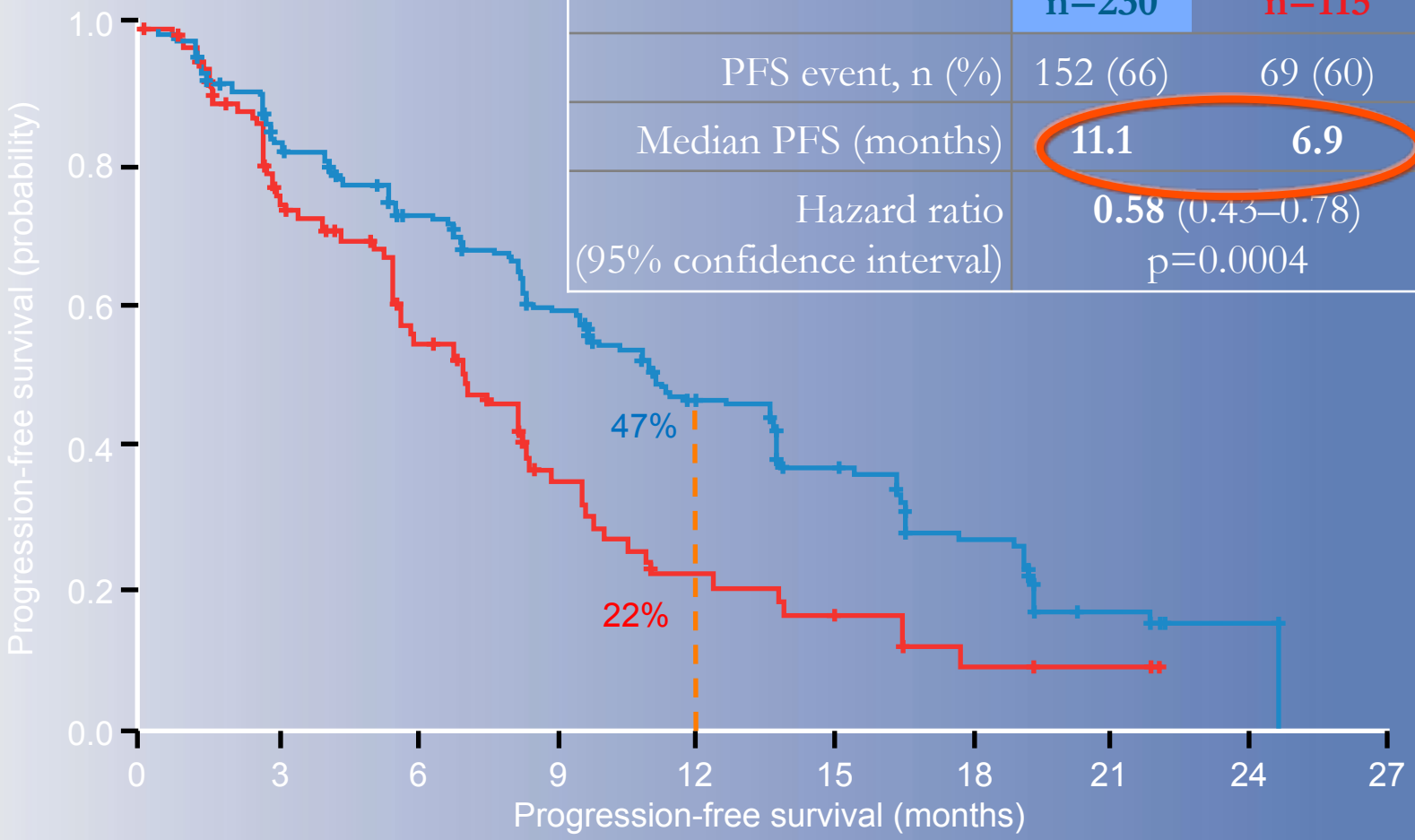


Rosell, Lancet Oncol. 2012 Mar;13(3):239-46.

AFATINIB in metastatic NSCLC in EGFR mutated patients

LUNG LUX 3 : PFS

	Afatinib n=230	Cis/pem n=115
PFS event, n (%)	152 (66)	69 (60)
Median PFS (months)	**11.1**	**6.9**
Hazard ratio (95% confidence interval)	**0.58** (0.43–0.78) p=0.0004	



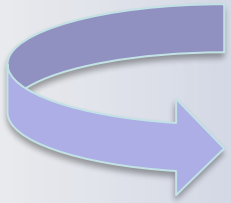
Sequist, et al. JCO 2013

TOXICITY: Randomized studies of EGFR TKI vs CT in first line therapy

Trial	EGFR TKI	**Diarrhea All grades (severe)**	**Skin All grades (severe)**
IPASS	Gefitinib	47% (4%)	66% (3%)
NEJSG 002	Gefitinib	34% (1%)	71% (5%)
WJTOG 3405	Gefitinib	54% (1%)	85% (2%)
First-SIGNAL	Gefitinib	50% (3%)	72% (29%)
OPTIMAL	Erlotinib	25% (1%)	73% (2%)
EURTAC	Erlotinib	57% (5%)	80% (13%)
TORCH	Erlotinib	38% (5%)	67% (11%)
LUX-Lung 3	Afatinib	95% (14%)	89% (16%)

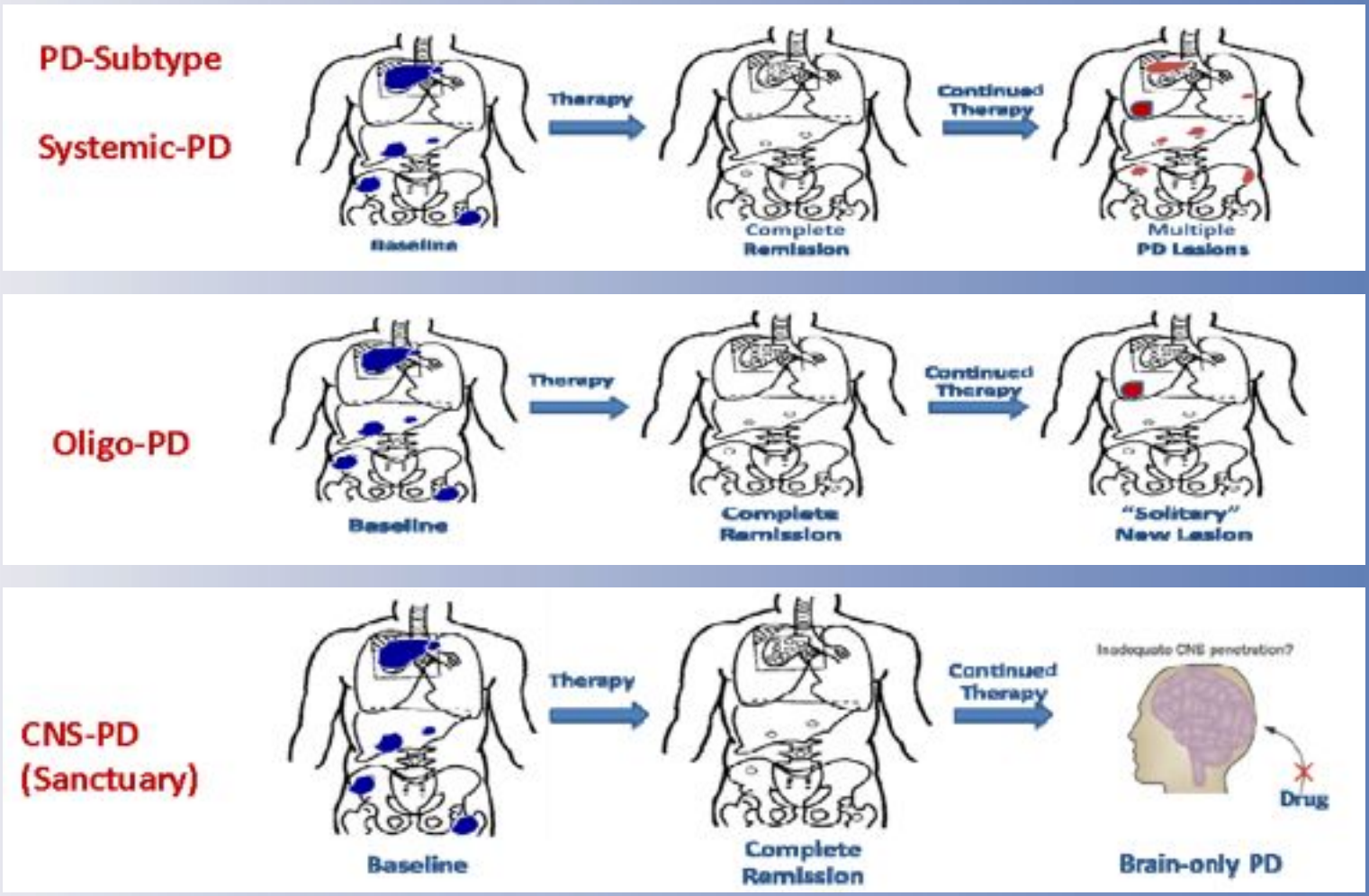
Randomized studies of EGFR TKI vs CT in first line therapy

Author	Study	N (EGFR m +)	RR (TKI vs CT)	PFS (HR, 95%CI)
Mok et al	IPASS CT vs Gefitinib	261	71.2% vs 47.3%	9.5 vs 6.3 months **HR 0.48** (0.36-0.64)
Kobayashi et al	NEJGSG002 CT vs Gefitinib	177	74.5% vs 29%	10.4 vs 5.5 months **HR 0.36** (0.25-0.51)
Zhou et al	OPTIMAL CG vs Erlotinib	154	83% vs 36%	13.1 vs 4.6 months **HR 0.16** (0.10-0.26)
Rosell et al	EURTAC P-X vs Erlotinib	174	58.1% vs 14.9%	9.7 vs 5.2 months **HR 0.37** (0.25-0.54)
Yang et al	LUX-LUNG 3 PA vs Afatinib	345	56.1% vs 22.6 %	11.1 vs 6.9 months **HR 0.58**



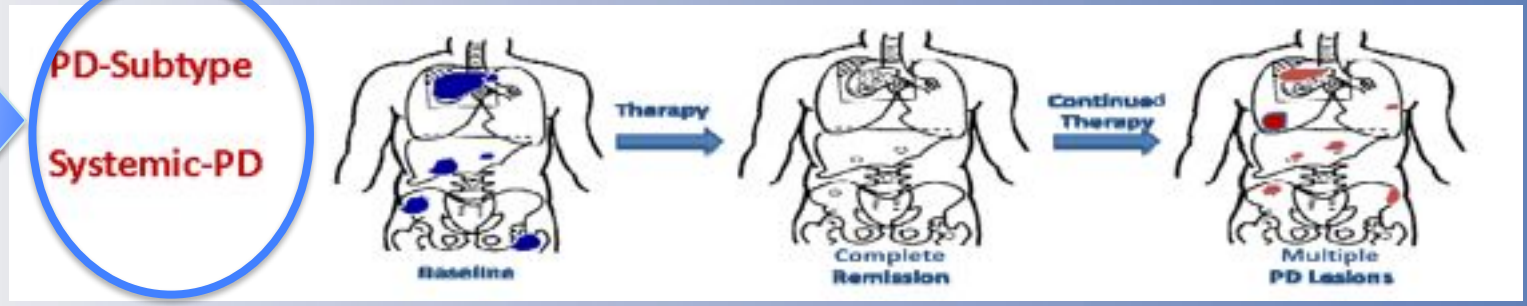
Existing Target Therapies are NOT able to eradicate the disease

NOT all patients with ACQUIRED RESISTANCE to target TKI are created equal: 3 subtypes



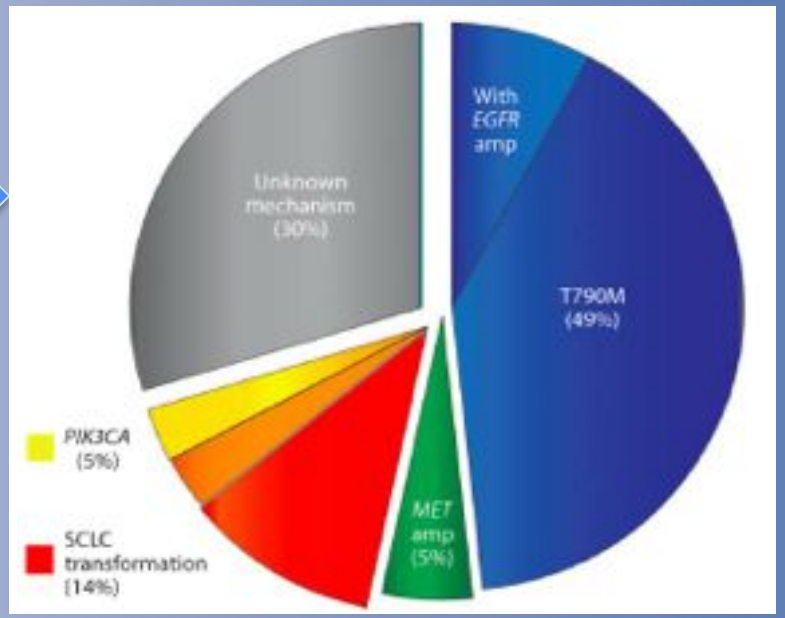
Gandara D, ASCO Educational 2013

NOT all patients with ACQUIRED RESISTANCE to target TKI are created equal: 3 subtypes



Chemotherapy → Re-challenge with TKI

New target agents →



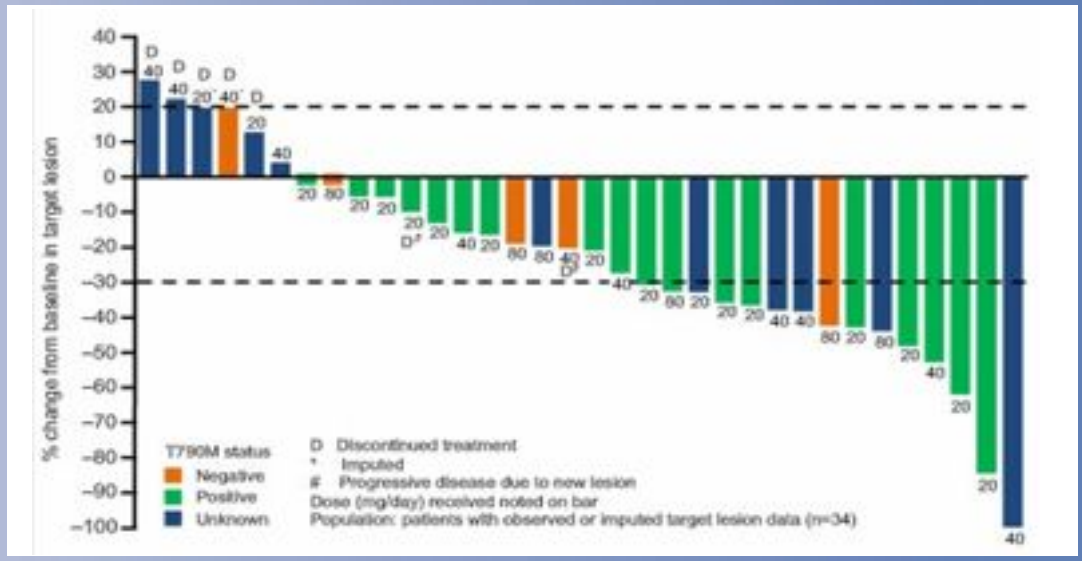
Sequist L, Science Transl Med 2011

Gandara D, ASCO Educational 2013

T790M (RESISTANCE MUTATION)

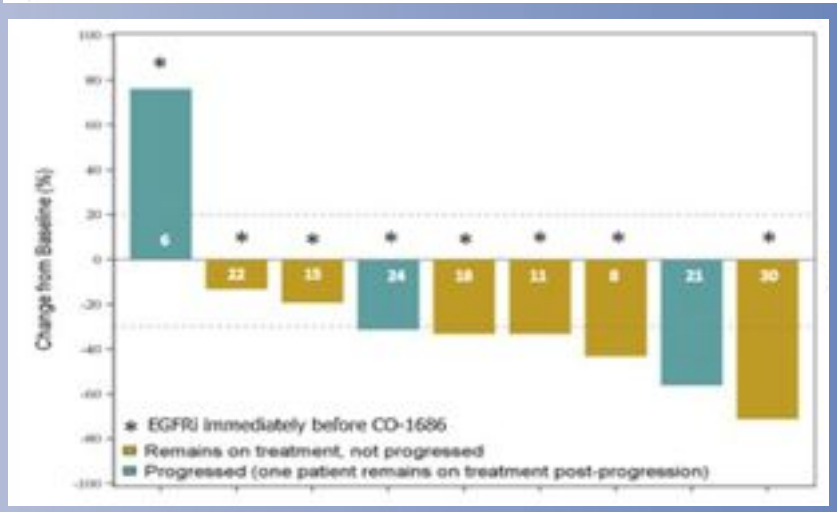
AZD9291

Ranson WCLC 2013

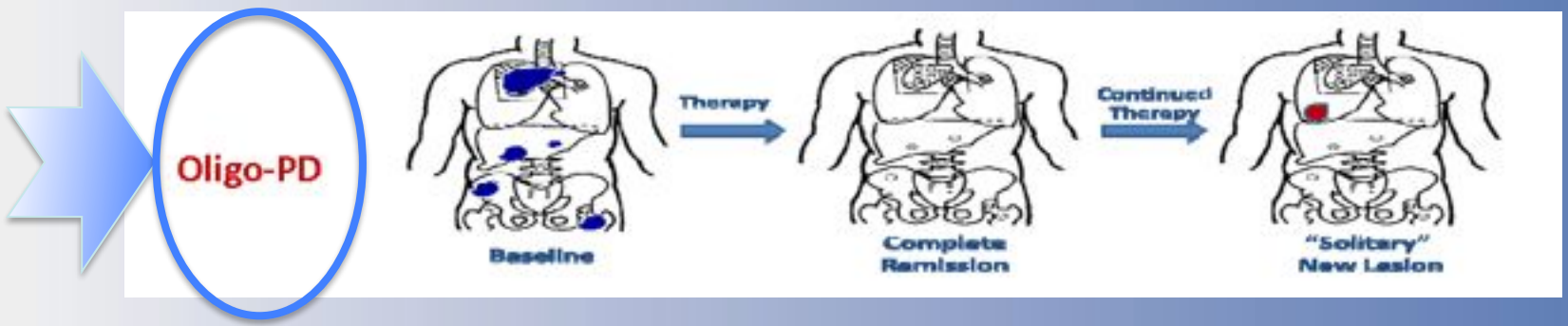


CO1686

Soria JC, WCLC 2013



NOT all patients with acquired resistance to target TKI are created equal: 3 subtypes



Gandara D, ASCO Educational 2013

LOCAL ABLATIVE THERAPY of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene addicted NSCLC

Site of first progression	Number of patients	PFS1 (months) (CI)	PFS2 (months)(CI)	Site of 2nd progression	
All patients	25	9.8 8.8 – 13.8	6.2 3.7 – 8.0	6 (24%)	no prog
				7 (28%)	CNS
				12 (48%)	eCNS

>6 months of additional disease control.

Weickhardt J Thorac Oncol. 2012

FEASIBILITY THORACIC RT and TKIs

NON SELECTED POPULATION:

Ready N,. *J Clin Oncol* 2006;24:Abstract 7024	63 patients
Stinchcombe TE. *J Thorac Oncol* 2008;3:250 –257	23 patients
Center A, J *Thorac Oncol.* 2010;5: 69–74	16 patients
Choong NW,. J Thorac Oncol 2008;3:1003–1011	34 patients
Ramella, Biomed Res Internat 2013	60 patients
Komaki, IASLC 2013, ASCO 2014	48 patients

NOT INCREASED TOXICITY

TARGET THERAPIES AND RADIOTHERAPY
The use of TKI and RT-CT

POOR OS

Table 2. Selected Phase I/II Studies of Concurrent EGFR-TKI and Chemoradiotherapy for NSCLC

Study	No. of Patients	Concurrent	*EGFR* Inhibition	RT (Gy)	Ind/Consol	Adverse Events (%)		Response Rate (%)	OS			
						Esophagitis Grades 3-4	Neutropenia Grades 3-4		Median (months)	1-Year (%)	2-Year (%)	3-Year (%)
University of Chicago[44]	16	Cisplatin, etopside	Erlotinib MTD: 150 mg/d	66	Consol: docetaxel	19	50	65	11			20
	15	Carboplatin, paclitaxel	Erlotinib MTD: 150 mg/d	66	Ind: carboplatin, paclitaxel	40	20	59	15			16
CALGB 30106 (good risk)[43]	39	Carboplatin, paclitaxel	Gefitinib 250 mg/d	66	Consol: carboplatin, paclitaxel	31	38	81	13	53		
Zurich[45]	14	Cisplatin (optional)	Gefitinib 250 mg/d	66	Ind: cisplatin based	22	11	21	12.5		NS	
University of North Carolina[47]	23	Carboplatin, paclitaxel	Gefitinib 250 mg/d	74	Ind: carboplatin, paclitaxel, irinotecan	19.5	19	NS	16		20	

	N° pts	*Concurrent*	*Tox G3-4*	*Median SVV*	*Notes*
MD Anderson (Komaki 2012)	48	Carbo-Taxol	NS	26 months	Response Rate 80%
Campus Bio-Medico 2012 (Ramella 2013)	60	Gem/Pem weekly	2-8%	23.3 months	SCC: Gem+ Erl NSCC:Pem+Erl

Biologically targeted therapies plus chemotherapy plus radiotherapy in stage III non-small-cell lung cancer: a case of the Icarus syndrome?

…we probably tried to get closer to the sun too quickly….

- ✓ Clear preclinical rationale
- ✓ Proper bio-marker selection
- ✓ Methodical addition of one new concept at a time

Raben and Bunn, JCO 2012; 32:3909-3912

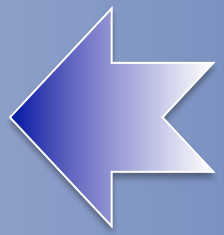
TARGET THERAPIES AND RADIOTHERAPY

CLINICAL EXPERIENCES

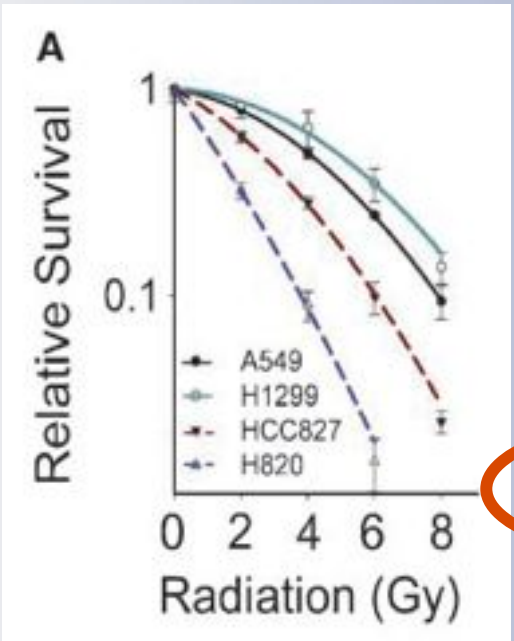
The use of TKI and RT-CT

UNSELECTED POPULATION

EGFR-MUTANT PATIENTS

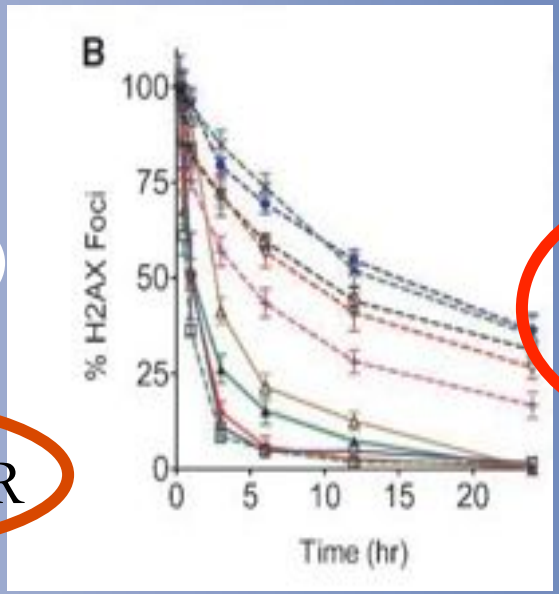


Non–Small Cell Lung Cancers with Kinase Domain Mutations in the Epidermal Growth Factor Receptor Are Sensitive to Ionizing Radiation



EGFR- WT

Mutated EGFR



Mutated EGFR

WT

HIGHER RADIOSENSITIVITY OF MUTATED CELLS

Significantly lower rate of DSB resolution

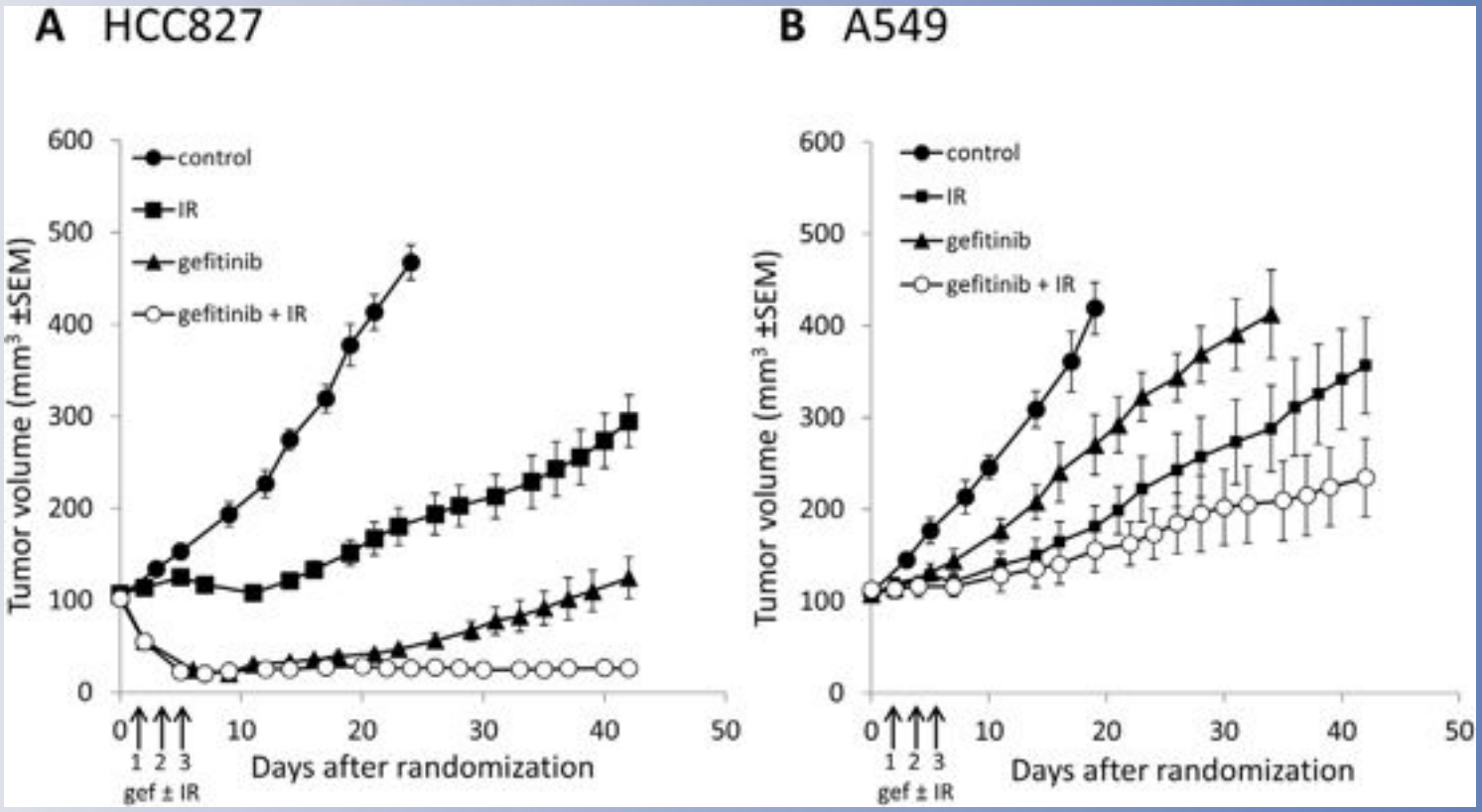
Das, Cancer Res. 2006 Oct 1;66(19):9601-8.

Biology Contribution

Short-Course Treatment With Gefitinib Enhances Curative Potential of Radiation Therapy in a Mouse Model of Human Non-Small Cell Lung Cancer

International Journal of Radiation Oncology biology • physics

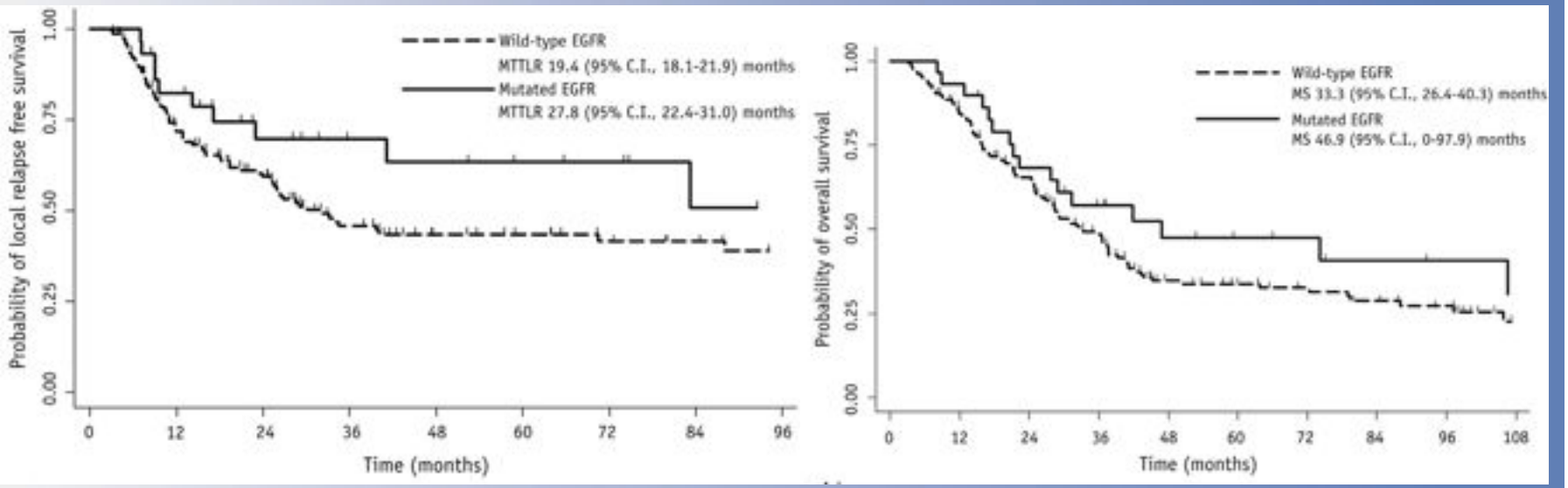
NSCLC cell lines with activating EGFR mutations (PC9 or HCC827)



Bokobza Int J Radiat Biol Oncol Phys 2014

Epidermal Growth Factor Receptor MUTATION Is Associated WITH LONGER LOCAL CONTROL After Definitive Chemo-radiotherapy in Patients With Stage III Non-squamous NSCLC

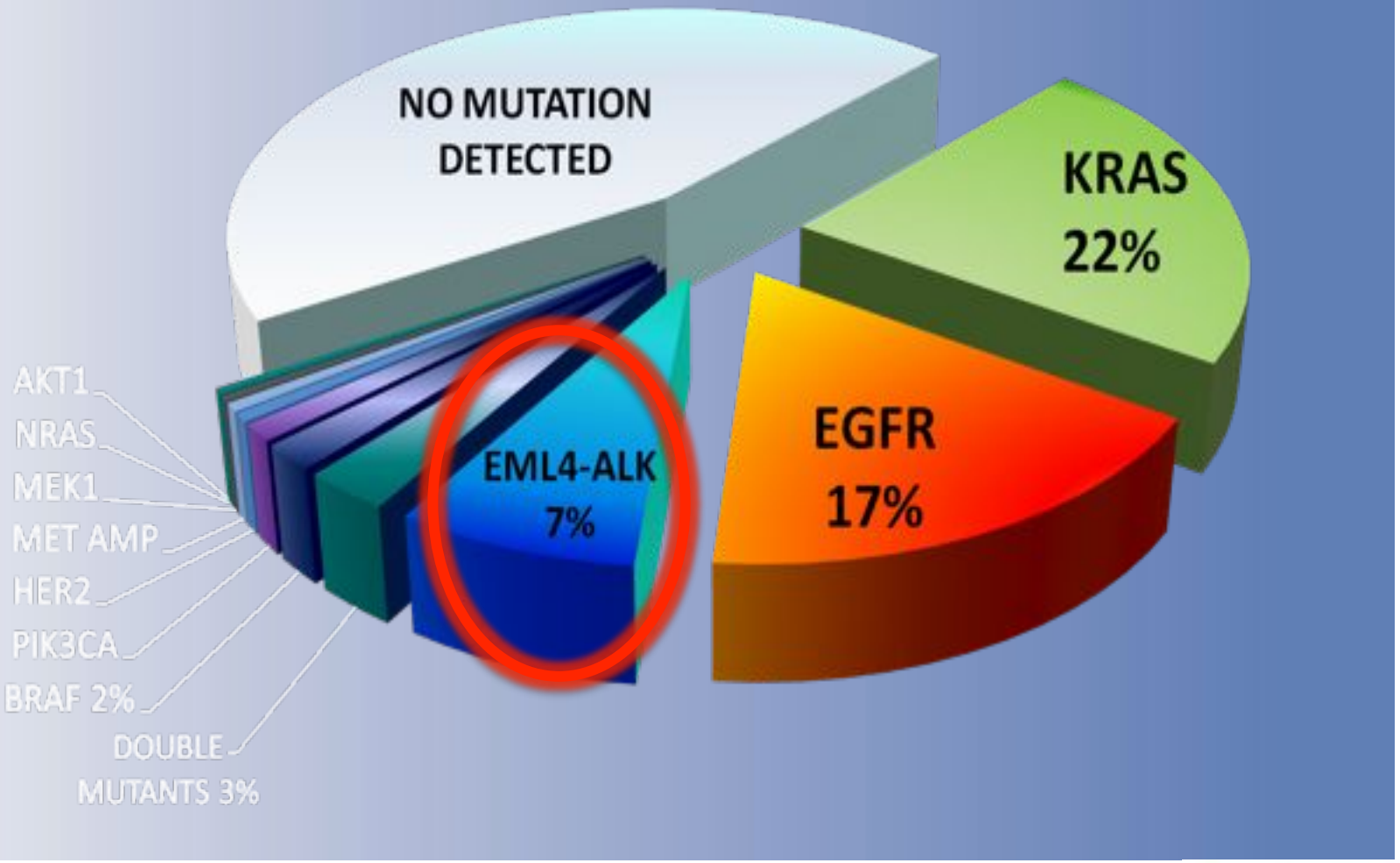
198 patients with known mutational status



Yagishita, Int J Radiat Oncol Biol Phys 2014

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations

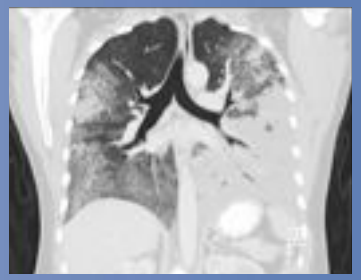


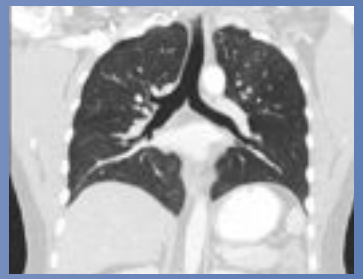
CRIZOTINIB IN ALK mutated patients
Efficacy data based on the Objective Response Rate

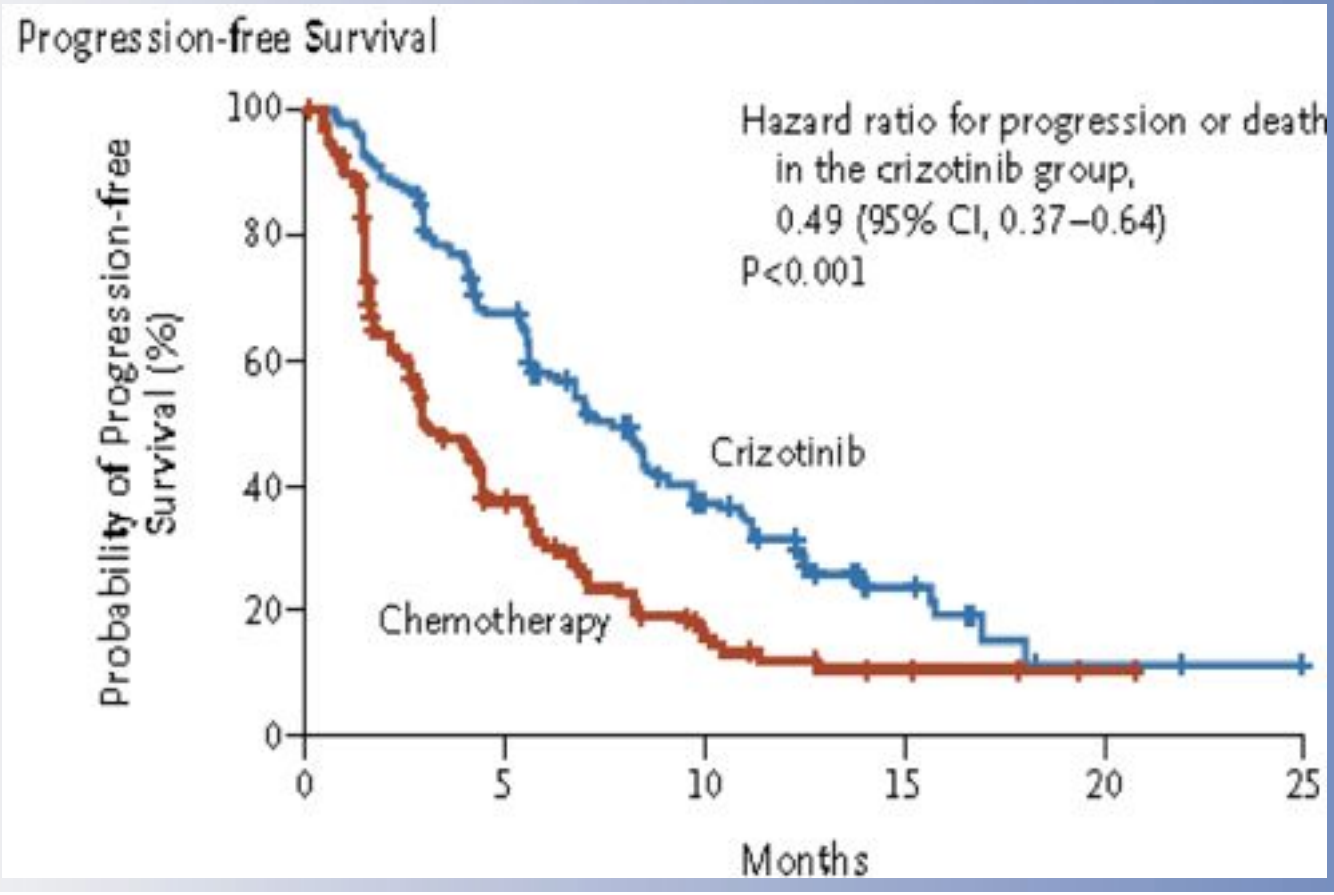
	PROFILE 1001[1] N=116	PROFILE 1005[2] N=133	PROFILE 1005[3] N=261
Best overall response			
Complete response	2 (1.5%)	1	4 (1.5%)
Partial response	69 (59.5%)	67	151 (58.3%)
Stable disease	31	45	69 (26.6%)
Progressive disease	6	10	19 (7.3%)
Other[†]	8	10	
Objective response (CR+PR) rate (95% CI)	61.2% (52%, 70%)	51% (42%, 60%)	59.8% (53.6%, 65.9%)
Duration of response[3]	48.1 weeks (median)	41.9 weeks (median)	45.6 (35.3, 53.6)
Duration of treatment, median	32 weeks	22 weeks	n/a
Median PFS	10.0 months (95% CI: 8.2, 14.7)	Not mature	8.1 months

Camidgeet al, ASCO 2011 Abs#25

CRIZOTINIB in ALK+
Profile 1007: study design and PFS (EMA approval in second-line)

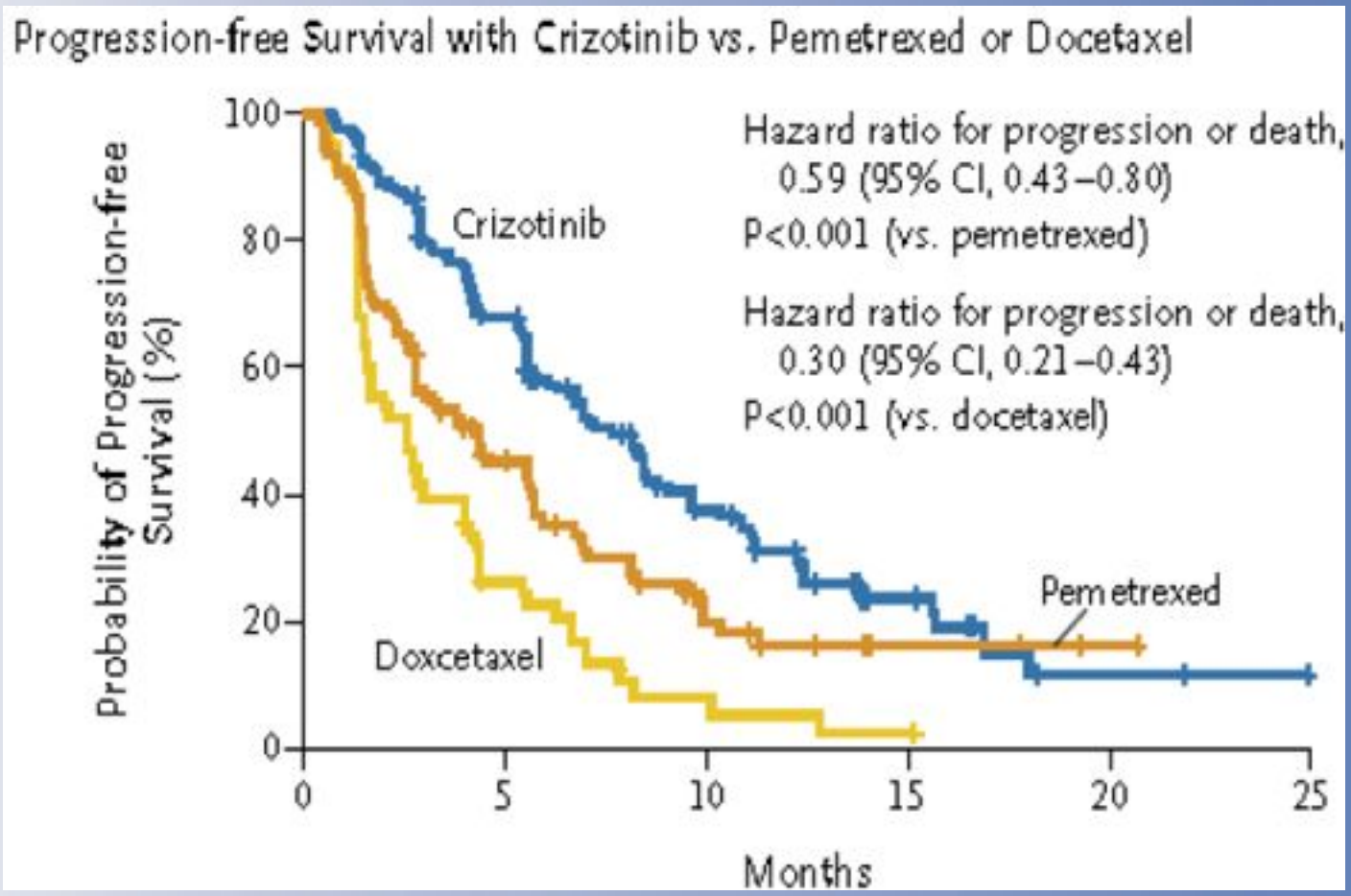






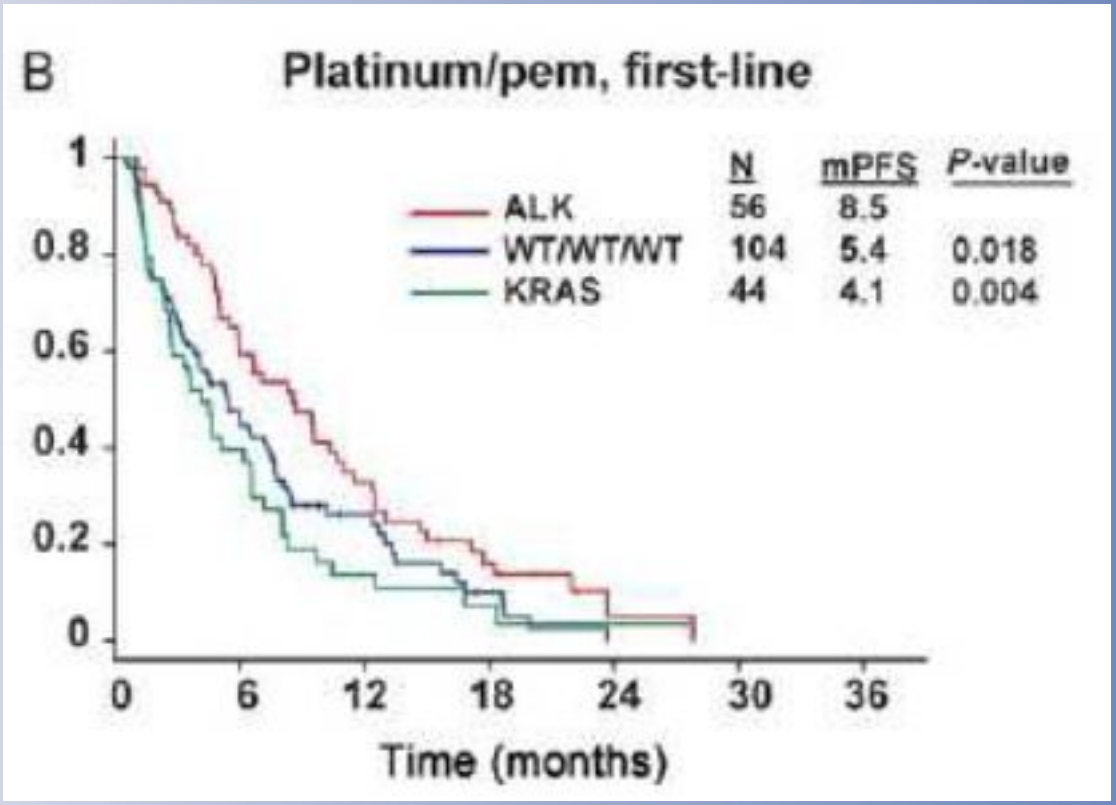
Shaw AT, NEJM 2013

Profile 1007: study design and PFS (EMA approval in second-line) PFS of Crizotinib vs Pemetrexed or Docetaxel



Shaw AT, NEJM 2013

Pemetrexed-based CT in patients with advanced ALK positive NSCLC



Shaw, Scagliotti, Ann Oncol 2013

Acquired Resistance in ALK+ NSCLC

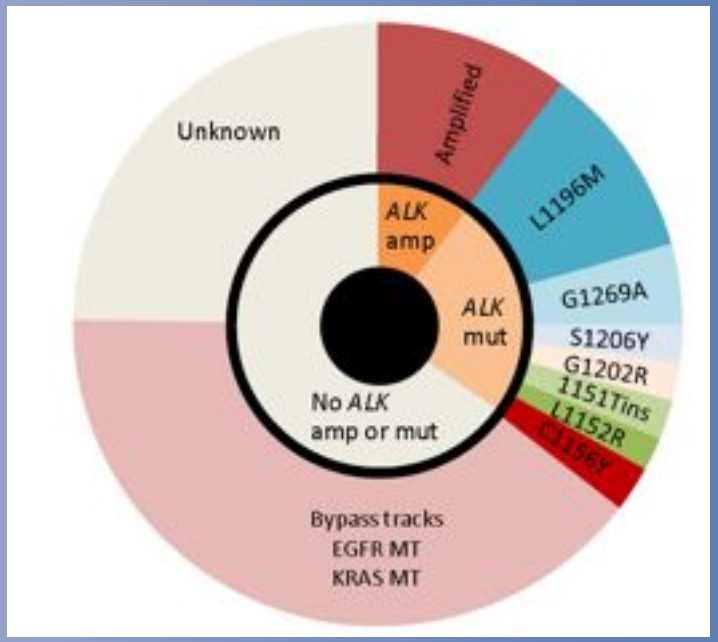
Mechanisms of resistance:

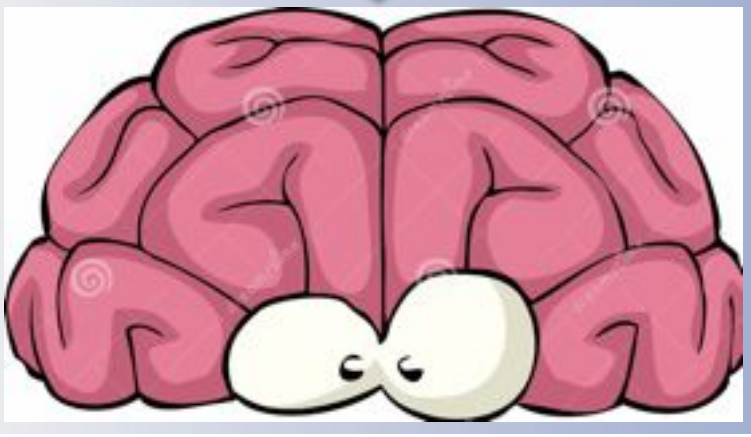
– ALK resistance mutations

– Alternative signaling pathways

– Usually within 1-2 yrs

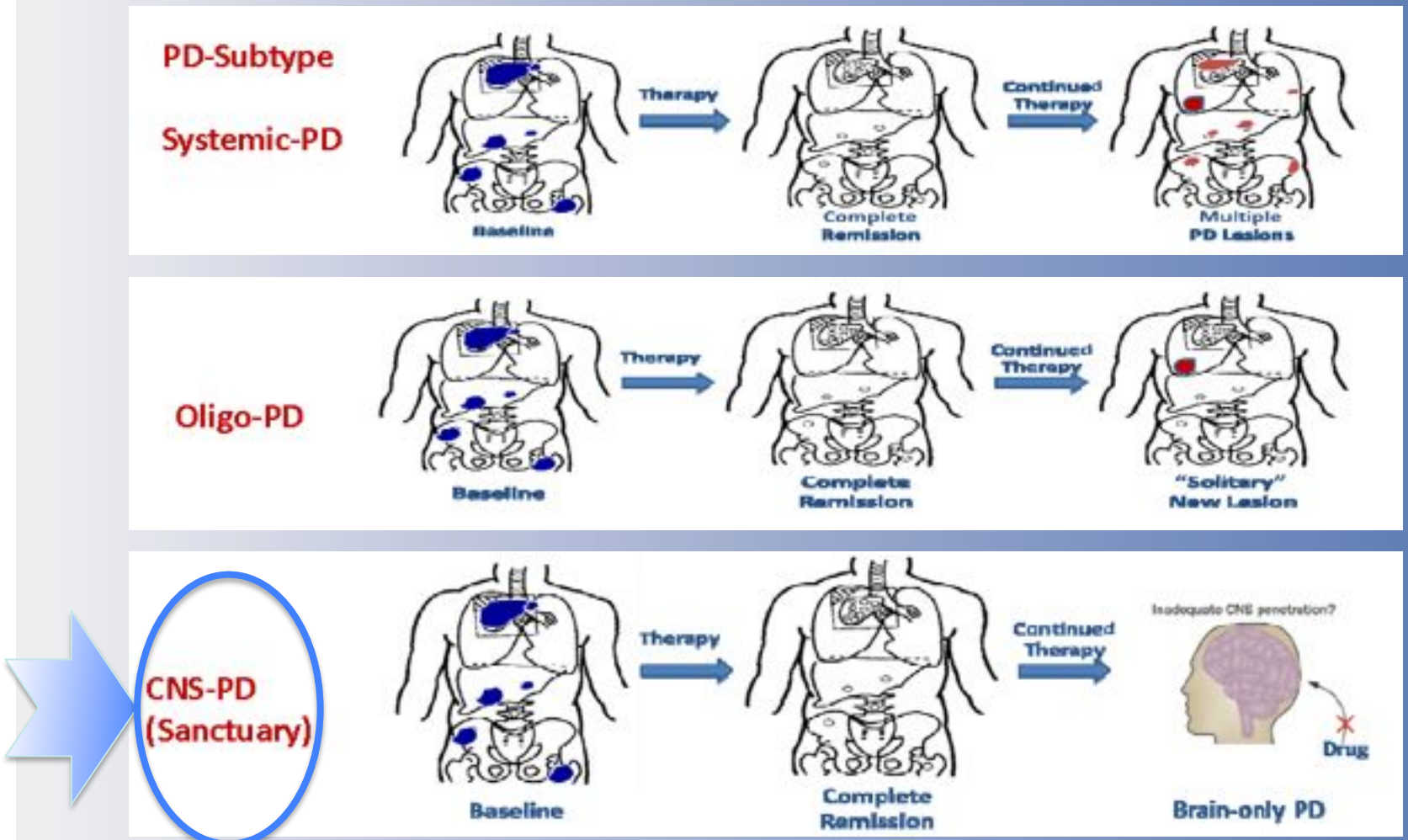
CNS relapses are common





Camidge DR, et al. Lancet Oncol. 2012;13:1011-1019. 2. Kim DW, et al. ESMO 2012. Abstract 1230PD. 3. Show AT, et al. ESMO 2012.Abstract LBA1_PR. 3. Katayama R, et al. Sci Trans Med. 2012;4:120ra17. 4. Doebele RC, et al. Clin Cancer Res. 2012;18:1472-1482. 5.

NOT all patients with acquired resistance to target TKI are created equal: 3 subtypes



Gandara D, ASCO Educational 2013

Isolated central nervous system progression on Crizotinib

An Achilles heel of non-small cell lung cancer with EML4-ALK translocation?

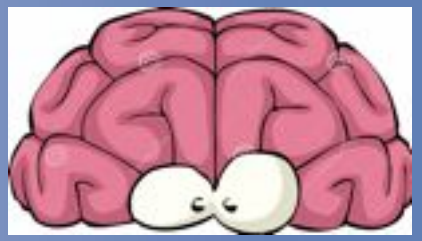
Crizotinib:
good plasma distribution (237 ng/mL),
but low cerebrospinal concentrations (0.617 ng/mL)

Frequent isolated central nervous system metastases
CNS is the primary site of initial treatment failure in 46% of ALK+

Costa DB, JCO 2011; 29:e443
Chun S, Cancer Biology & Therapy 2012; 13: 1376-1383

Indications and limitations of chemotherapy and targeted agents in non-small cell lung cancer BRAIN METASTASES

Due to poor penetration of CRIZOTINIB to the CNS, RADIOTHERAPY SHOULD BE CONSIDERED first in patients with ALK-rearranged lung cancer

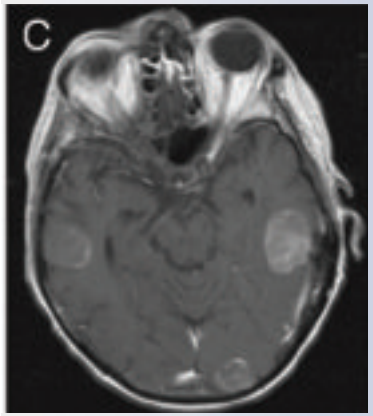


ALK+:
CRIZOTINIB+RADIOTHERAPY

Zimmermann, Canc Treat Rev 2014: 40: 716-722

Indications and limitations of chemotherapy and targeted agents in non-small cell lung cancer BRAIN METASTASES

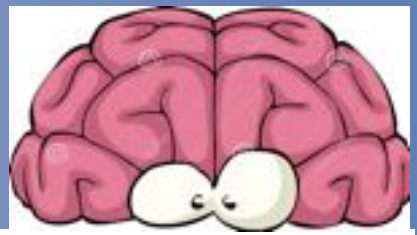
EGFR+ → RADIOTHERAPY



Due to their high response rates, first-line EGFR TKI therapy in EGFR mutated lung cancer may be used in first intention, before radiotherapy, in patients with asymptomatic brain metastases.

Zimmermann, Canc Treat Rev 2014: 40: 716-722

EGFR TKI in non-small cell lung cancer
BRAIN METASTASES



Trials studyng the activity of EGFR TKI in NSCLC with brain M+

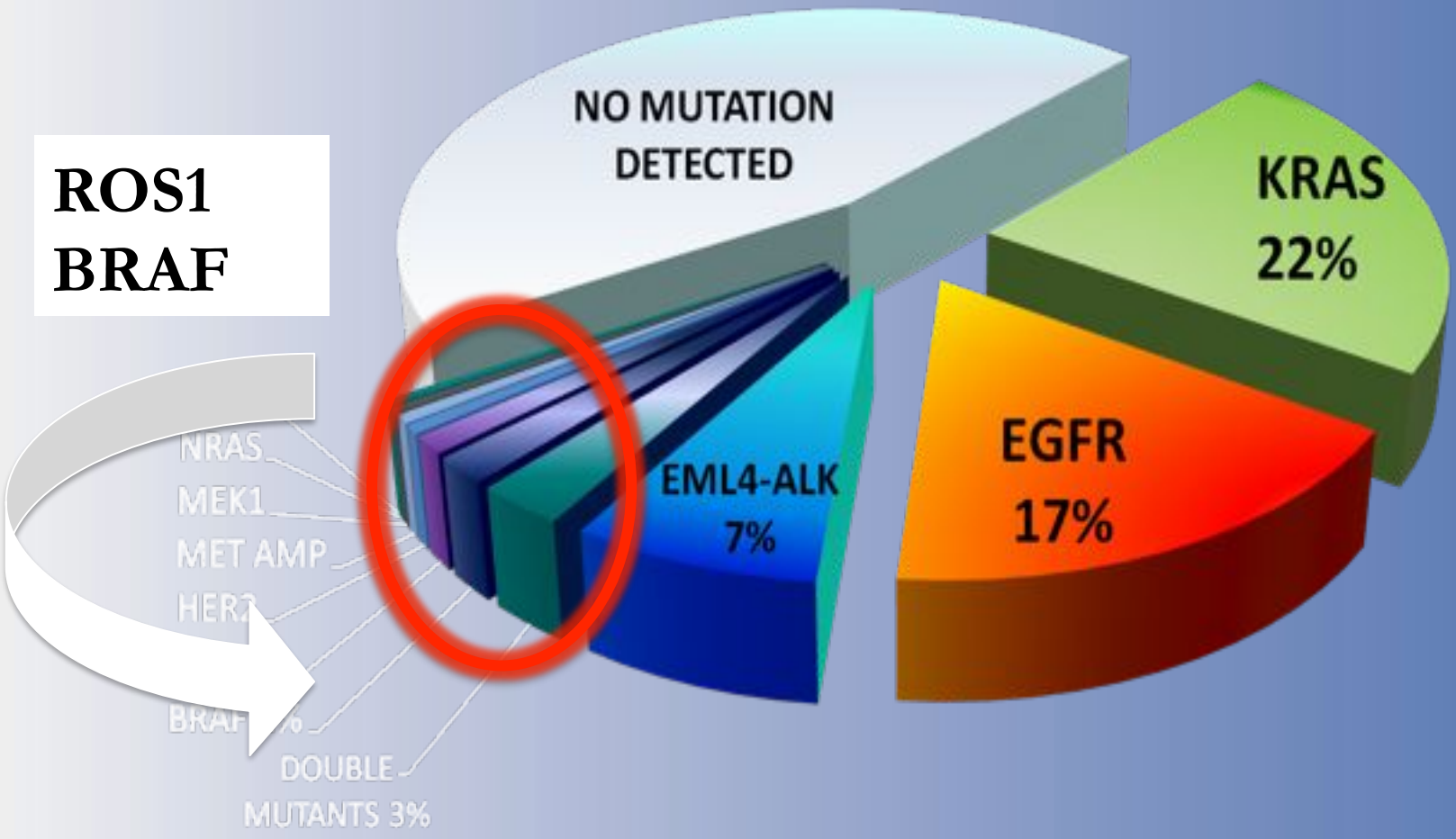
Author (Ref.)	Treatment	Brain RR (%)	MST (months)
Porta et al. [65]	Erlotinib	82	NR
Park et al. [66]	Gefitinib or erlotinib	83	15.9
Li [68]	Gefitinib	89	NR
Kim et al. [67]	Gefitinib or erlotinib	74	18.8
Welsh et al. [78]	Erlotinib	86	11.8
Luchi et al. [80]	Gefitinib	87.8	21.9

Significant improvement of overall survival to between *12.9 to 19.8 months* and improvement in PFS to between *6.6 and 23.3 months* depending on the study reported

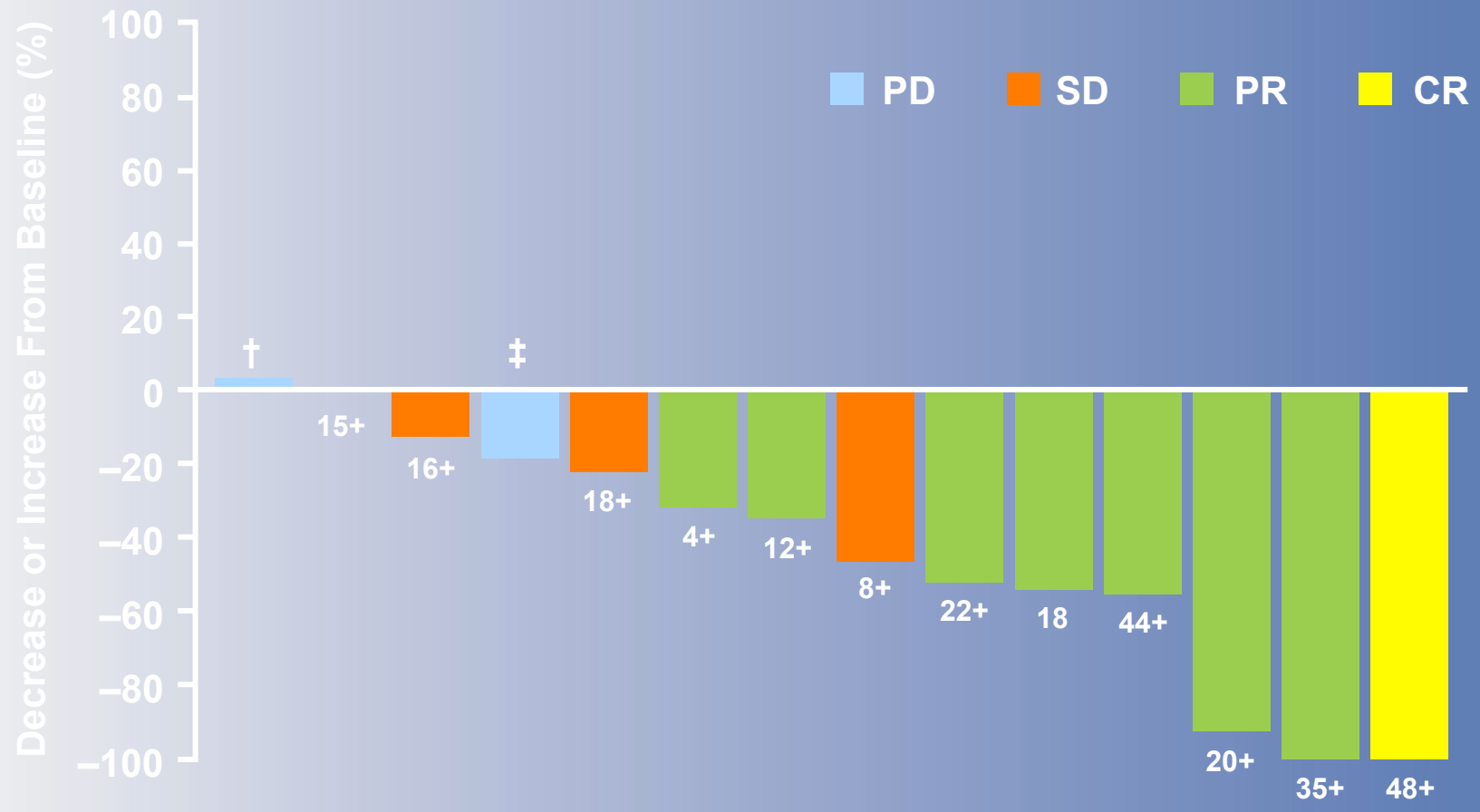
Zimmermann, Canc Treat Rev 2014: 40: 716-722

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations

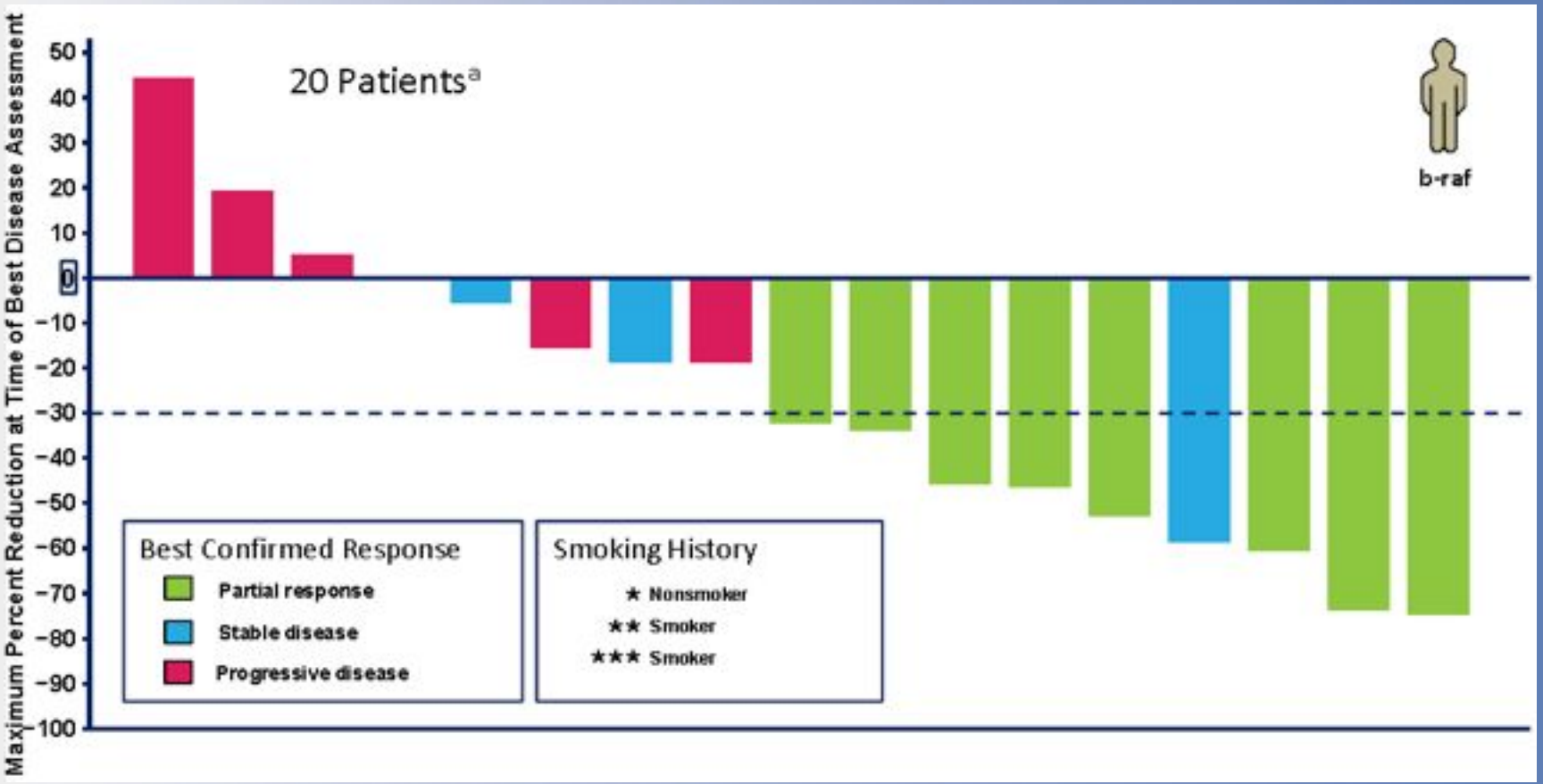


Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (CRIZOTINIB)



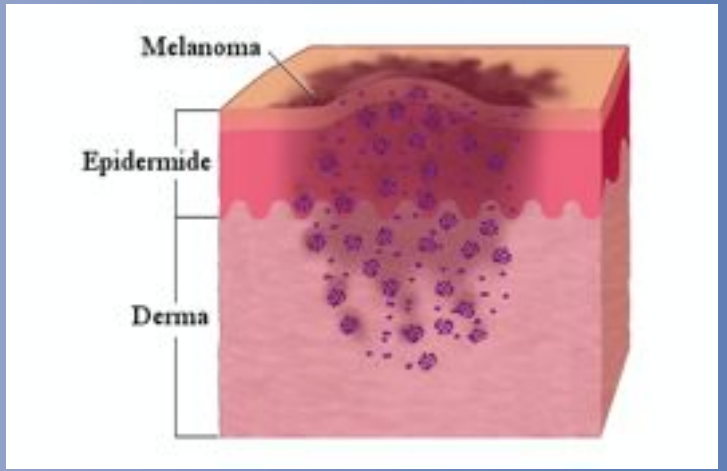
D'Apres et al, ASCO 2013

Dabrafenib in **BRAF V600E** mutation-positive NSCLC patients



Planchard D. et al Proc. ASCO 2013

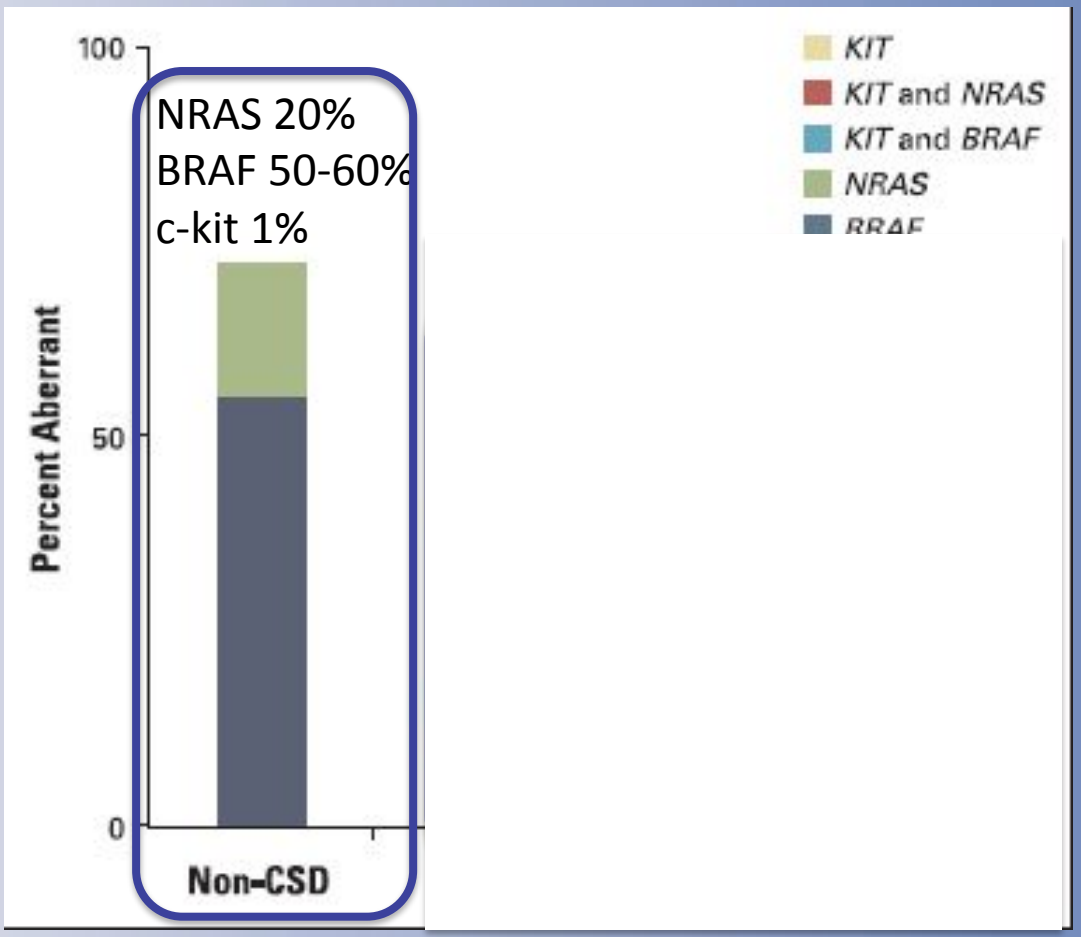
Mutually Exclusive Driver Oncogenes and MAP Kinase Pathway in **MELANOMA**



- **BRAF** **~ 55%**
- *NRAS* ~ 20%
- PTEN 20-40%
- *CKIT* ~ 1%
  - Primarily acral (36%), mucosal (39%) and CSD (28%)
- *GNAQ/GNA11* ~ 1%
  - Almost exclusively uveal (>50%)

Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.
Smalley KS, et al. Semin Oncol. 2012;39:204-214.

Distinct sets of genetic alterations in melanoma



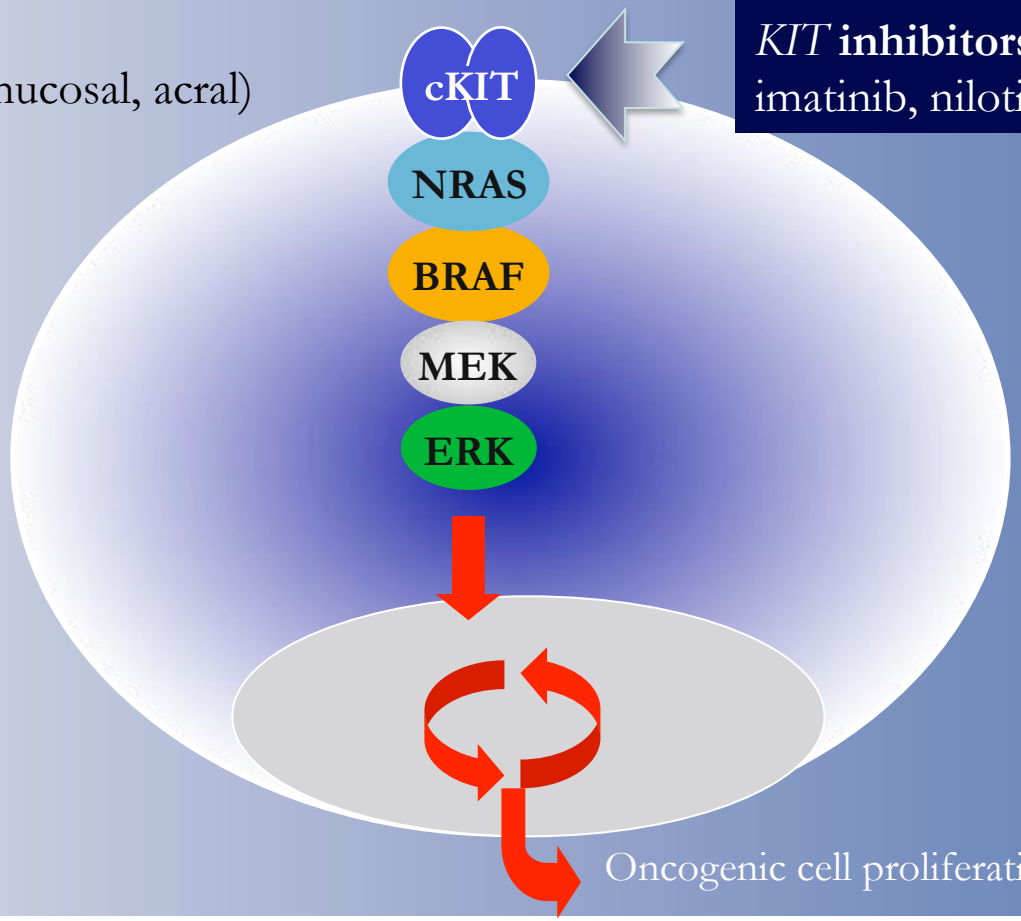
CSD: cronic sun induced disease

Curtin, et al., JCO 24 (26)

MAP Kinase Pathway Targeting in Melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]

< 5% melanomas (mucosal, acral)

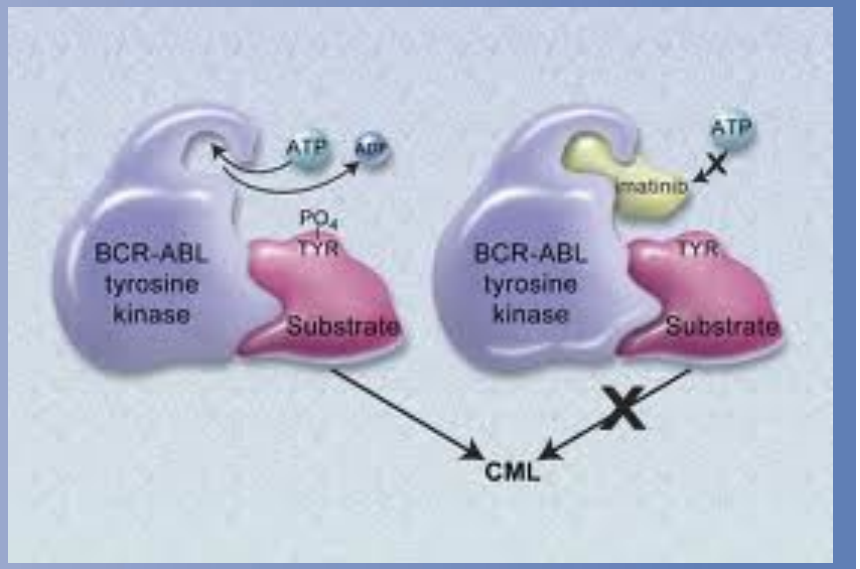


***KIT* inhibitors:**
imatinib, nilotinib, dasatinib[4]

1. Sosman JA, et al. ASCO 2011 Educational Book. 2. Arkenau HT, et al. Br J Cancer. 2011;104:392-398. 3. Thomas N, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:991-997. 4. Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

INIBITORI DI cKIT: IMATINIB

Imatinib rappresenta il primo esempio in oncologia ed ematologia di un farmaco ideato razionalmente e diretto specificamente contro la proteina anomala (Bcr-Abl ad esempio, prodotta dal cromosoma Philadelphia o Ph) che causa un tumore umano (la LMC in questo caso).

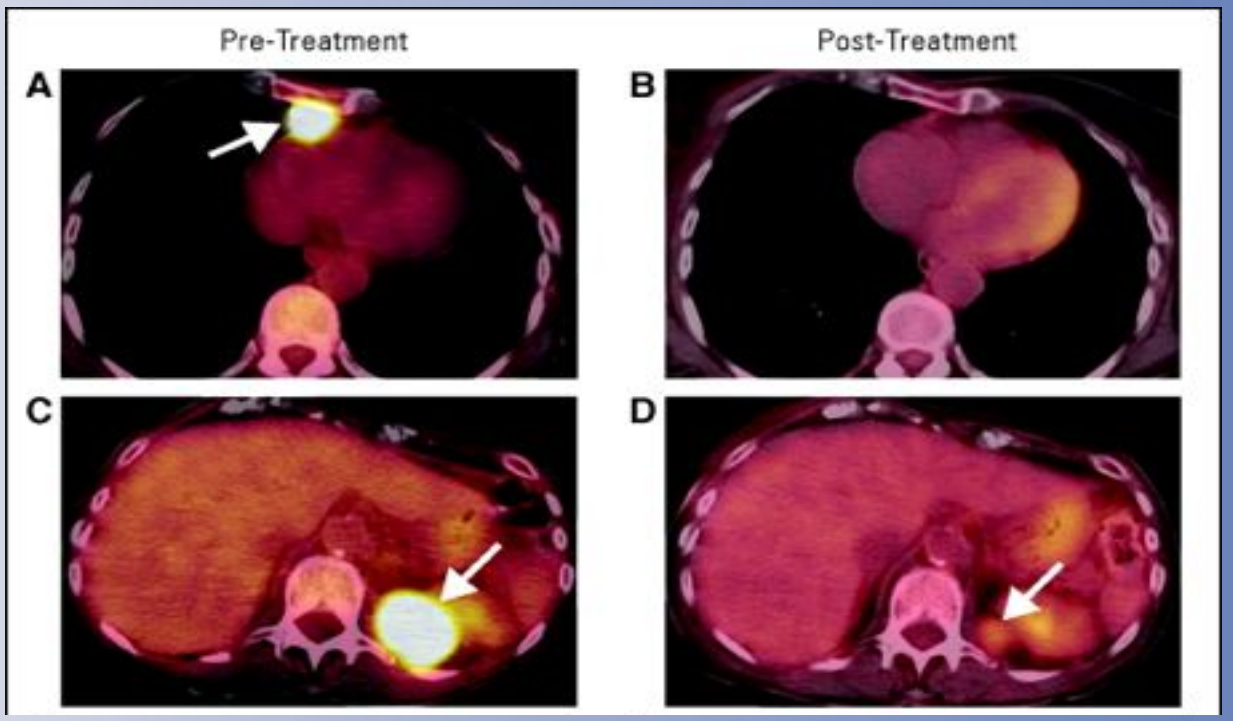


Imatinib è usato nel trattamento di:

- ✓ leucemia mieloide cronica (LMC)
- ✓ tumori stromali gastrointestinali (GISTs)
- ✓ Pochi tumori maligni in cui gene ABL, KIT, PDGFR è coinvolto

c-KIT mutations in Melanoma

First report of a response to IMATINIB in a patient with metastatic mucosal melanoma harboring a c-kit mutation



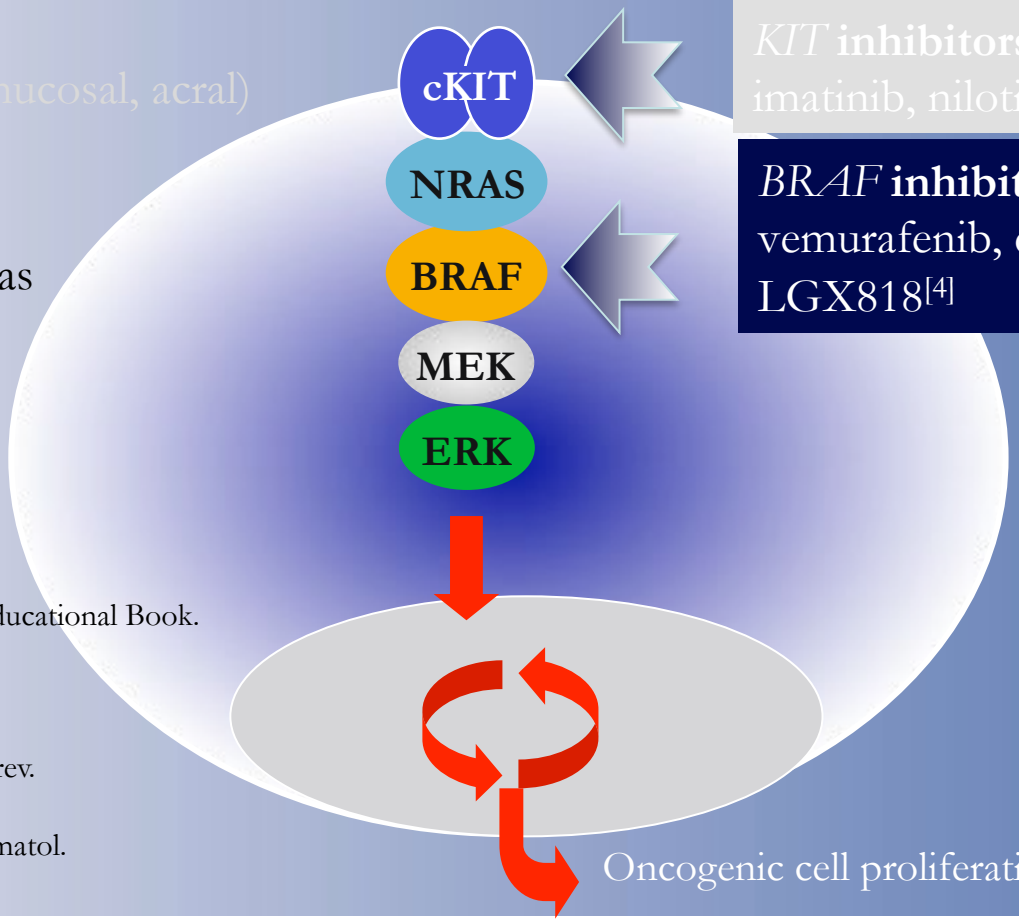
Phase III study (Protocol AB08026)

MAP Kinase Pathway Targeting in Melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]

< 5% melanomas (mucosal, acral)

~42-55% melanomas



KIT **inhibitors:**
imatinib, nilotinib, dasatinib[4]

BRAF **inhibitors:**
vemurafenib, dabrafenib, LGX818[4]

Sosman JA, et al. ASCO 2011 Educational Book.
Arkenau HT, et al. Br J Cancer. 2011;104:392-398.
Thomas N, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:991-997.
Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

Relative frequency of BRAF mutations

BRAF mutation location (by amino acid position and substitution)	% of all BRAF mutations
V600E	97.3%
V600K	1.0%
K601E*	0.4%
G469A*	0.4%
D594G*	0.3%
V600R	0.3%
L597V*	0.2%

Phase III BRIM-3 Study design

Screening

$BRAF^{V600E}$ mutation

Stratification
- Stage
- ECOG PS (0 vs 1)
- LDH level (↑ vs nl)
- Geographic region

Randomisation
N=675

Vemurafenib

960 mg po bid
(N=337)

Dacarbazine

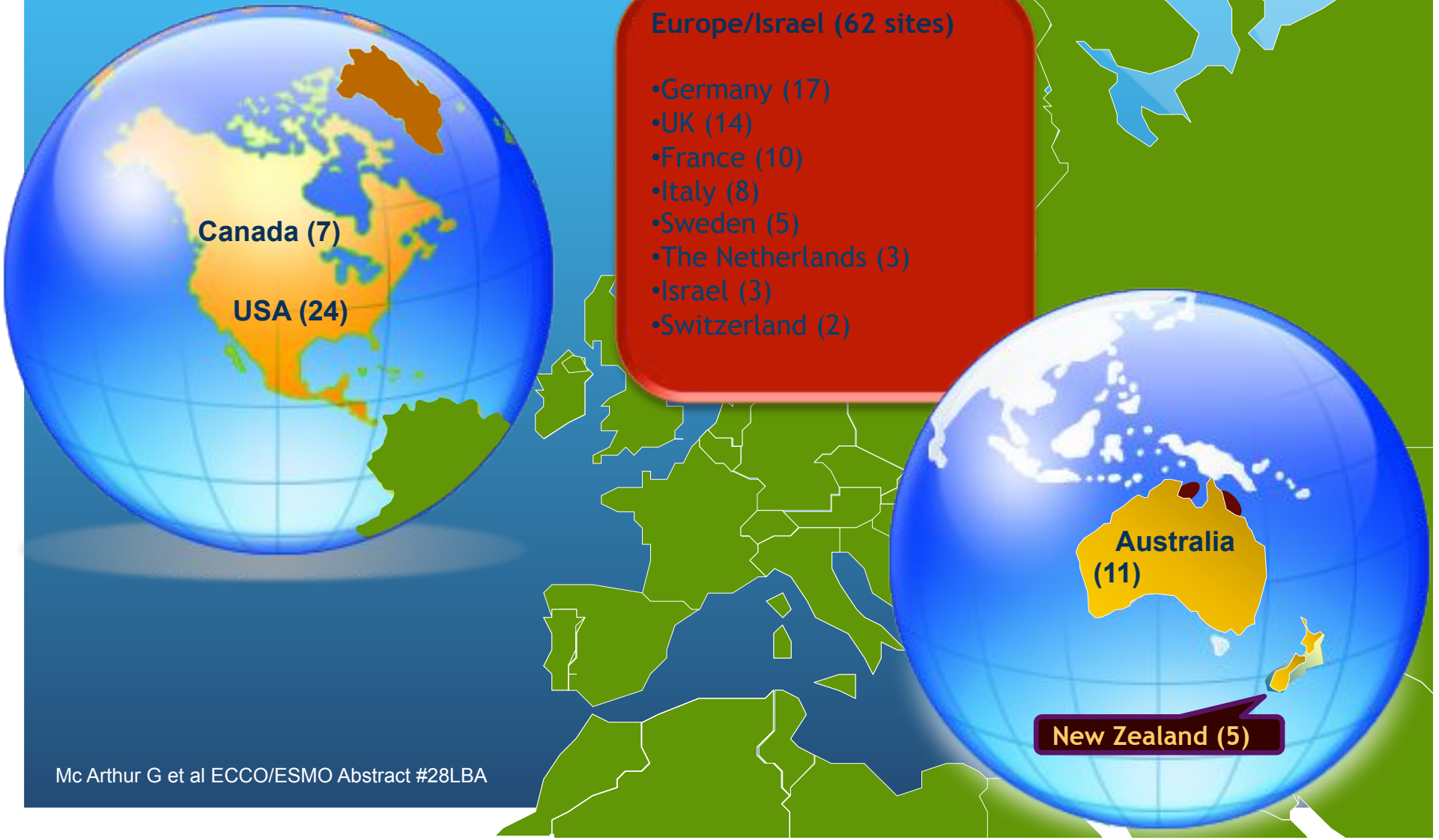
1000 mg/m² iv q3w
(N=338)

Co-primary endpoints:
- **Overall Survival**
- **Progression Free Survival**

Mc Arthur G et al ECCO/ESMO Abstract #28LBA

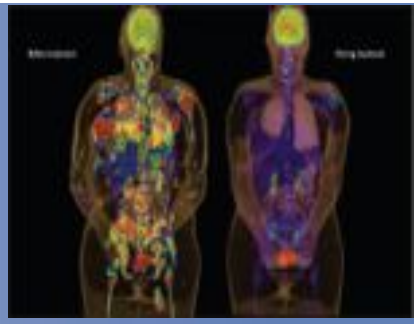
BRIM-3 trial: A worldwide study

104 centers in 12 countries enrolled patients



Mc Arthur G et al ECCO/ESMO Abstract #28LBA

Confirmed OBJECTIVE RESPONSE RATES across vemurafenib clinical trial programme

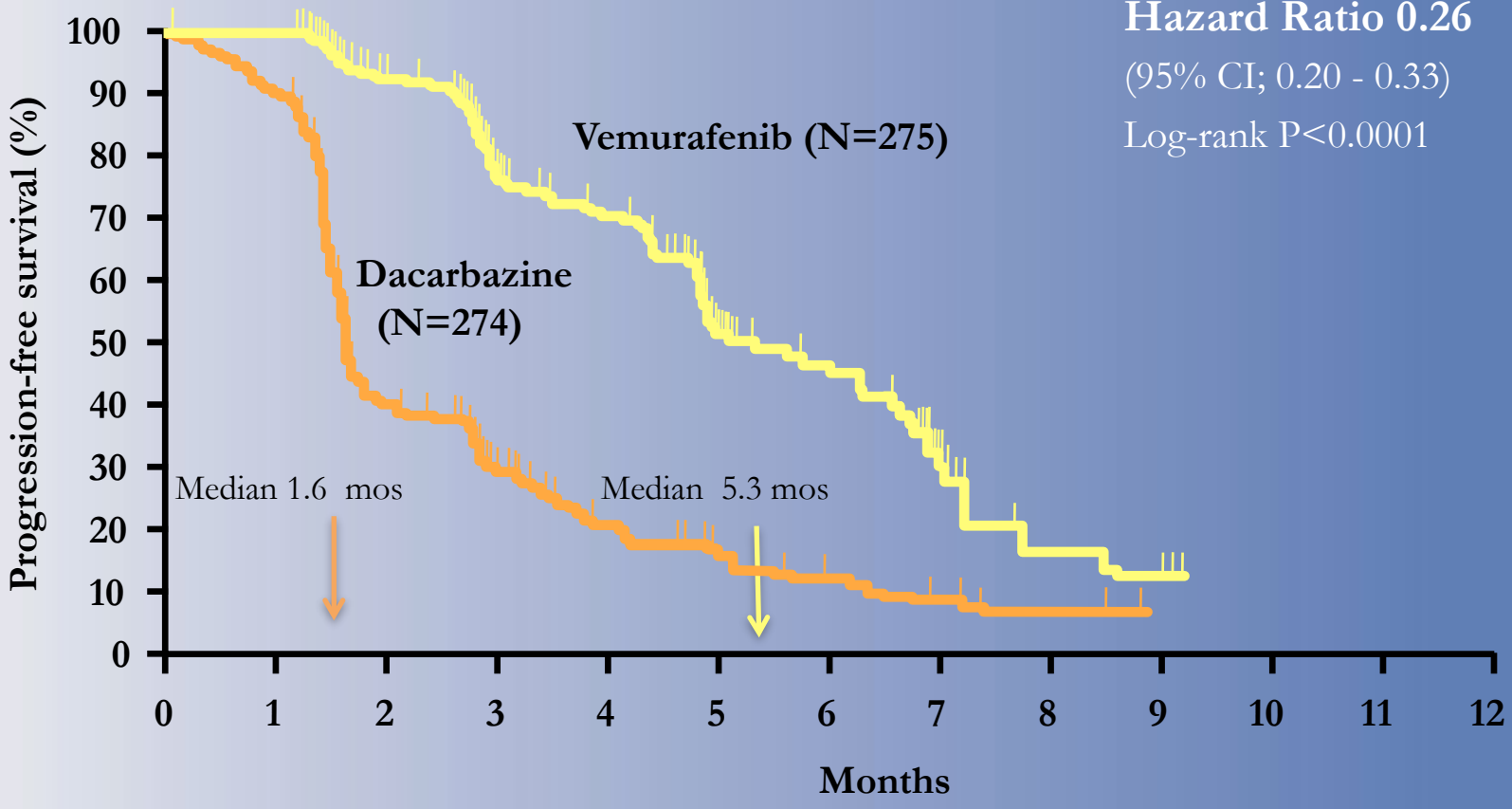


	PLX 06-02 Phase I	BRIM 2	BRIM-3 ORR (final analysis at OS IA, 30 Dec 2010)
Vemurafenib	**56.0%**	**53.0%**	**48.4%**
(95% CI)	**(38–74)**	**(44–62)**	**(42–55)**
Dacarbazine	–	–	**5.5%**
(95% CI)			**(3–9)**

Mc Arthur G et al ECCO/ESMO Abstract #28LBA

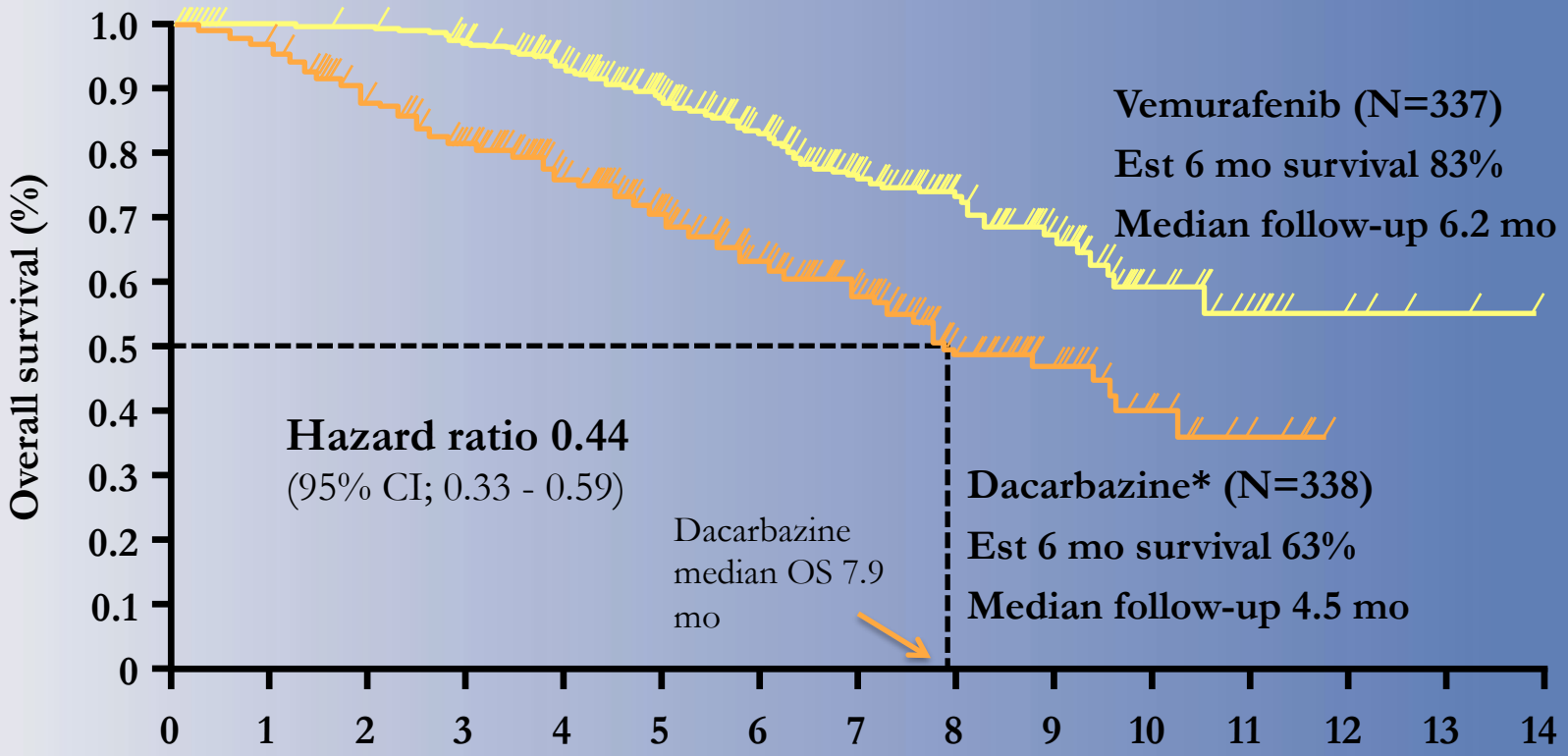
Progression-free survival

(30 Dec 2010, final pre-planned analysis at IA)



Mc Arthur G et al ECCO/ESMO Abstract #28LBA

Overall survival (March 31, 2011 cutoff)



Mc Arthur G et al ECCO/ESMO Abstract #28LBA

Safety and efficacy of vemurafenib in *BRAF*V600E and *BRAF*V600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study

Extended follow-up analysis

675 ELIGIBLE PATIENTS were enrolled from 104 centres in 12 countries between Jan 4, 2010, and Dec 16, 2010.

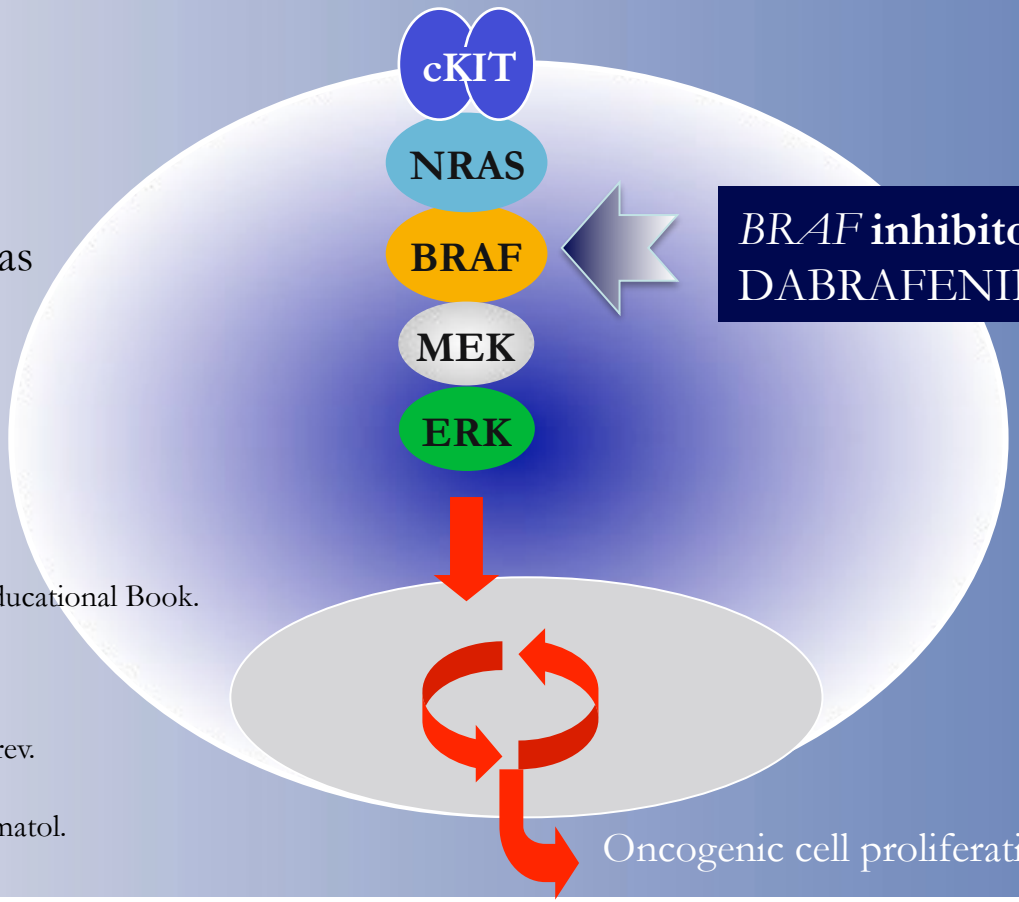
	Median OS	**Median PFS**
Vemurafenib	13.3	6.9
Dacarbazina	10.0	1.6
	HR 0.75, p<0.0001	HR 0.39 P<0.0001

Mc Arthur, The Lancet Oncology 2014; 15:323-332

MAP Kinase Pathway Targeting in Melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]

~42-55% melanomas



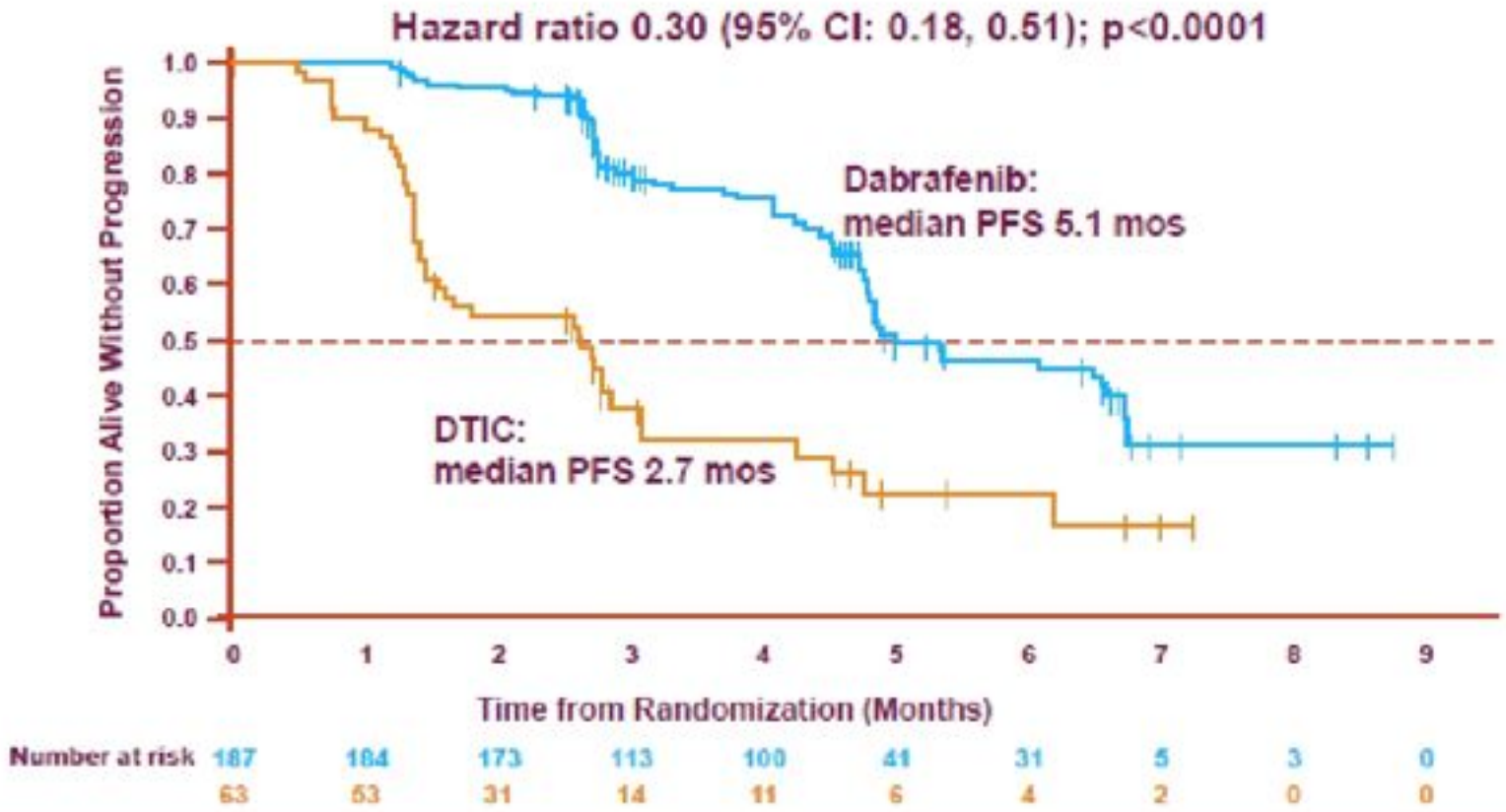
***BRAF* inhibitors:**
DABRAFENIB

Sosman JA, et al. ASCO 2011 Educational Book.
Arkenau HT, et al. Br J Cancer. 2011;104:392-398.
Thomas N, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:991-997.
Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

Primary endpoint: PFS

Investigator-assessed (cut-off: 19 December 2011)

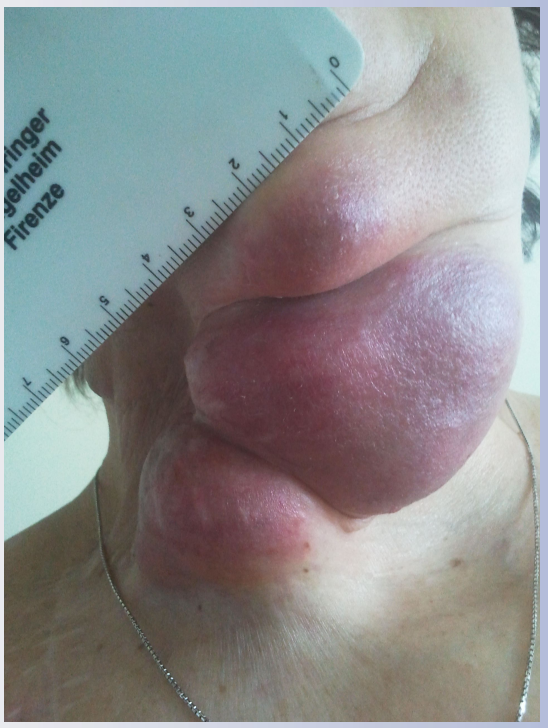
BREAK-3



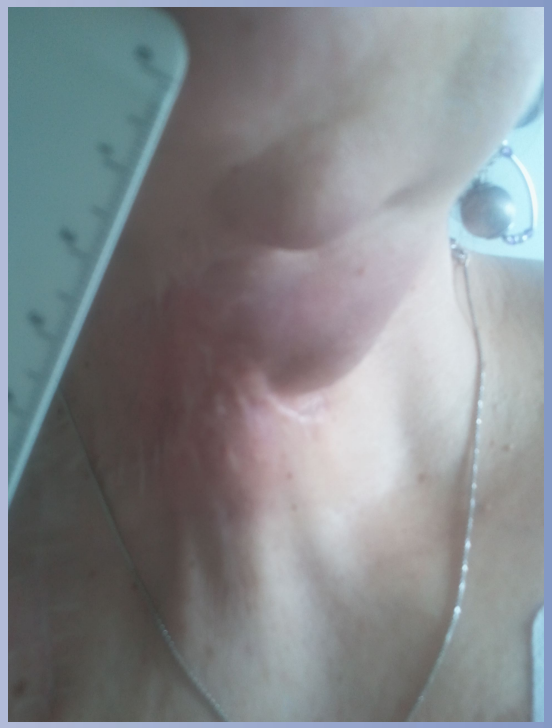
On randomized study treatment at cut-off: dabrafenib 57%, DTIC 27%
Median follow-up time: 4.9 months (dabrafenib 5.1 mos, DTIC 4.8 mos.)

PRESENTED AT: ASCO Annual '12 Meeting

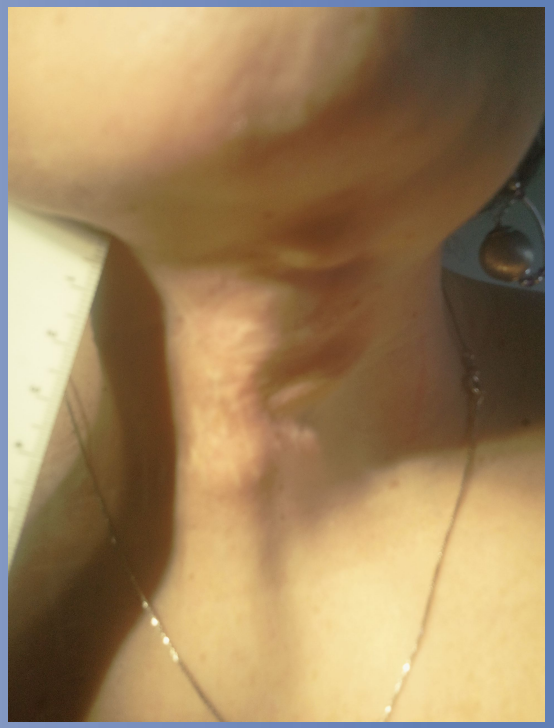
Dabrafenib activity in real life – BRF115252 - IT15 - IDI IRCCS



Baseline



1 week

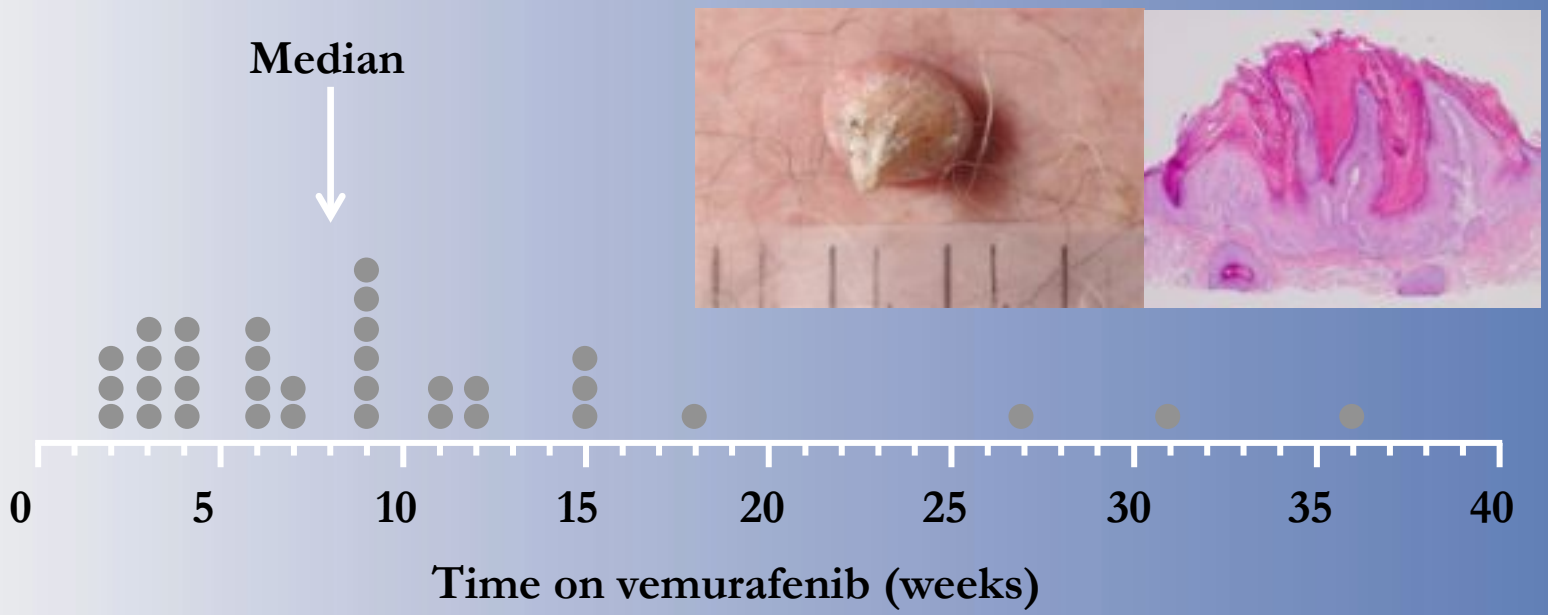


4 weeks

Selected adverse events (% of patients) (March 31, 2011)

	Vemurafenib, n=336			Dacarbazine, n=287		
Adverse events	All	Grade 3	Grade≥ 4	All	Grade 3	Grade ≥4
Arthralgia	53	4	-	3	<1	-
Rash	37	8	-	2	-	-
Fatigue	38	2	-	33	2	<1
Photosensitivity	33	3	-	4	-	-
↑LFTs	22	8	<1	5*	1*	-*
Cutaneous SCC	17	16	-	<1	<1	-
Keratoacanthoma	9	9	-	-	-	-
Skin papilloma	21	<1	-	-	-	-
Nausea	35	2	-	43	2	-
Neutropenia	<1	-	<1	12	6	3
Uveitis**	3	<1	-	-	-	-

Time to incidence of first cuSCC/KA



- Median time 8 weeks (2–36)
- Median number of cuSCC/KAs per patient 1 (range 1 to 7)
- Each dot represents weeks to development of first cuSCC/KA lesion

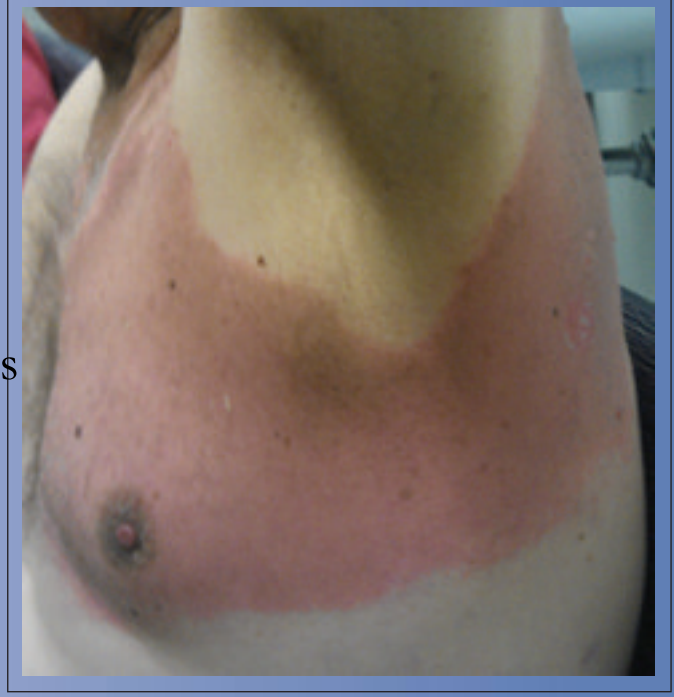
JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

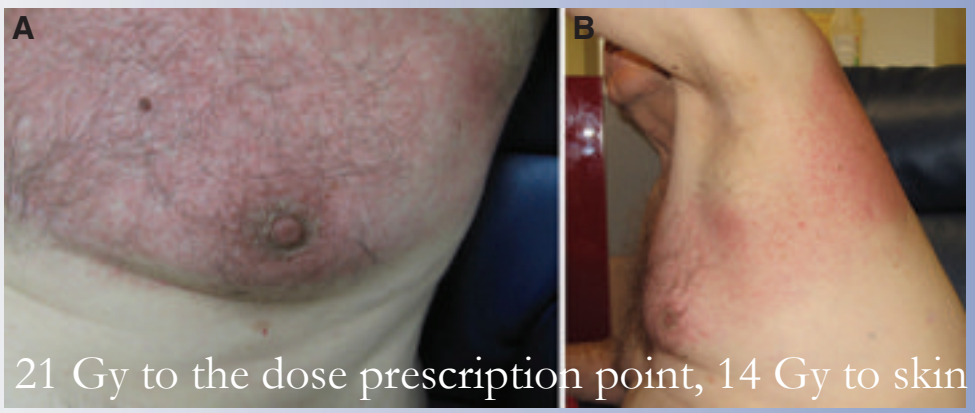
ACUTE RADIATION SKIN TOXICITY ASSOCIATED WITH BRAF INHIBITORS

A 71-year-old man with widespread metastatic melanoma

Disease progression in the axilla was treated with palliative radiotherapy of 36 Gy in 12 fractions and Vemurafenib.



27 Gy to the dose prescription point, 18 Gy to skin



21 Gy to the dose prescription point, 14 Gy to skin

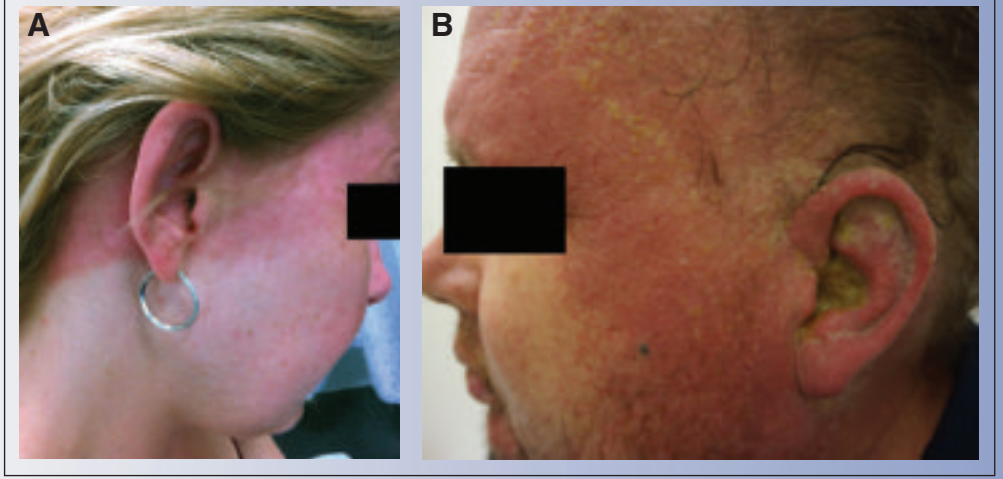
Pulvirenti ,J Clinical Oncol Vol 32, 2014

JOURNAL OF CLINICAL ONCOLOGY

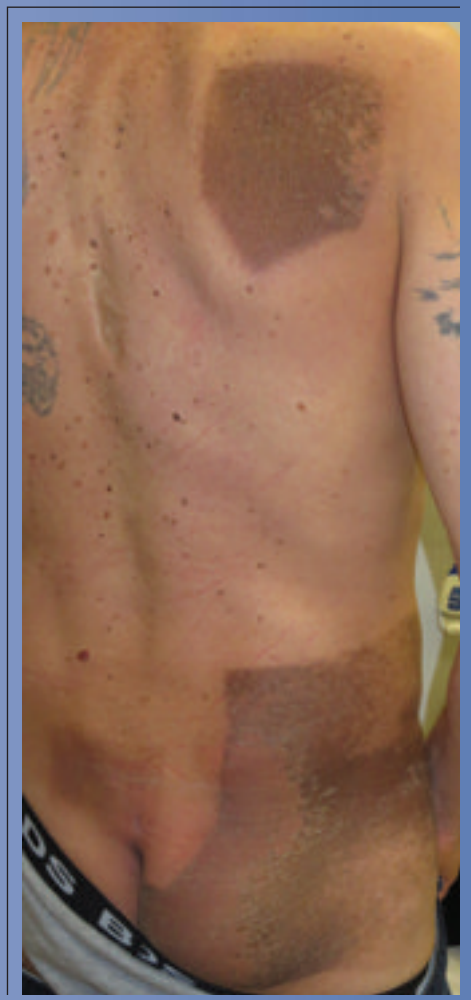
DIAGNOSIS IN ONCOLOGY

ACUTE RADIATION SKIN TOXICITY ASSOCIATED WITH BRAF INHIBITORS

RT 8 Gy to painful bony metastases in the left humerus, left ribs, and sacrum.After radiotherapy, he began receiving dabrafenib. He underwent 8 Gy to these new sites of metastatic disease, concurrently with dabrafenib. There was no overlap with his previous radiotherapy fields.



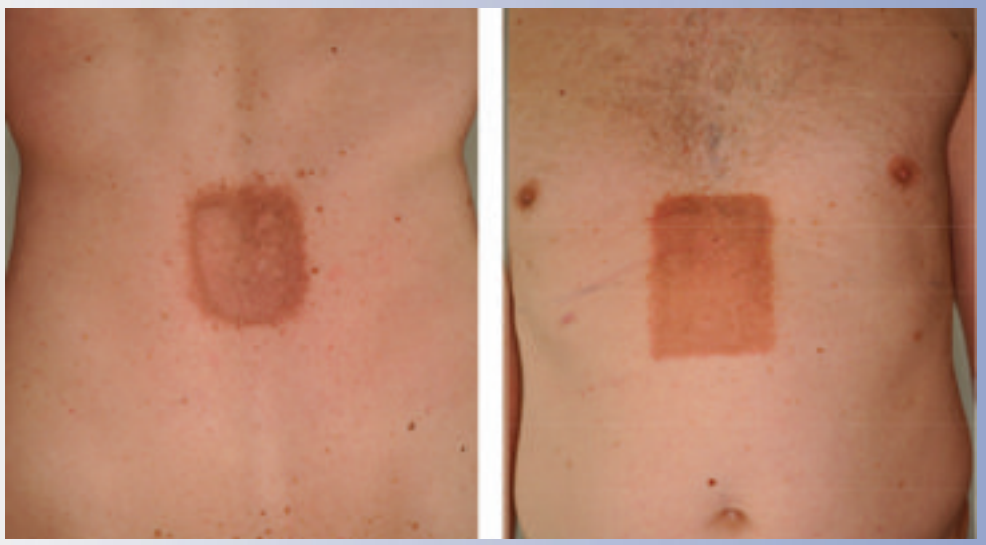
Whole-brain radiotherapy at a dose of 30 Gy in 10 fractions concurrent with dabrafenib



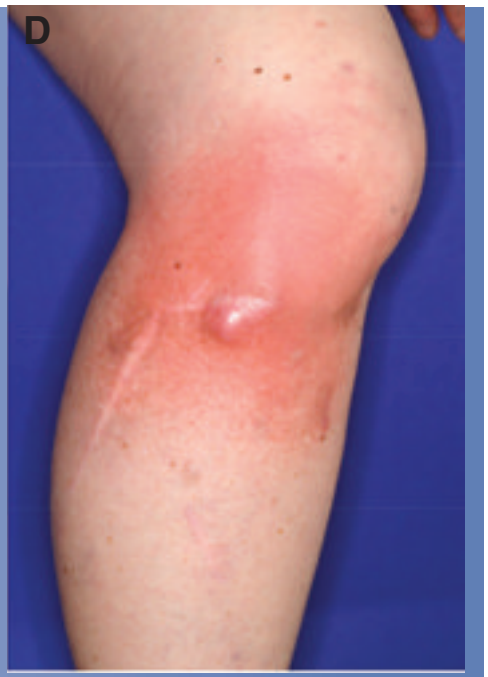
Pulvirenti ,J Clinical Oncol Vol 32, 2014

JOURNAL OF CLINICAL ONCOLOGY

Serious Skin Toxicity With the Combination of BRAF Inhibitors and Radiotherapy



A 47-year-old man received 2 months of treatment with dabrafenib, after which a new bone metastasis measuring 1.1 cm in diameter was noted in his spine (D12). Two months later, this metastasis increased to 1.9 cm, and a total of 36 Gy of irradiation was applied.



A 73-year-old woman presented with growing subcutaneous metastases 7 months after initiation of dabrafenib therapy and therefore received concomitant RT. Grade 3 radiation dermatitis was noted after 52 Gy were applied to the upper leg and grade 2 was observed after 34 Gy

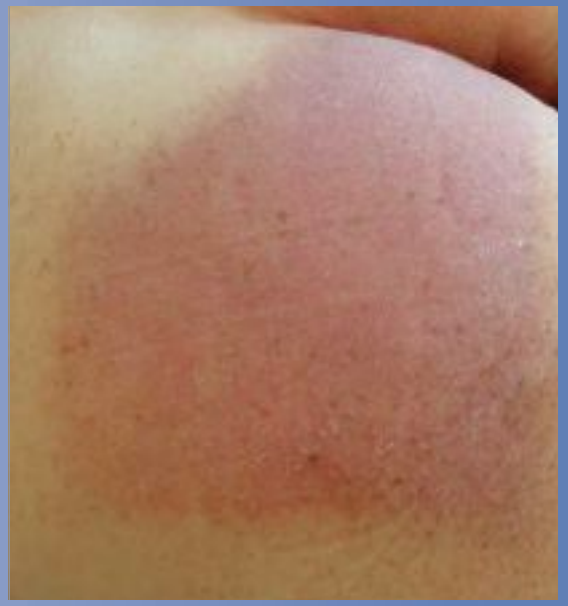
Imke Satzger, Journal of Clinical Oncology, Vol 31, No 13 (May 1), 2013

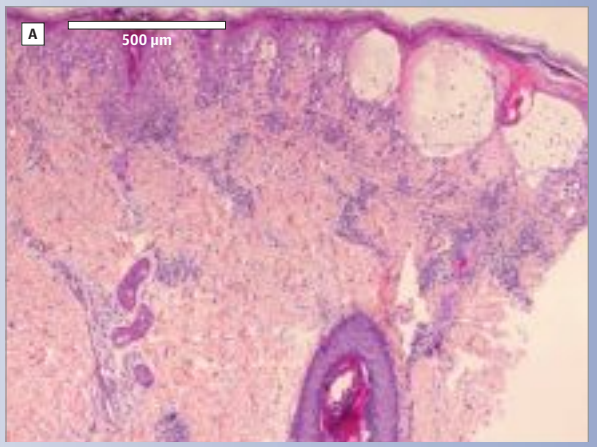
Case Report/Case Series

Vemurafenib and Radiosensitization

Lise Boussemart, MD; Catherine Boivin, MD; Joël Claveau, MD; Yun Gan Tao, MD; Gorana Tomasic, MD; Emilie Routier, MD; Christine Mateus, MD; Eric Deutsch, MD, PhD; Caroline Robert, MD, PhD

RT: Left hip 20Gy in 5 fractions. The patient began vemurafenib therapy 23 days after she last received radiotherapy, at a dose of 960 mg twice daily. Seven days after the initiation of vemurafenib, she developed a pruriginous rectangular eczematous plaque on her left buttock





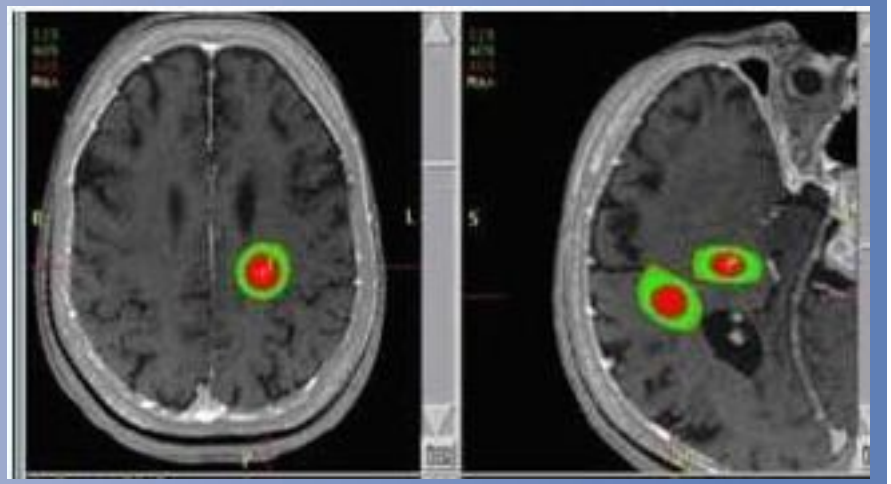
Boussemart L, Boivin C, Claveau J, et al: Vemurafenib and radiosensitization. JAMA Dermatol 149:855-857, 2013

Combination of BRAF Inhibitors and Brain Radiotherapy in Patients With Metastatic Melanoma Shows

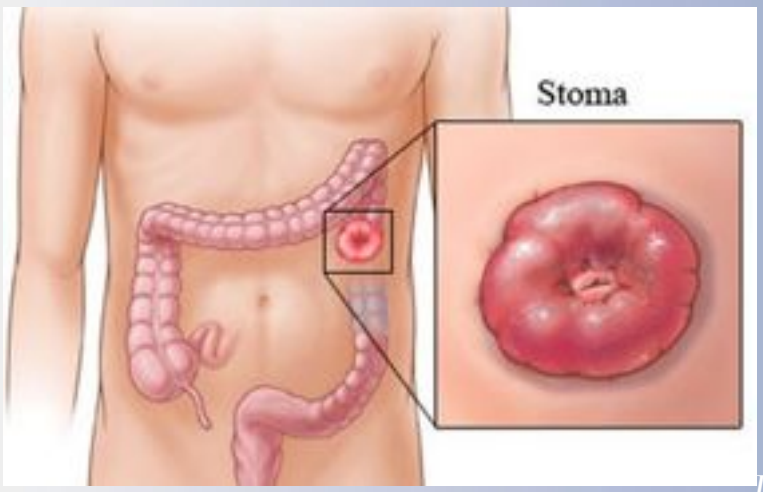
The increased severity of radiation dermatitis during concomitant BRAF inhibitor therapy could be DOSE DEPENDENT, given that it only occurred in patients receiving WBRT. Finally, there was no evidence of increased intracranial toxicity

Vemurafenib is a strong radiosensitizer. Patients receiving radiotherapy under simultaneous vemurafenib treatment should be MONITORED VERY CLOSELY.

Severe radiotherapy-induced EXTRACUTANEOUS TOXICITY under vemurafenib.



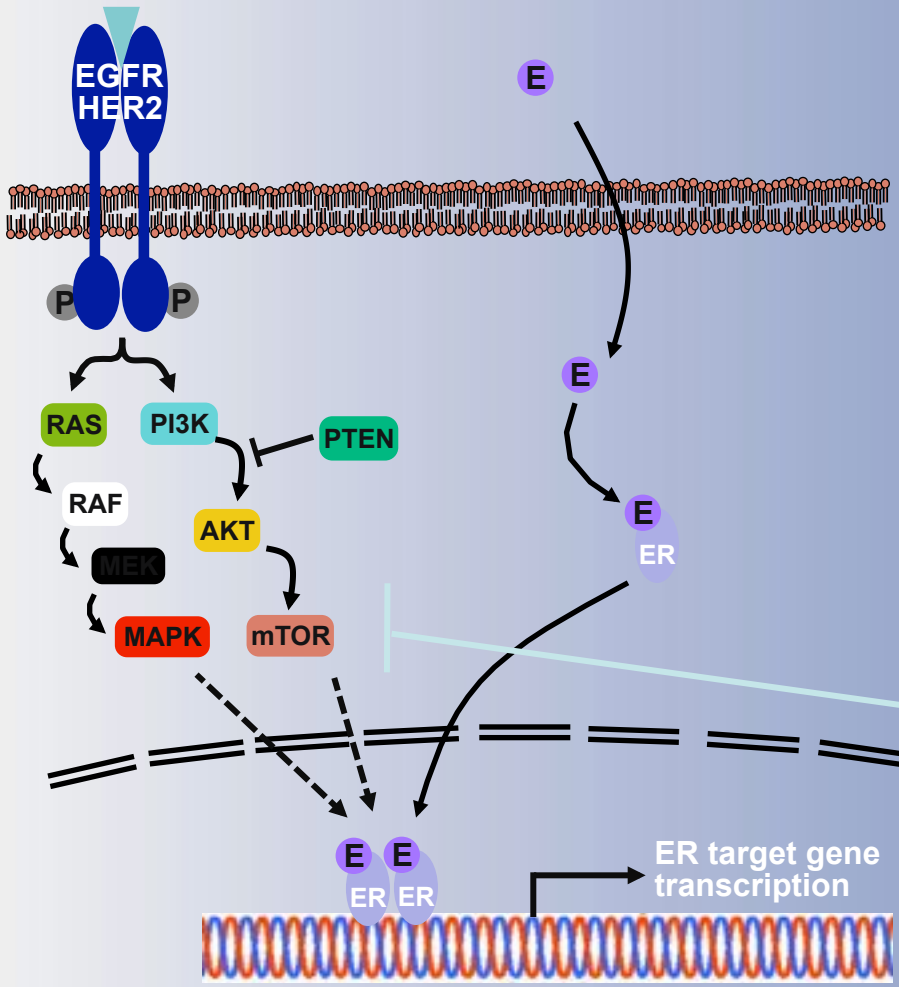
The first patient, a female aged 32, treated with vemurafenib for three months, presented a steroid-dependent RADIONECROSIS after brain stereotactic radiosurgery. Symptoms persisted until her death six months later.



The second patient, a male aged 64 and treated with vemurafenib for nineteen days, presented a radiation-induced ANORECTITIS complicated by diarrhoea, anorexia and weight loss following the concomitant radiation of a primary rectal tumour. A colostomy was needed after ten months in order to improve local status and general health.

Peuvrel L, Eur J Dermatol. 2013 Nov-Dec;23(6):879-81.

Crosstalk Between ER and PI3K/AKT/mTOR Signaling: Rationale for Dual Inhibition



- mTOR activates ER in a ligand-independent manner
- Estradiol suppresses apoptosis induced by mTOR blockade
- Hyperactivation of the mTOR pathway is observed in endocrine therapy–resistant breast cancer cells

mTOR Inhibitors
Everolimus
Sirolimus
Temsirolimus

EVEROLIMUS Approvals and indications

1. Advanced kidney cancer (approved in March 2009)

2. Progressive or metastatic pancreatic neuroendocrine tumors not surgically removable (May 2011)

1. Breast cancer in post-menopausal women with advanced hormone-receptorpositive, HER2-negative type cancer, in conjunction with exemestane (July 2012)

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm254350.htm
"US FDA approves Novartis drug Afinitor for breast cancer". Reuters. 20 Jul 2012.

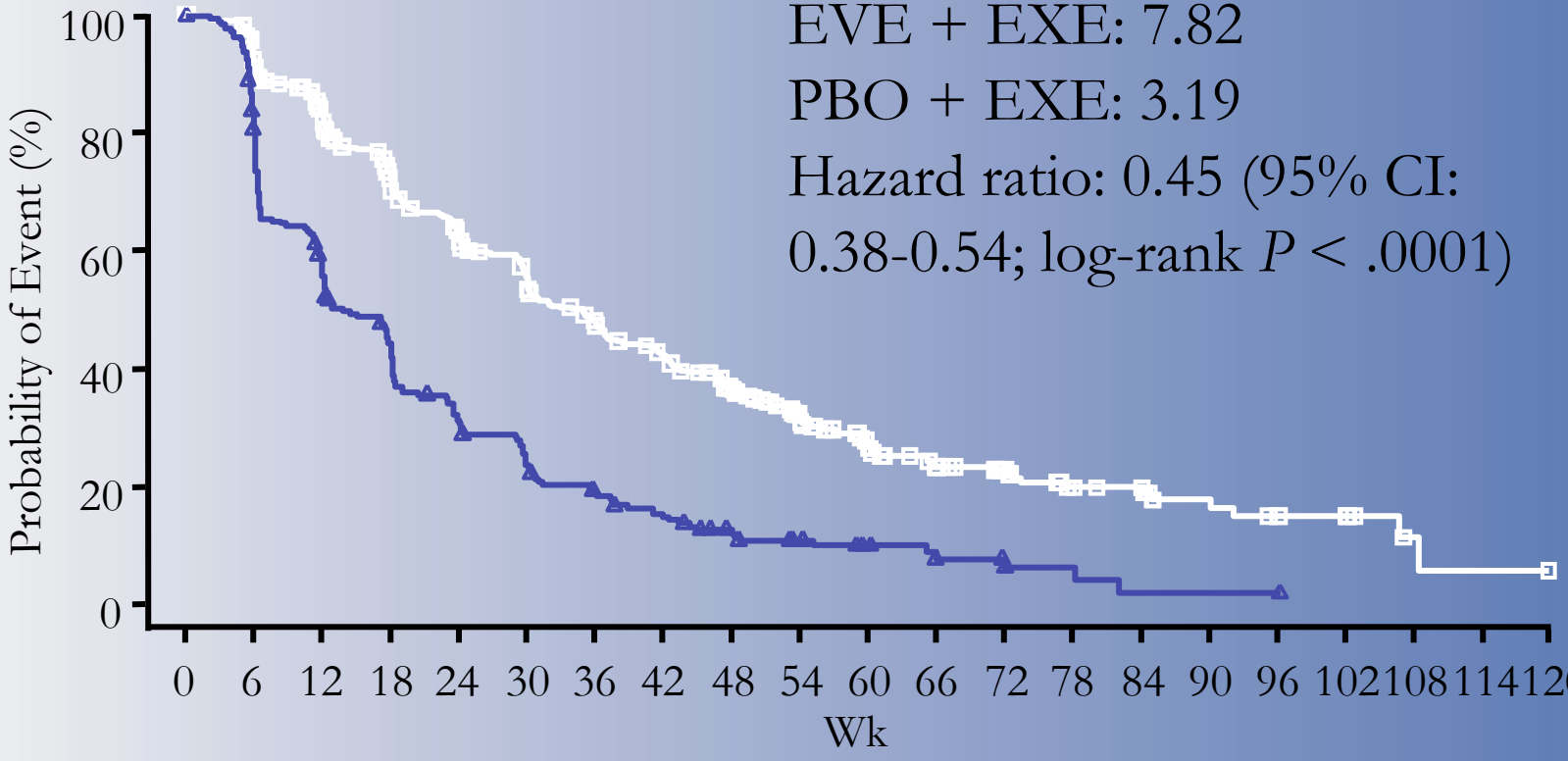
BOLERO-2: PFS at 18-Mo Follow-up

Median PFS, Mos

EVE + EXE: 7.82

PBO + EXE: 3.19

Hazard ratio: 0.45 (95% CI: 0.38-0.54; log-rank $P < .0001$)



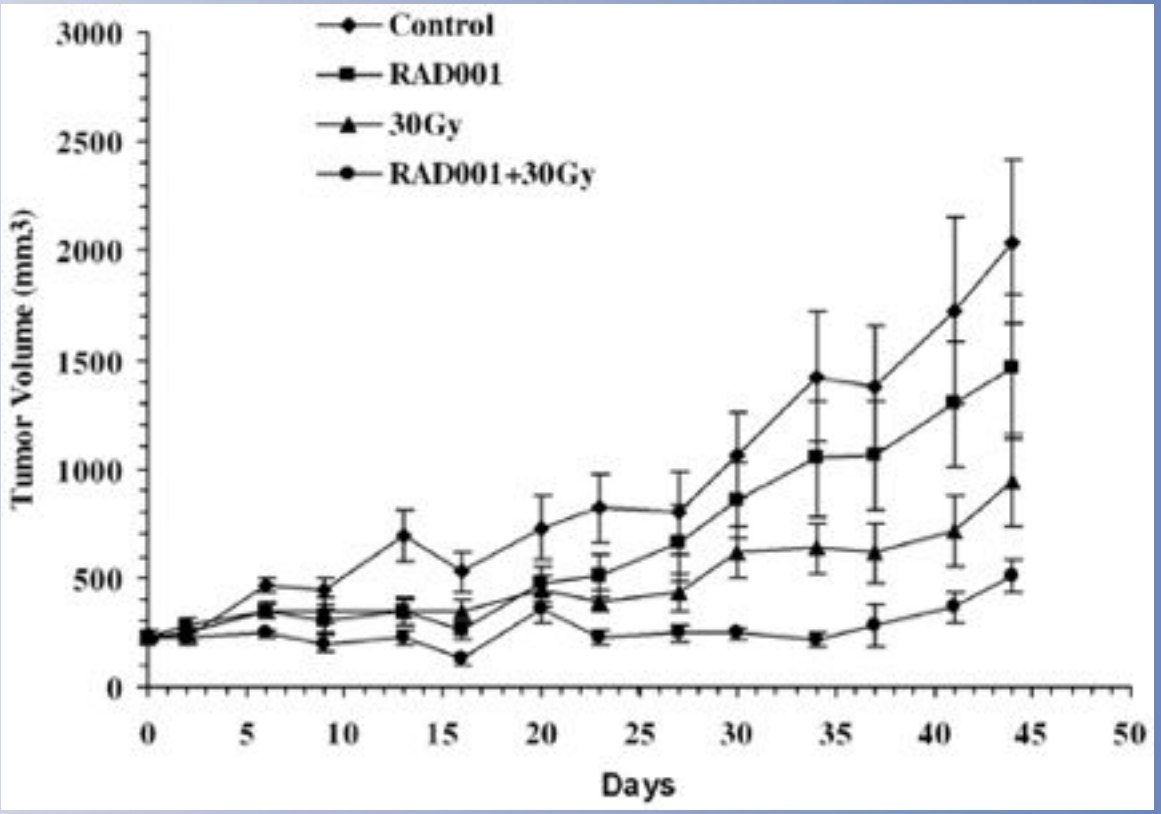
Piccart-Gebhart M, et al. ASCO 2012. Abstract 559.

BOLERO-2: Adverse Events at 18-Mo Follow-up

	Everolimus + Exemestane (n = 482)			Placebo + Exemestane (n = 238)		
	Grade			Grade		
Adverse Event, %	All	3	4	All	3	4
Total	100	44	9	91	23	5
Stomatitis	59	8	0	12	< 1	0
Rash	39	1	0	7	0	0
Fatigue	37	4	< 1	27	1	0
Diarrhea	34	2	< 1	19	< 1	0
Nausea	31	< 1	< 1	29	1	0
Appetite decreased	31	1	0	13	1	0
Noninfectious pneumonitis	16	3	0	0	0	0
Hyperglycemia	14	5	< 1	2	< 1	0

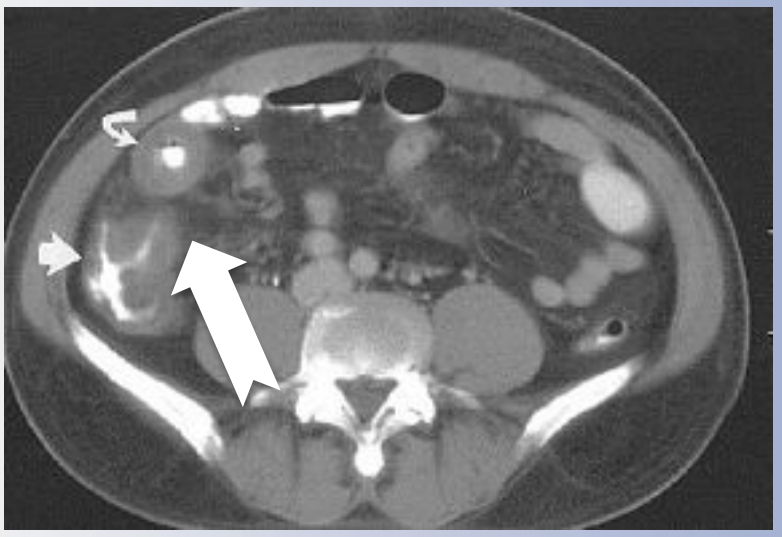
Everolimus exhibits efficacy as a radiosensitizer in a model of non-small cell lung cancer

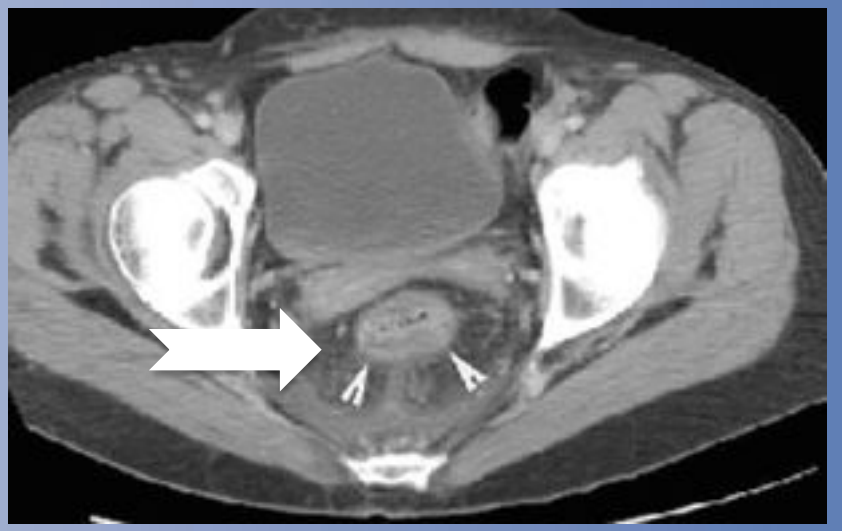
HELENA J. MAUCERI[1], HAROLD G. SUTTON[1], THOMAS E. DARGA[1], MASHA KOCHERGINSKY[2], JOEL KOCHANSKI[3], RALPH R. WEICHSELBAUM[1,5] and EVERETT E. VOKES[4,5]



ONCOLOGY REPORTS 27: 1625-1629, 2012

TOTAL RECALL OF RADIOTHERAPY WITH MTOR INHIBITORS: A NOVEL AND POTENTIALLY FREQUENT SIDE EFFECT? *Bourgier C, Ann Oncol 2011*

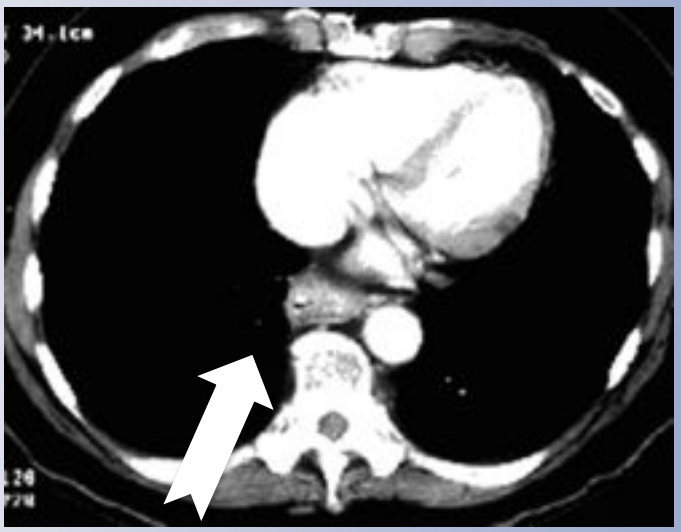


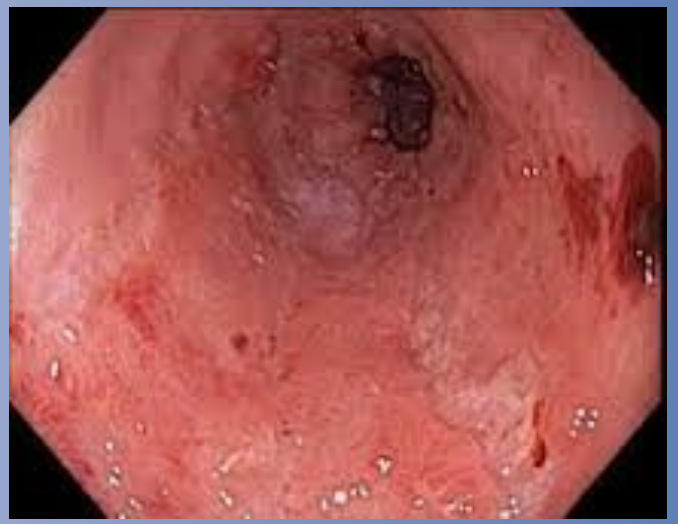


COLITIS :
Ovarian Cancer and phase I trial mTor

PROCTITIS:
Prostate Cancer and then pancreatic cancer

Radiation-Induced Esophagitis exacerbated by Everolimus





ESOPHAGITIS:
Breast Cancer Vertebral M+:
RT D12 (30Gy/10 fx)

Miura, Case Rep Oncol 2013; 6:320-324

Clinical Investigation: Head and Neck Cancer

A Phase 1 Study of Everolimus + Weekly Cisplatin + Intensity Modulated Radiation Therapy in Head-and-Neck Cancer

Fury M, Int J Radiation Oncol Biol Phys, Vol. 87, No. 3, pp. 479e486, 2013

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Central Nervous System Cancer

RTOG 0913: A Phase 1 Study of Daily Everolimus (RAD001) in Combination With Radiation Therapy and Temozolomide in Patients With Newly Diagnosed Glioblastoma

Prakash Chinnaiyan, Int J Radiation Oncol Biol Phys, Vol. 86, No. 5, pp. 880e884, 2013

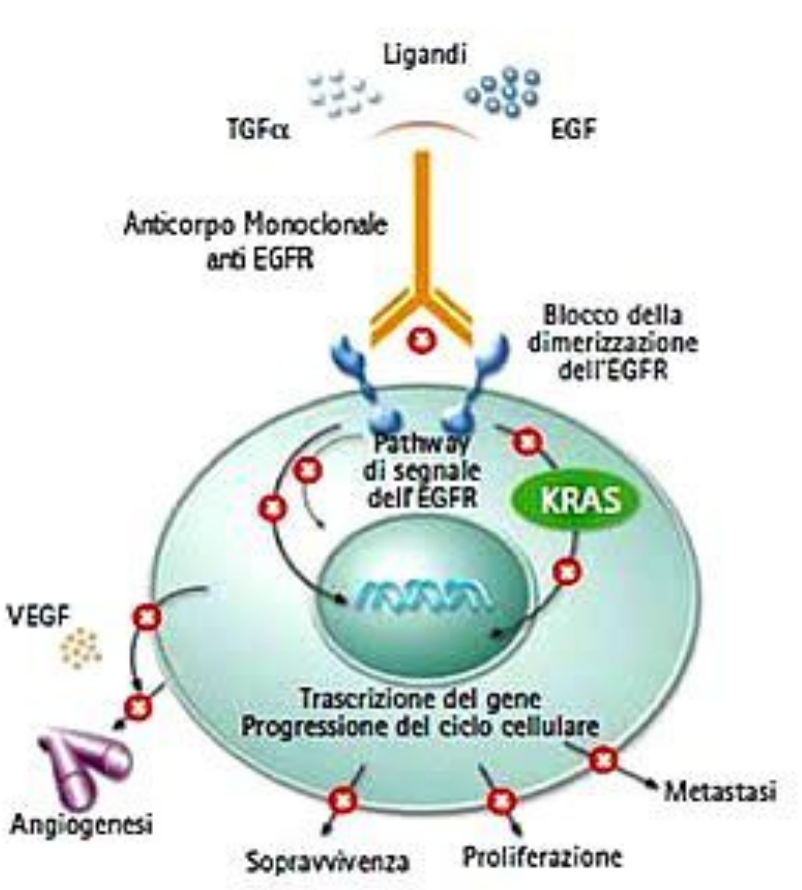
International Journal of Radiation Oncology biology • physics

www.redjournal.org

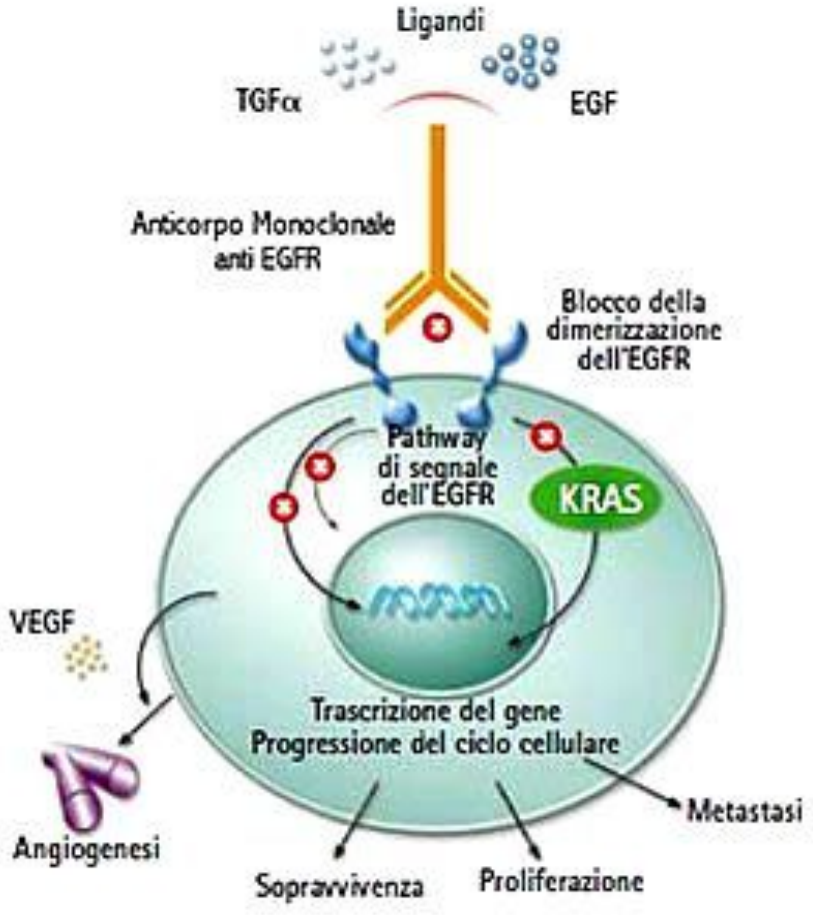
RACCOMANDAZIONE:

Periodo di 4 settimane dall'eventuale trattamento RT prima di iniziare Everolimus, con le eccezioni per le lesioni litiche a rischio di frattura per le quali erano sufficienti 2 sett.

KRAS NEL TUMORE DEL COLON METASTATICO
MUTAZIONE DI RESISTENZA

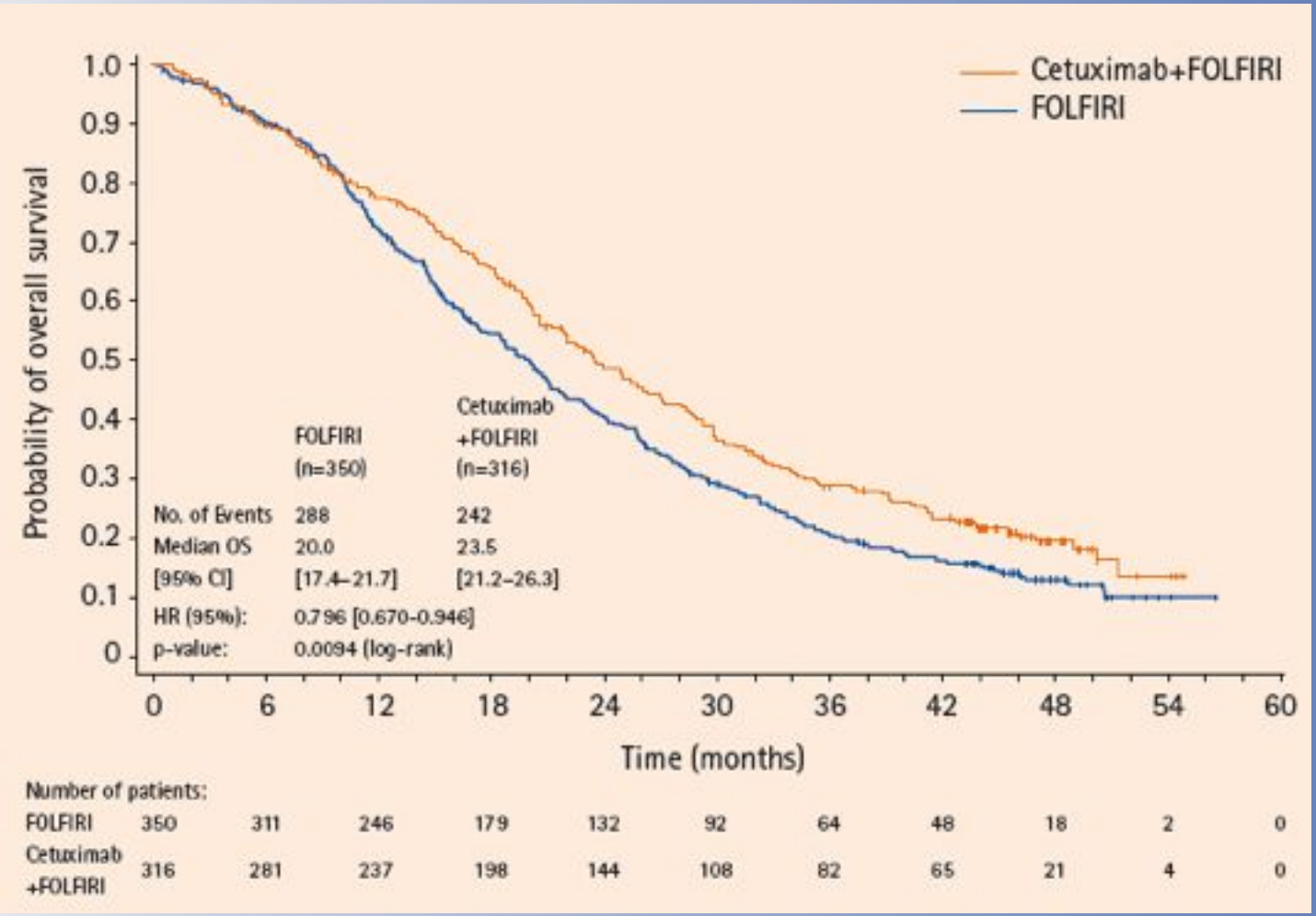


Gene KRAS normale o 'wild type'



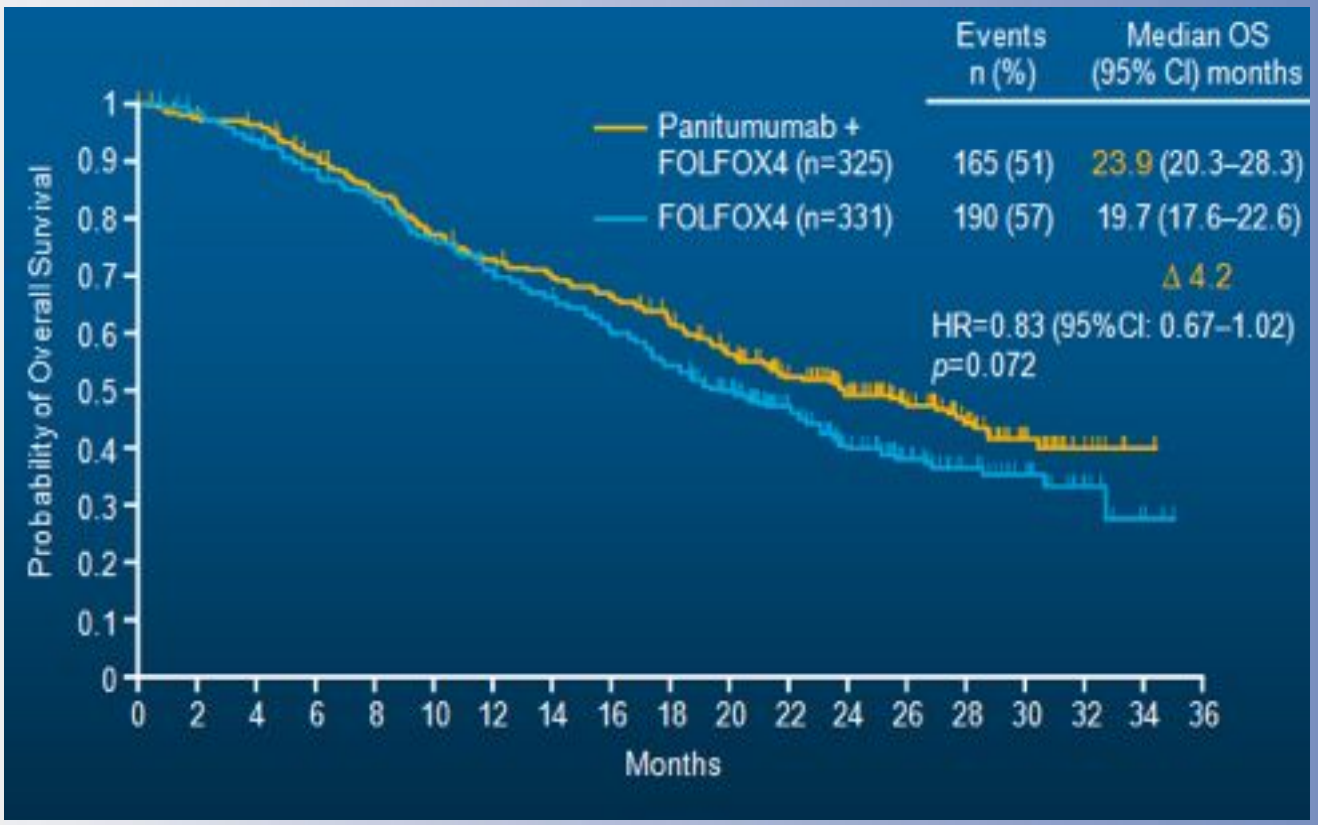
Gene KRAS mutato

Overall survival in KRAS WILD TYPE patients



Van Cutsem E, et al. ECCO/ESMO Congress 2009; Abstract No: 6077

PRIME: OS in KRAS WILD TYPE patients



Douillard JY, et al. J Clin Oncol 2010; 28:4697-705.

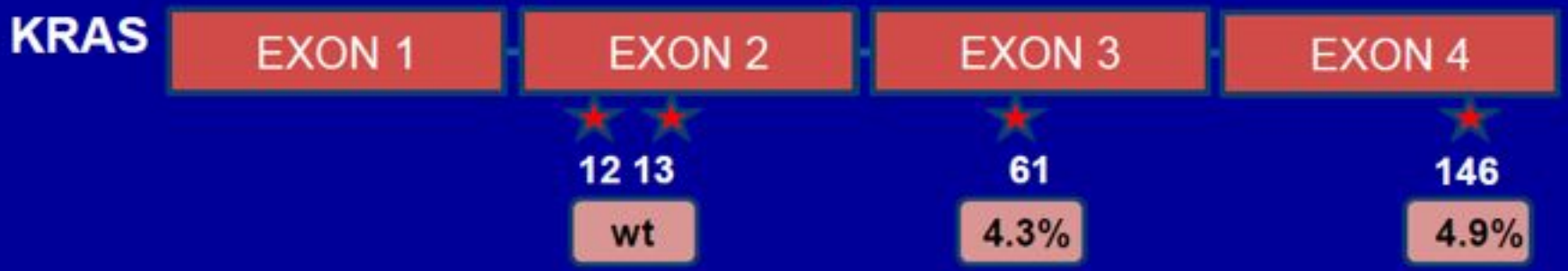
FINAL RESULTS FOR PRIME TRIAL

Median overall survival (OS) for WT KRAS mCRC 23.9 vs 19.7 months

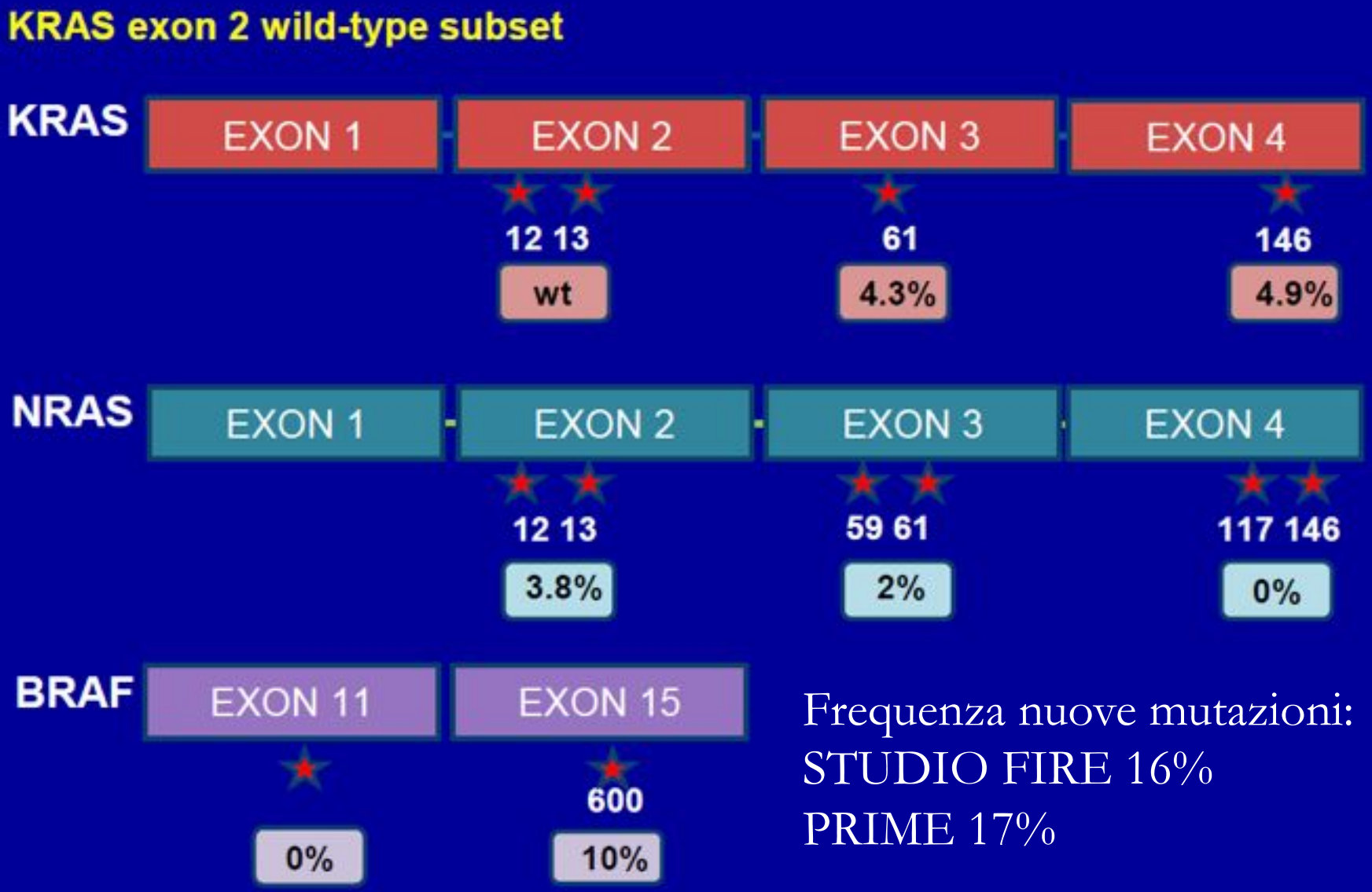
Ann Oncol. 2014 Jul;25(7):1346-55

Tested Mutations

KRAS exon 2 wild-type subset



Tested Mutations



Frequenza nuove mutazioni:
STUDIO FIRE 16%
PRIME 17%

Evaluation of OS

PFS	FOLFIRI + Cetuximab months	95%-CI	FOLFIRI + Bevacizumab months	95%-CI	Hazard ratio	p
KRAS exon 2 WT ITT population (N= 592)	28.7	24.0 – 36.6	25.0	22.7 – 27.6	0.77 (0.62 – 0.96)	0.017
RAS WT (N= 342)	33.1	24.5 – 39.4	25.6	22.7 – 28.6	0.70 (0.53 – 0.92)	0.011

3.7 months

7.5 months

KRAS MUTATION PROFILE differences between rectosigmoid localized adenocarcinomas and colon adenocarcinomas.

	Colon, N (%)
Total case	49 (100.0)
KRAS wild type	34 (69.4)
KRAS mutant	15 (30.6)

Baskin Y, J Gastrointest Oncol. 2014 Aug;5(4):265-9.

KRAS mutation does not predict the efficacy of neo-adjuvant chemoradiotherapy in rectal cancer: A SYSTEMATIC REVIEW AND META-ANALYSIS.

696 patients KRAS MUTATION 33%

KRAS Mutated vs Wild-Type	*pCR*	*Downstaging*	*Cancer Mortality*
ODD RATIO	0.78	0.84	1.23
CI	0.42-1.42	0.33-2.16	0.60-2.53
pvalue	0.418	0.728	0.555

CONCLUSIONS:

Based on these data, the presence of KRAS mutation does not affect tumor down-staging or cancer specific survival following neo-adjuvant CRT and surgery for rectal cancer.

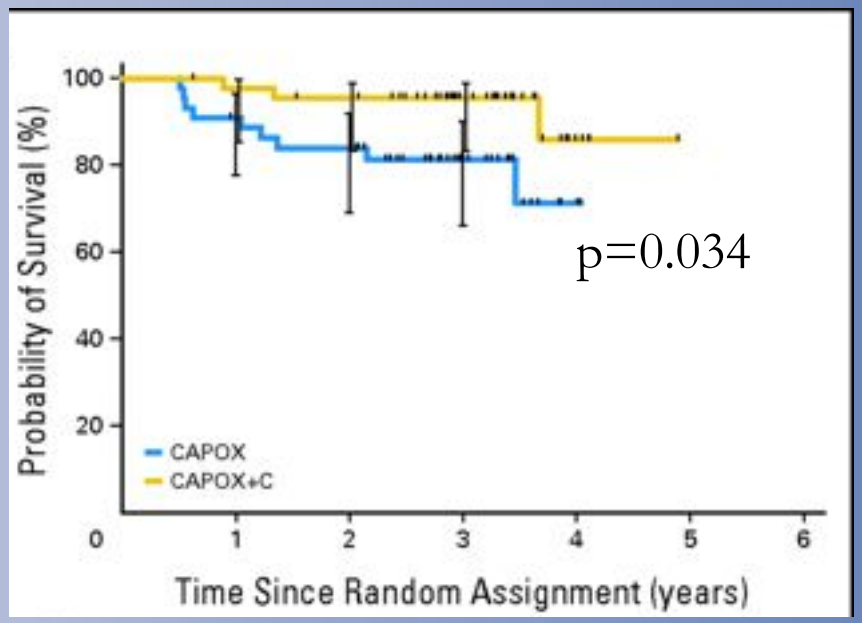
Clancy C, Surg Oncol. 2013 Jun;22(2):105-11.

Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy WITH OR WITHOUT CETUXIMAB followed by total mesorectal excision in patients with high-risk rectal cancer

EXPERT-C Trial

COMPLETE RESPONSE (9% *v* 11%, respectively; $p = 1.0$; OR 1.22)

90/149 KRAS/BRAF WILD-TYPE PATIENTS



Dewdney, J Clin Oncol. 2012 May 10;30(14):1620-7.

RAS mutations and cetuximab in locally advanced rectal cancer: results of the EXPERT-C trial.

PAN-RAS WILD TYPE *78/149 pts (52%)*	*pCR (%)*	*5y PFS (%)*	*5y OS (%)*
CAPOX	7.5	67.5	70
CAPOX-Cetuximab	15.8	75.5	83.8
	p=0.31	*p=0.20*	*p=0.20*

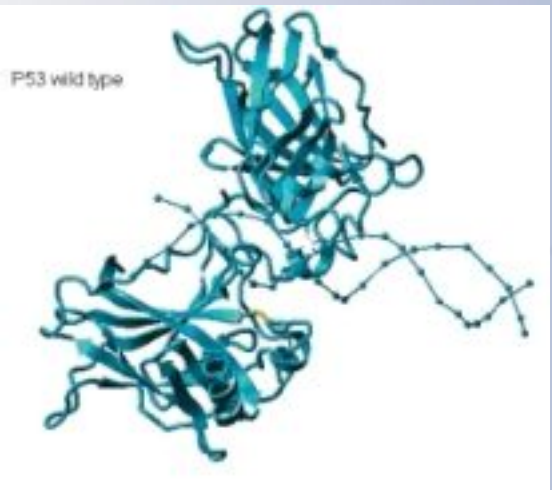
CONCLUSIONS:

Given the small sample size, no definitive conclusions on the effect of additional RAS mutations on cetuximab treatment in this setting can be drawn and further investigation of RAS in larger studies is warranted.

SCLAFANI, Eur J Cancer. 2014 May;50(8):1430-6

TP53 mutational status and cetuximab benefit in rectal cancer: 5-year results of the EXPERT-C trial.

INDEPENDENT PREDICTIVE BIOMARKER FOR CETUXIMAB BENEFIT.



	5y PFS	5y OS
Cetuximab	89.3	92.7
No-Cetux	65 p=0.02	67.5 p=0.02

Sclafani F, J Natl Cancer Inst. 2014 Jun 23;106(7).

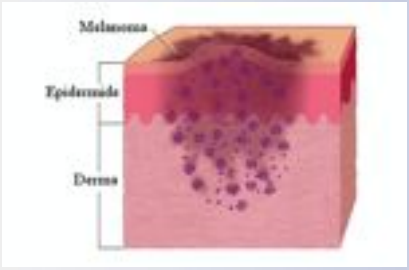
DOMANDE PRATICHE 1/2

Nella neoplasia polmonare gli EGFR-TKI ed il Crizotinib hanno dimostrato risultati correlati all'esistenza di mutazioni attivanti EGFR o traslocazione di ALK. Tossicità aumentata in associazione alla RT?

NO

Popolazione mutata più radiosensibile

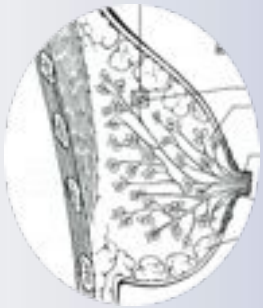
Gli inibitori di BRAF (Vemurafenib, Dabrafenib), aumentano la tossicità in associazione con la RT?



SI, documentata la tossicità cutanea e non ben conosciuta quella extracutanea

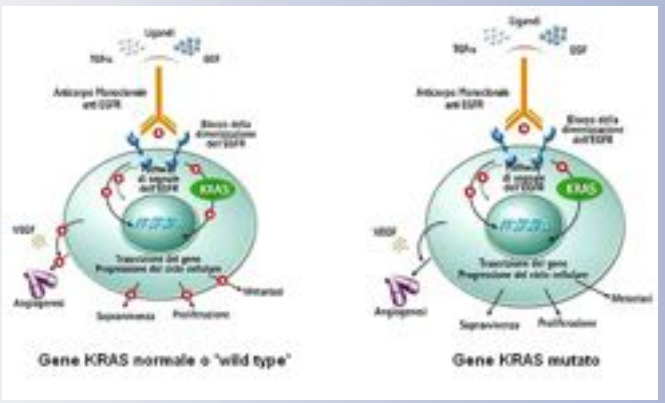
DOMANDE PRATICHE 2/2

L'Everolimus e la Radioterapia possono essere associati?



Attenzione alla prossimità dell'apparato gastroenterico!!!

La mutazione di RAS è una mutazione di sensibilizzazione o di resistenza?



E' una mutazione di resistenza agli anticorpi monoclonali. Non tossicità aumentata ma risultati sono ancora poco chiari


NIKE DI
SAMOTRACIA
"…colpita da un vento impetuoso che tuttavia ne fa risaltare le forme…"
Luke Willer
Grazie dell'Attenzione!!!!!!!