Personalised Healthcare Strategies in R&D

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Fitting treatments to patients

Delivering better, safer and more efficacious treatments

Personalised Healthcare means:

- To better understand disease diversity or subtypes
- To identify the differences between patients
- To identify the best drug targets
- To improve the quality and efficiency of R&D results
- To provide biomarkers and diagnostic tests

Optimising patient care

Making development of new tests and drugs more efficient

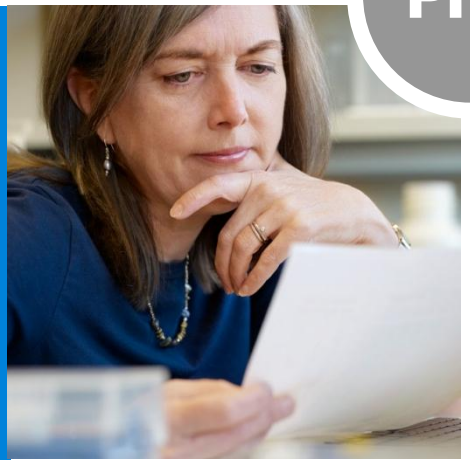
PHC benefits all stakeholders in healthcare

Patients
→ Best treatment

Physicians & Providers
→ Maximum benefit
→ Minimum toxicity

PHC

Payers & Reimbursers
→ Efficient use of healthcare budgets



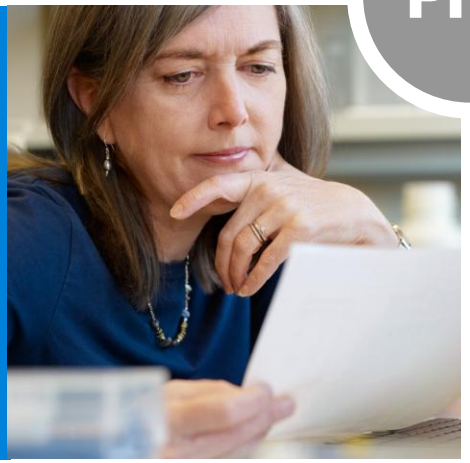
Regulators & Policy Makers
→ Increased efficacy & safety

PHC benefits

Focus on patients and payers

Patients

Payers & Reimbursers



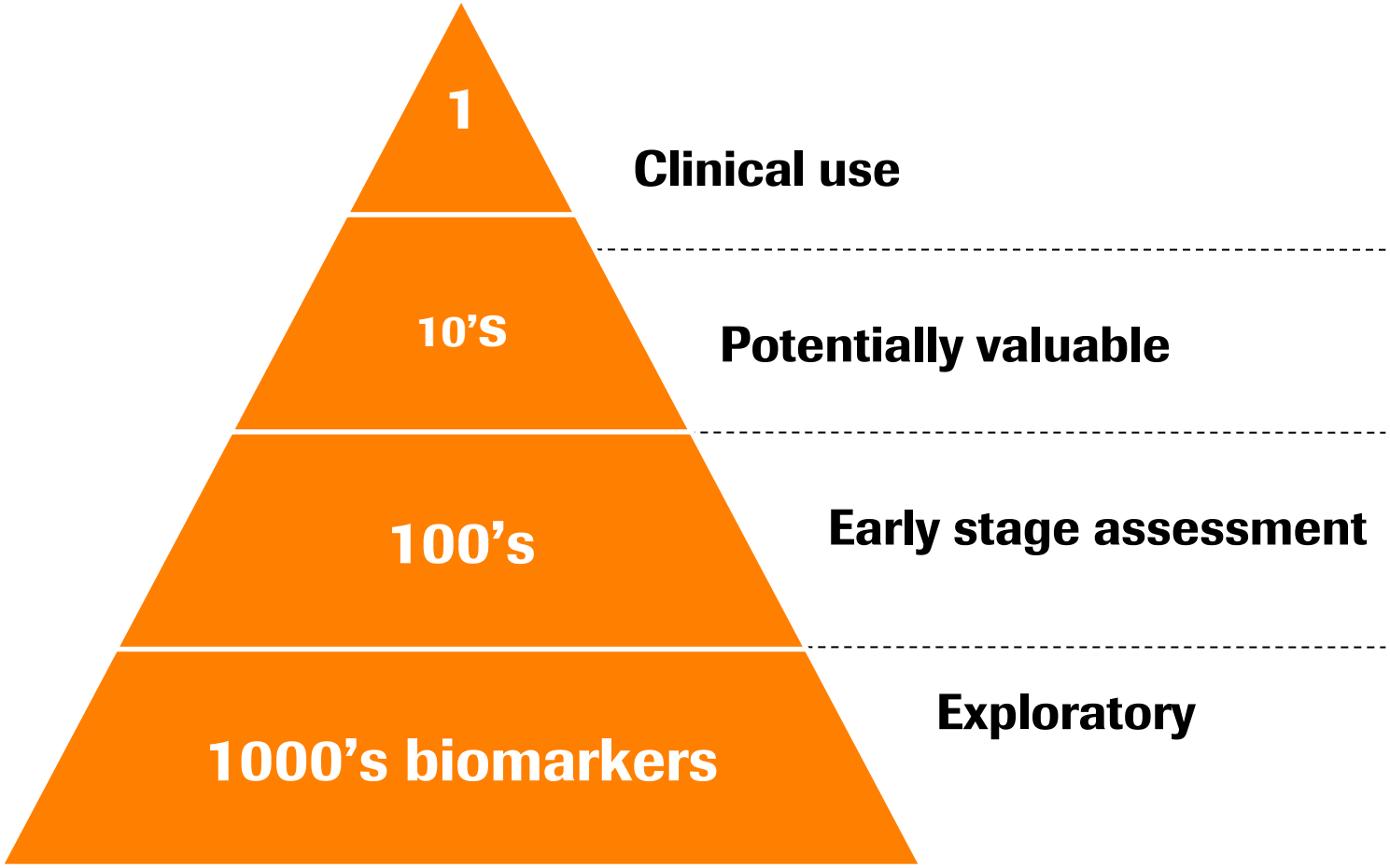
PHC

Benefits can be:

- Better and more predictable clinical outcomes
- Improved quality of life and lifetime gained
- Reduced morbidity
- Fewer unnecessary treatments / side effects and associated costs
- Better compliance due to better results
- Optimized use of resources in healthcare

Complexity of Science

A biomarker might be more difficult to find than a drug

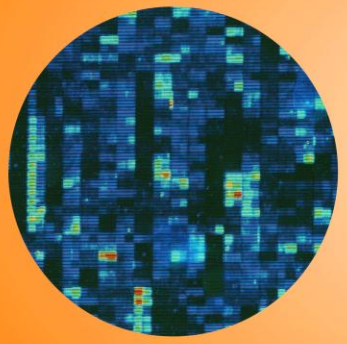


Biomarker = Any biological parameter used as indicator of disease process or drug response

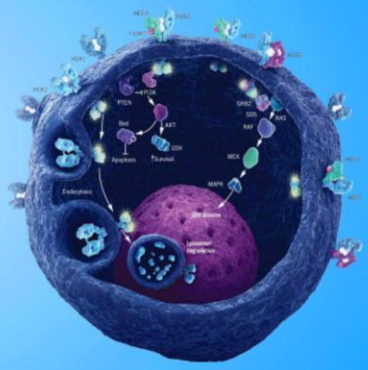
Roche uniquely positioned to drive PHC

Translating excellence in science into effective treatments for patients

Diagnostics



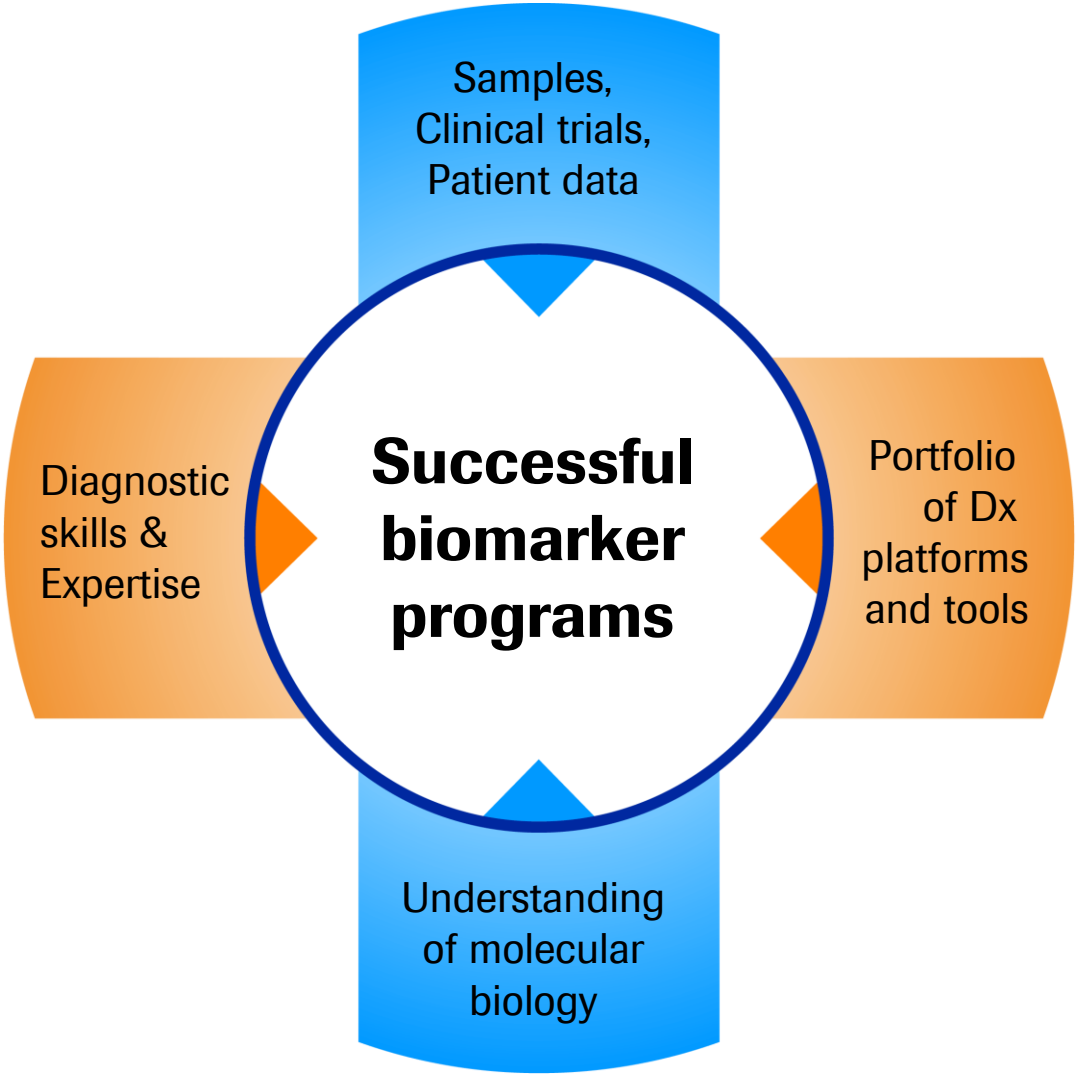
Pharmaceuticals



→ Combine expertise in molecular biology and technologies to benefit patient

Biomarker development – what it takes

A plethora of tools, skills and capabilities



Pharmaceuticals
+
Diagnostics
=
Highly linked information network

Cancer – a Global Challenge
WHO World Cancer Report

7.6 Million People

Will die of cancer in 2011

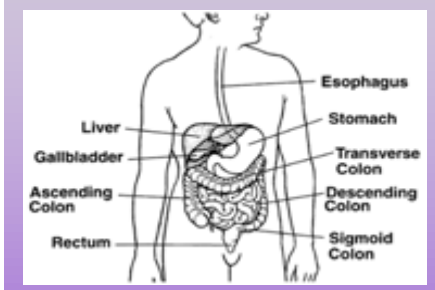
26 Million People

Will be diagnosed with cancer in 2030

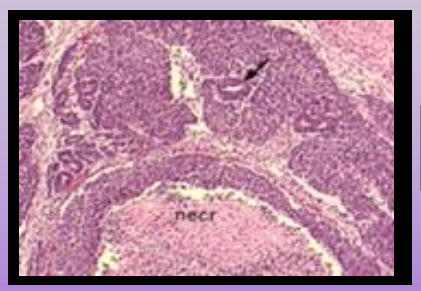
Over 800 drugs are in development in oncology

Paradigms in Cancer Therapy are changing

Tumor Site



Tumor Histology



Old Paradigm

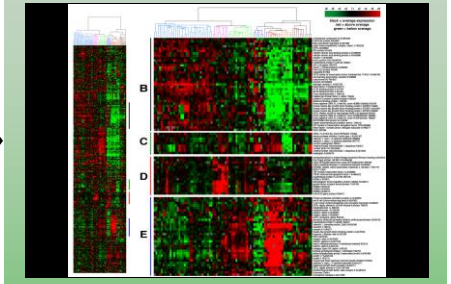
Toxic, non-selective, chemotherapy drugs

Molecular Biology

Targeted Therapies

Wider therapeutic index, derived from molecular biology discoveries of the ’80s

Molecular Profile



Future Paradigm

Integration of molecular diagnostics with targeted therapies for integrated cancer care

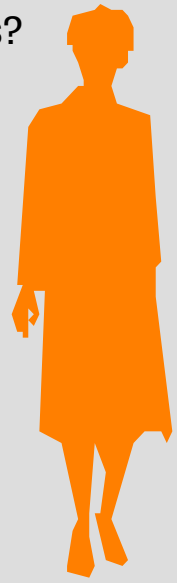
PHC in metastatic melanoma:
Targeted treatment for patients with BRAF mutations

What is my prognosis?

How much time

do I still have?

Am I BRAF-positive‘?



Metastatic melanoma

- About 160,000 new cases diagnosed worldwide each year
- Incidence expected to double within next 10 years
- No significant therapeutic advances in this field for 30 years
- High medical need, but no effective therapy available today

BRAF kinase – attractive drug target

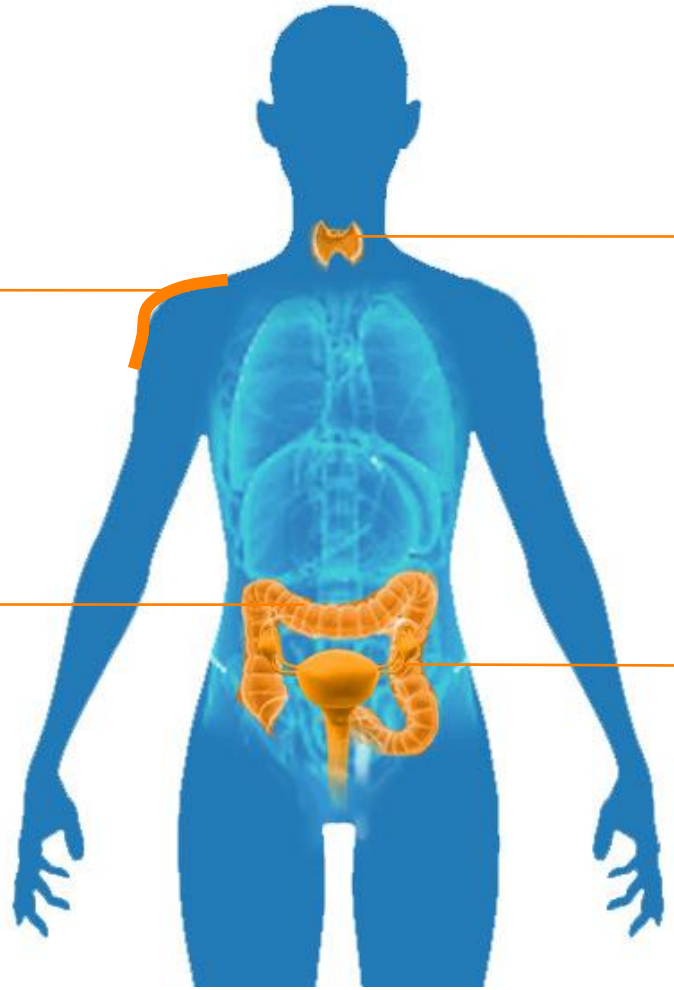
Cancer with mutant B-RAF gene has poor prognosis

Metastatic Melanoma

BRAF > 50 %

Metastatic Colon

BRAF 7–8%



Metastatic Thyroid

BRAF
- Papillary 60–70 %
- Anaplastic 83 %

Metastatic Serous Low Grade Ovarian

BRAF ~70 %

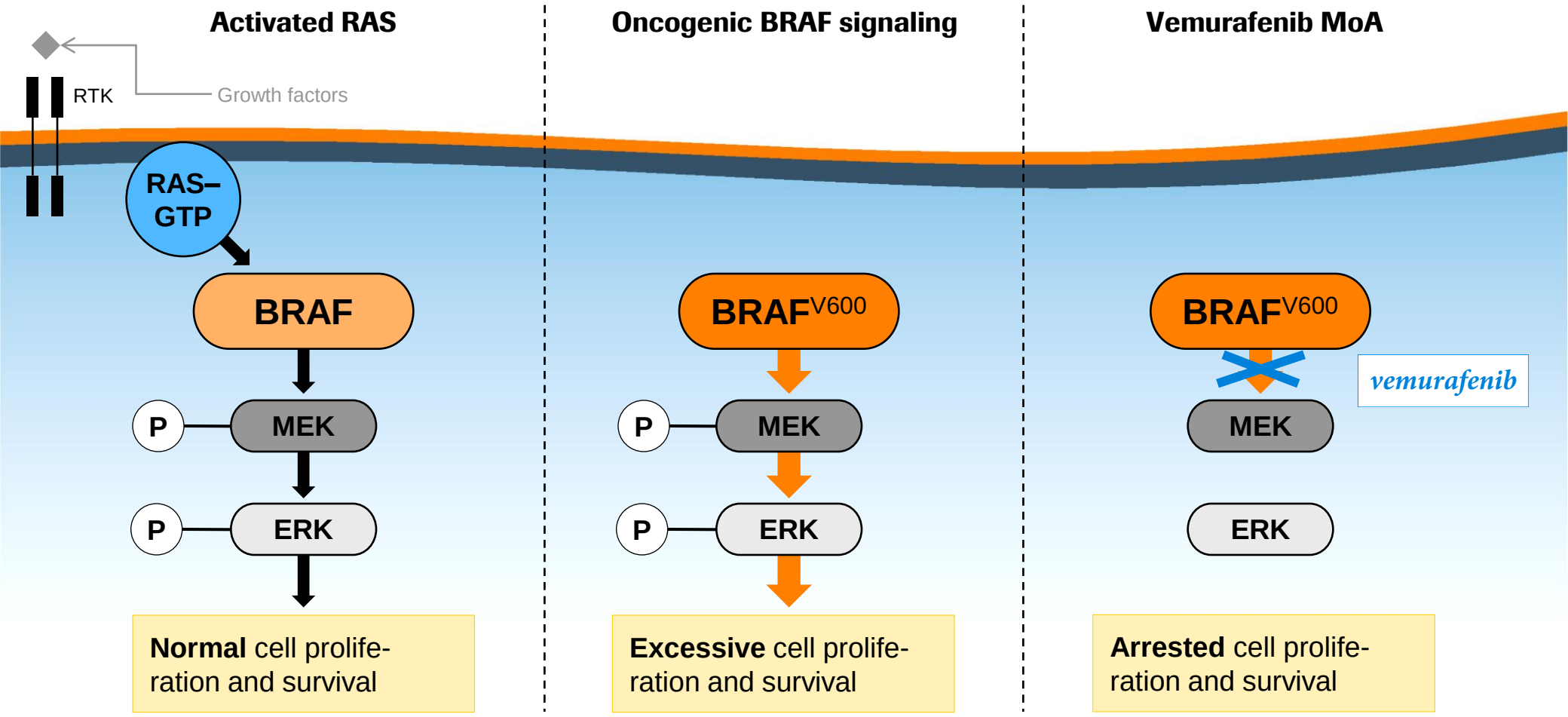
~90% activating B-Raf mutations are V600E

Vemurafenib – targeting the Ras–Raf pathway

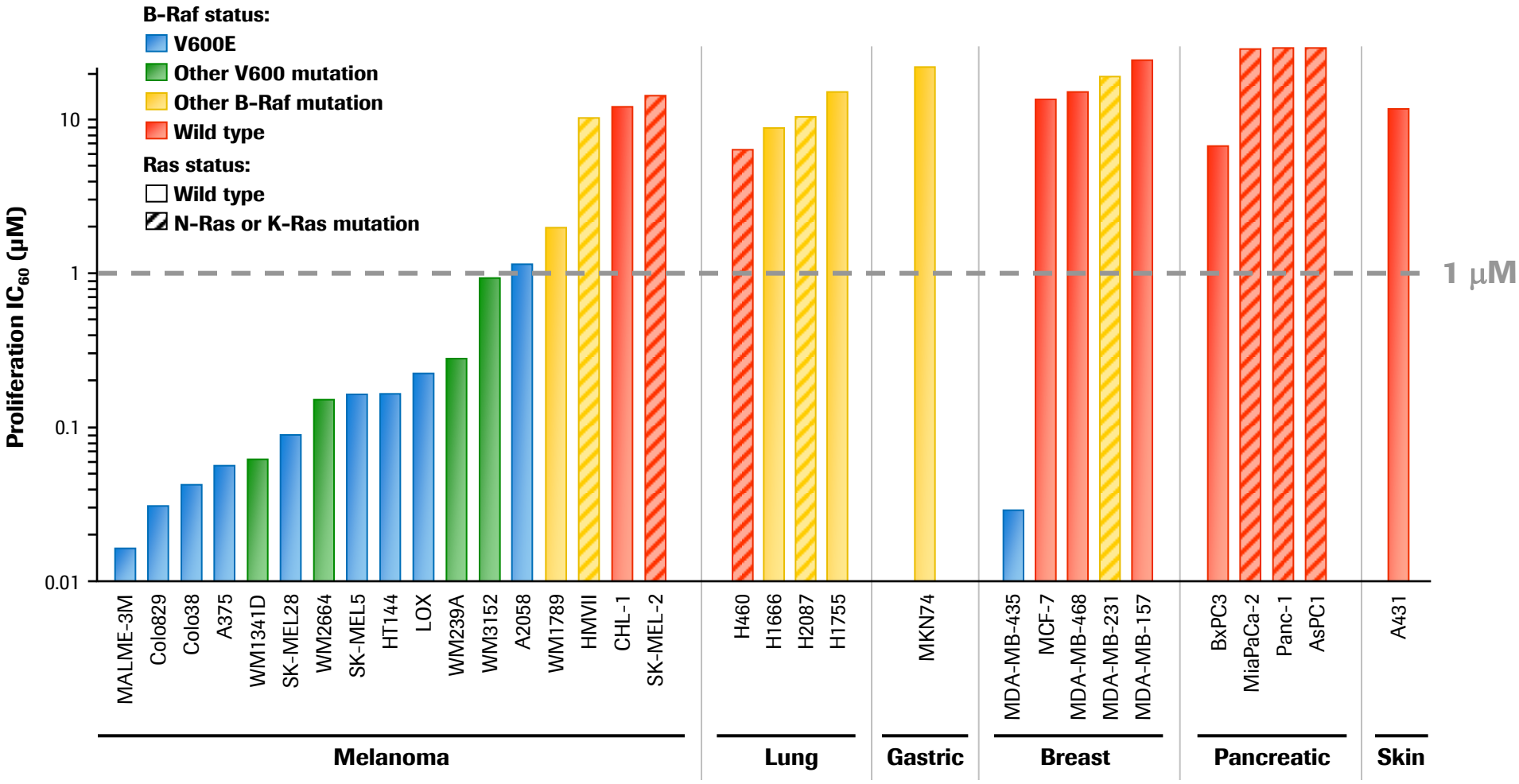
A highly selective BRAF inhibitor

Oncogenic BRAF Inhibitor vemurafenib

Mode of action



Vemurafenib Selectively Inhibits Proliferation of Tumor Cell Lines Containing $BRaf^{V600}$ Mutations



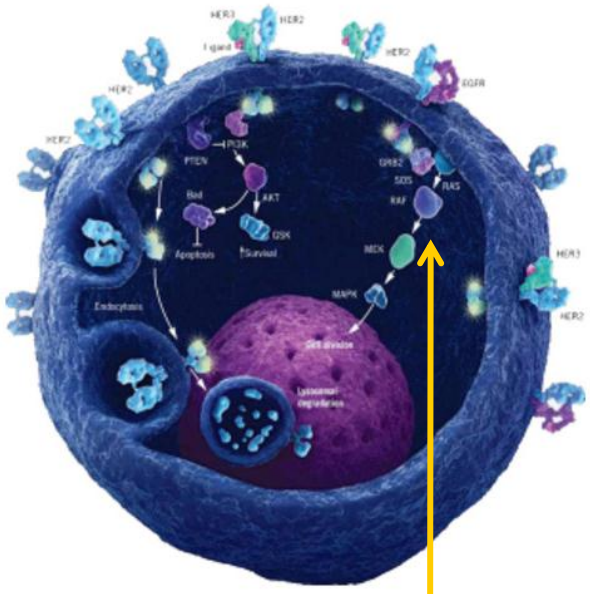
Yang et al, Canc. Res., Jul 2010

Mutation in BRAF kinase

Co-development of test and drug in oncology

Oncogenic BRAF inhibitor vemurafenib

Combined test & drug development



Single mutation in BRAF gene ($BRAF^{V600}$) causes activation in absence of normal growth factor stimulation

- Identifies patients whose tumor DNA carries BRAF V600 mutation
- Increases feasibility of drug clinical development and probability of success
- IVD timelines aligned with vemurafenib accelerated development plan
  → joint launch

Personalised Healthcare for Targeted Treatment of V600E-positive Tumors

Roche

Oncologist

Surgeon

4

B-Raf V600E Positive

5

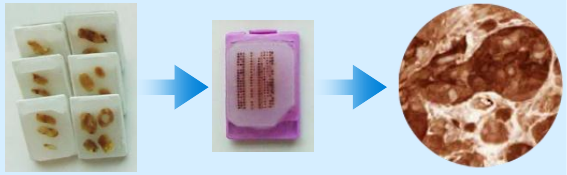
Targeted *vemurafenib* **Therapy**

1 Tumor

V600E status returned to Oncologist

3

Pathologist



Tumor block FF/FFPET

Sections

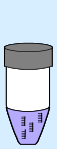
H&E staining

2

Tissue sections

Molecular Testing Center

Genomic DNA Isolation



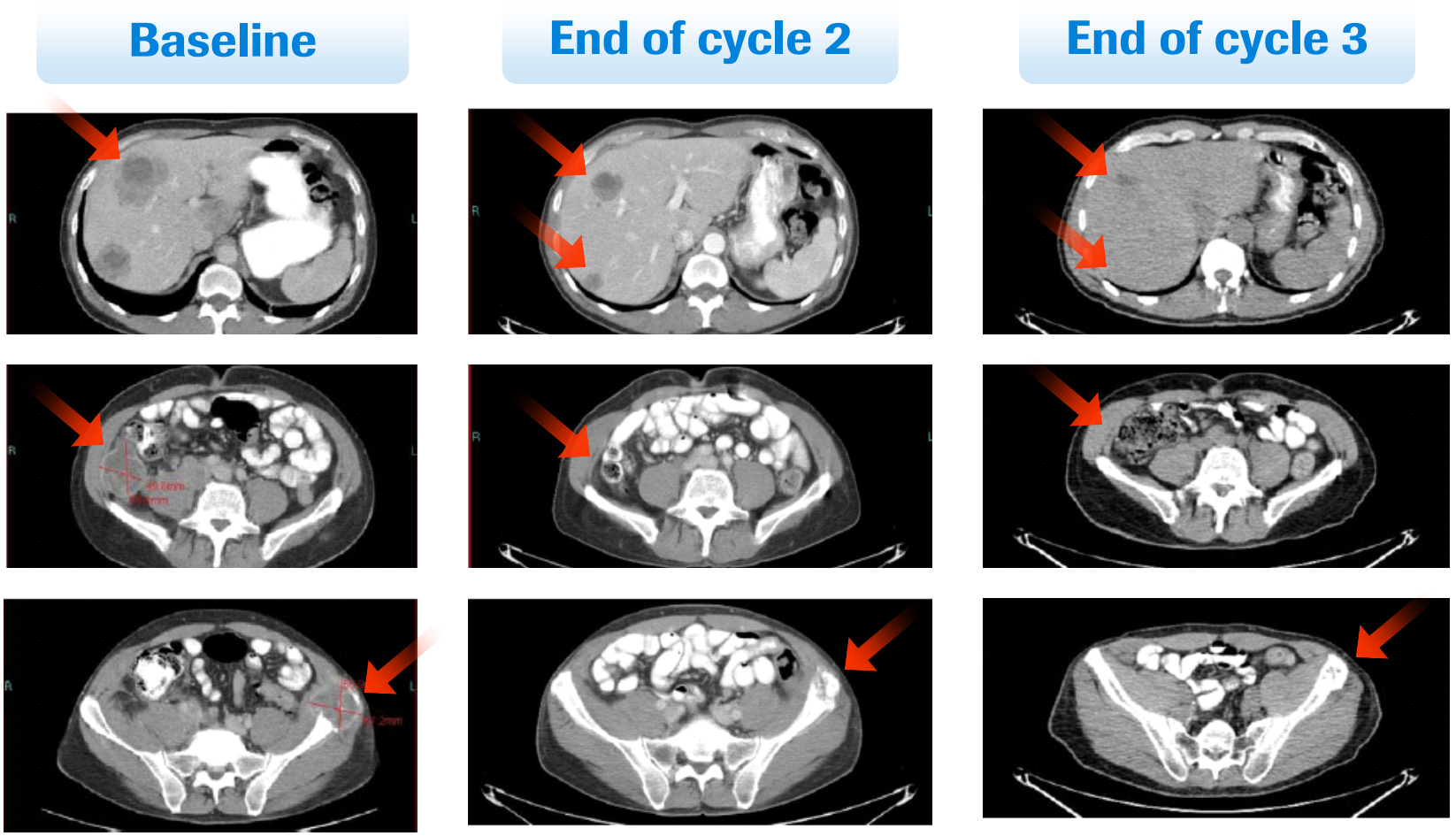
DNA Quantification

cobas® 4800 v2.0

PCR Setup

Vemurafenib – Early evidence of activity in BRaf^{V600E} patients

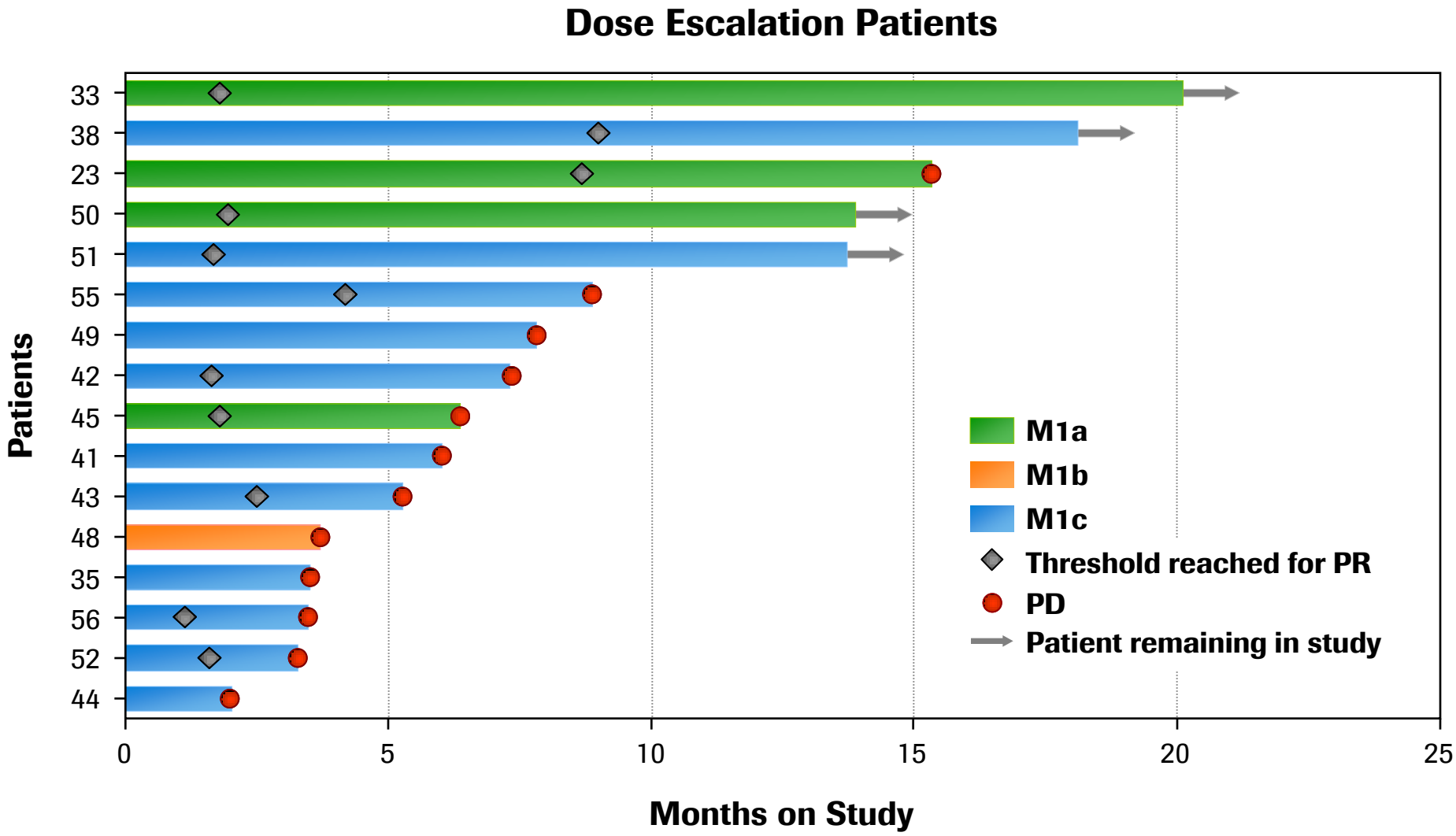
85% Partial Response seen at 720 mg BID



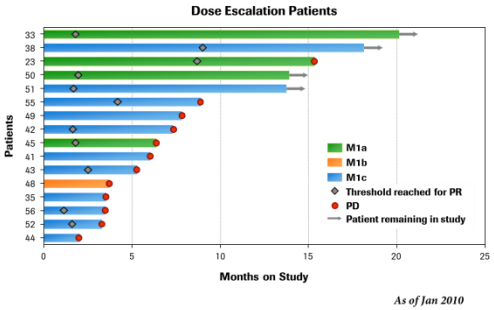
Substantial tumor regression in visceral organs

Vemurafenib Treatment of BRaf^{V600E} Melanoma Patients

Frequent rapid objective responses



January 2010



Drive Towards the PHC Paradigm

Integrated and Iterative Development

Biomarkers

Pharmacodynamic
Predictive
Safety
Mechanistic

Companion
Diagnostic

New Target

New Drug Candidate

Exploratory Human Trials

Surrogate Endpoints

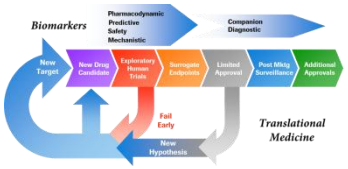
Limited Approval

Post Mktg Surveillance

Additional Approvals

New Hypothesis

Translational Medicine



Vemurafenib Melanoma Biomarker Sample Plan – *Paired biopsies & biopsies at progression*

Roche

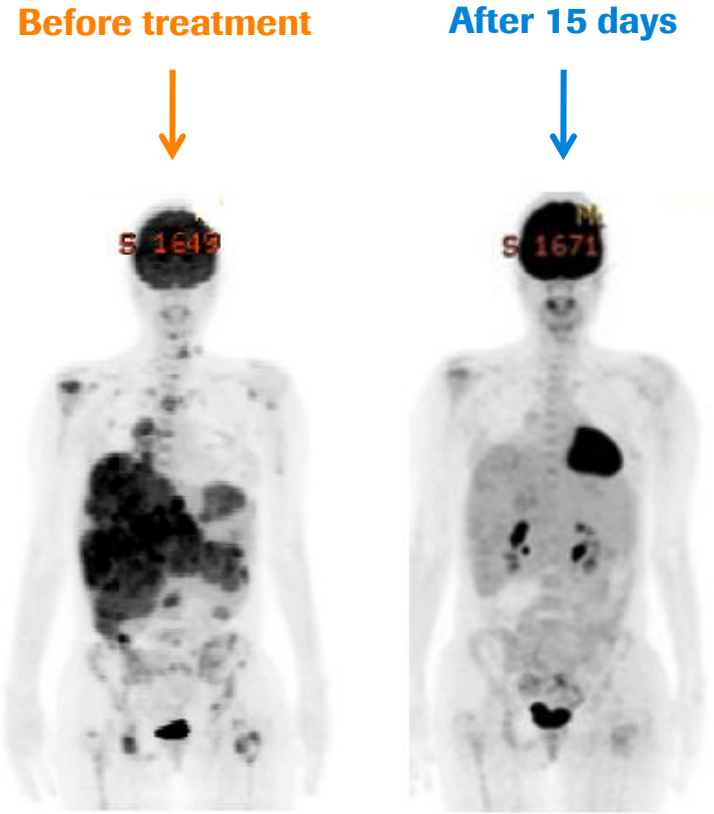
Biomarker Categories	Melanoma Extension Cohort
Patient selection biomarker	B-Raf mutation analysis of FFPE tissue
Clinical and safety biomarkers	AE, SAE, ECG, blood chemistry, etc. (includes LDH for melanoma, CEA for CRC)
Imaging biomarkers	Tumor size, FDG-PET, CT*
Tumor PD biomarkers	pERK, pMEK, Cyclin D1, p27
Plasma PD biomarkers	IL-8
Biomarkers of tumor activity	Ki-67, Tunel
Monitoring biomarkers	MIA, S100b
Exploratory biomarkers (plasma)	VEGF-A, sVEGFR1, sVEGFR2, Ang-2, PLGF, E-selectin IL-6, IL-10, IL-21, TNFalpha
Resistance biomarkers	Sanger sequencing and Sequenom: mutations in MEK1, B-Raf (beyond V600E), PI3KCA, H/N/KRAS, KIT etc. IHC: PTEN, pAKT, Cyclin D1, C-RAF FISH: Cyclin D1 Gene expression profiling (hypothesis generating)

PHC in metastatic melanoma – survival benefit shown

Clinical studies demonstrate encouraging results

Oncogenic BRAF inhibitor vemurafenib

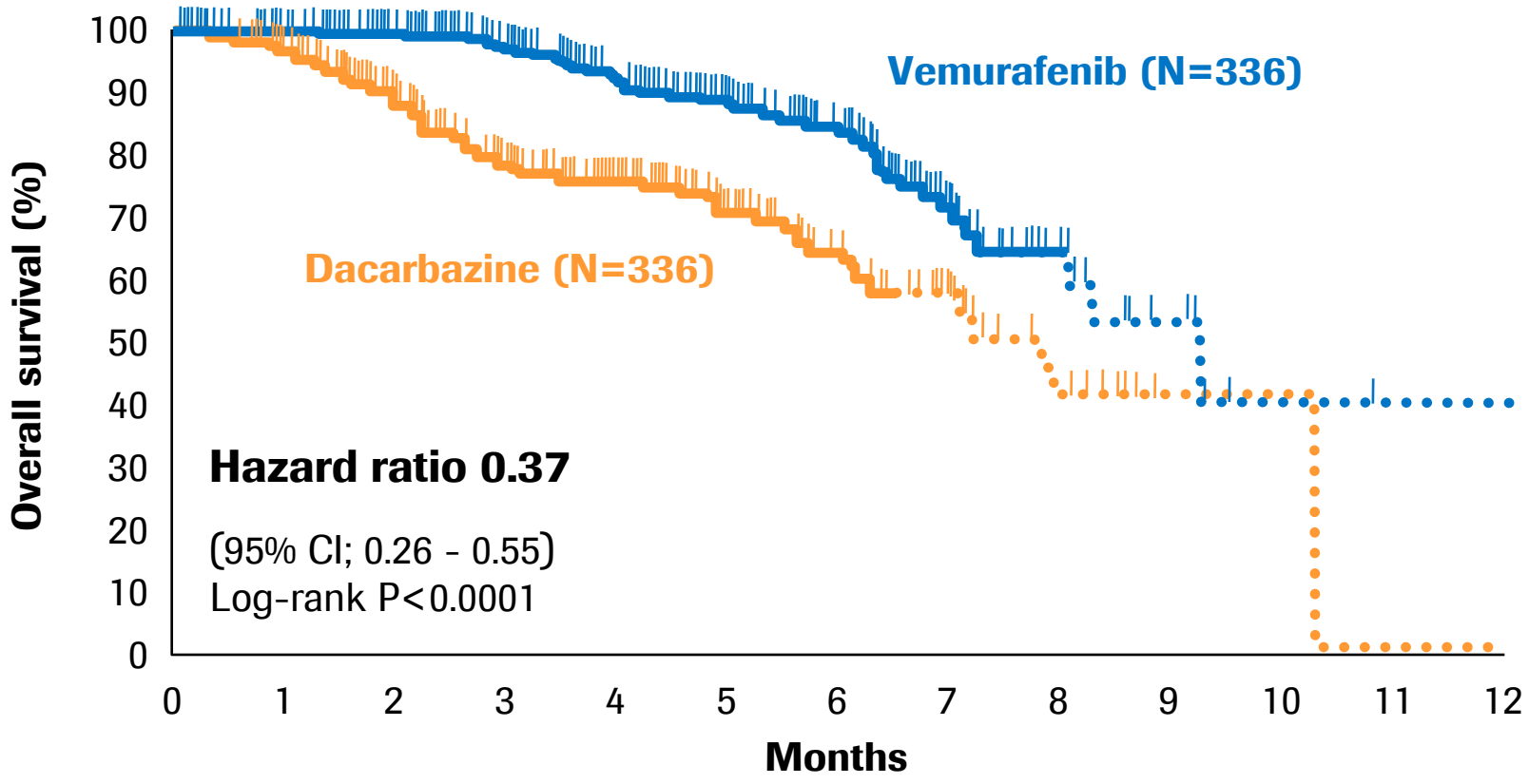
Study results



Results from Vemurafenib clinical studies in BRAF-positive metastatic melanoma patients:

- Tumors shrank by 30 % or more for at least two consecutive scans in 52% of the patients (BRIM 2)
- On average, patients lived at least six months without their disease growing or spreading (median progression-free survival or PFS) (BRIM 2)
- Data from interim analysis showed that BRIM 3 met its co-primary endpoints of overall survival (OS) and progression-free survival (PFS), demonstrating significant patient benefit in this population
- Based on these results, patients on the dacarbazine arm of BRIM 3 will now be allowed to crossover to receive vemurafenib

Zelboraf (BRIM3 Study): Overall survival

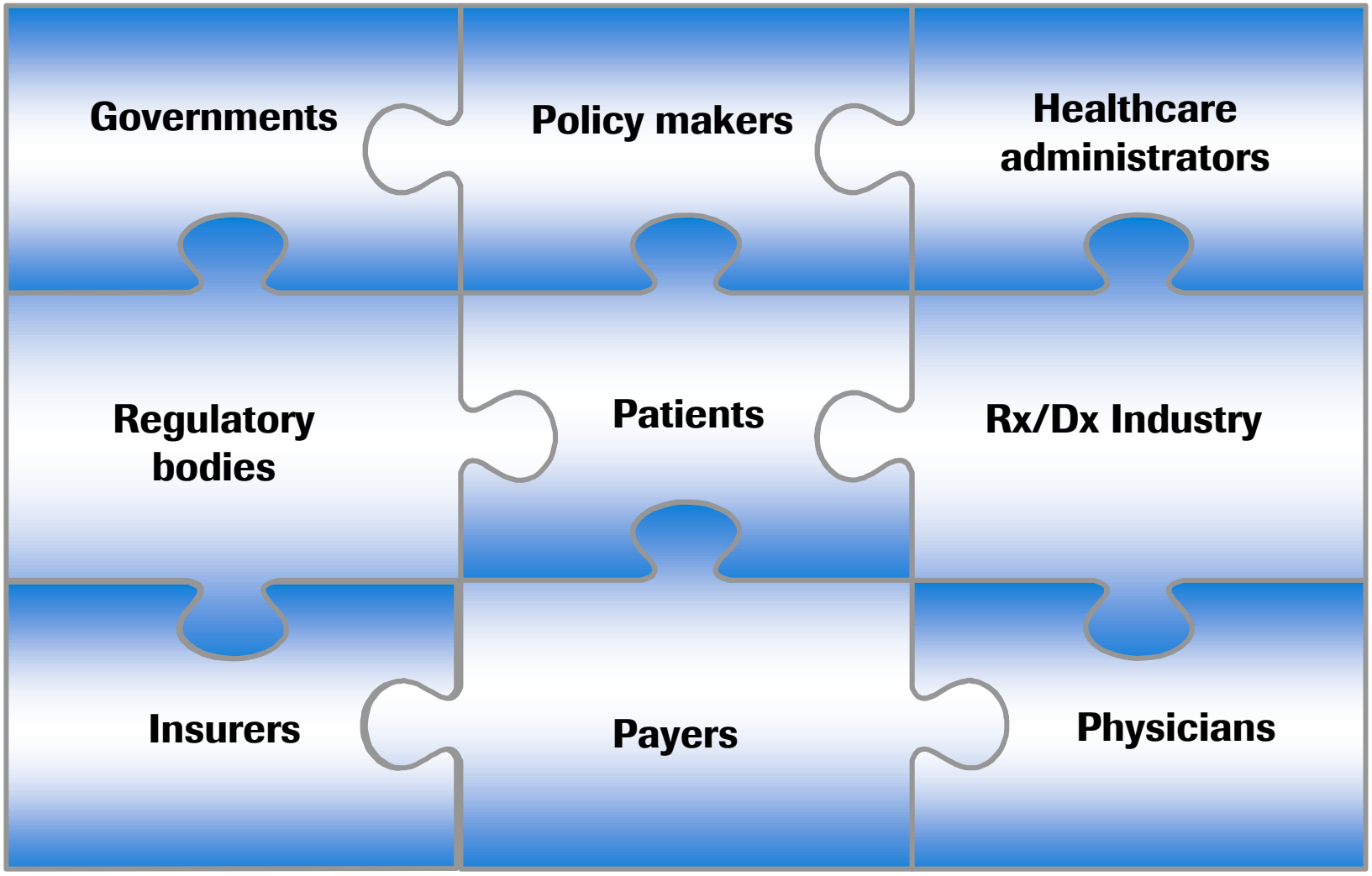


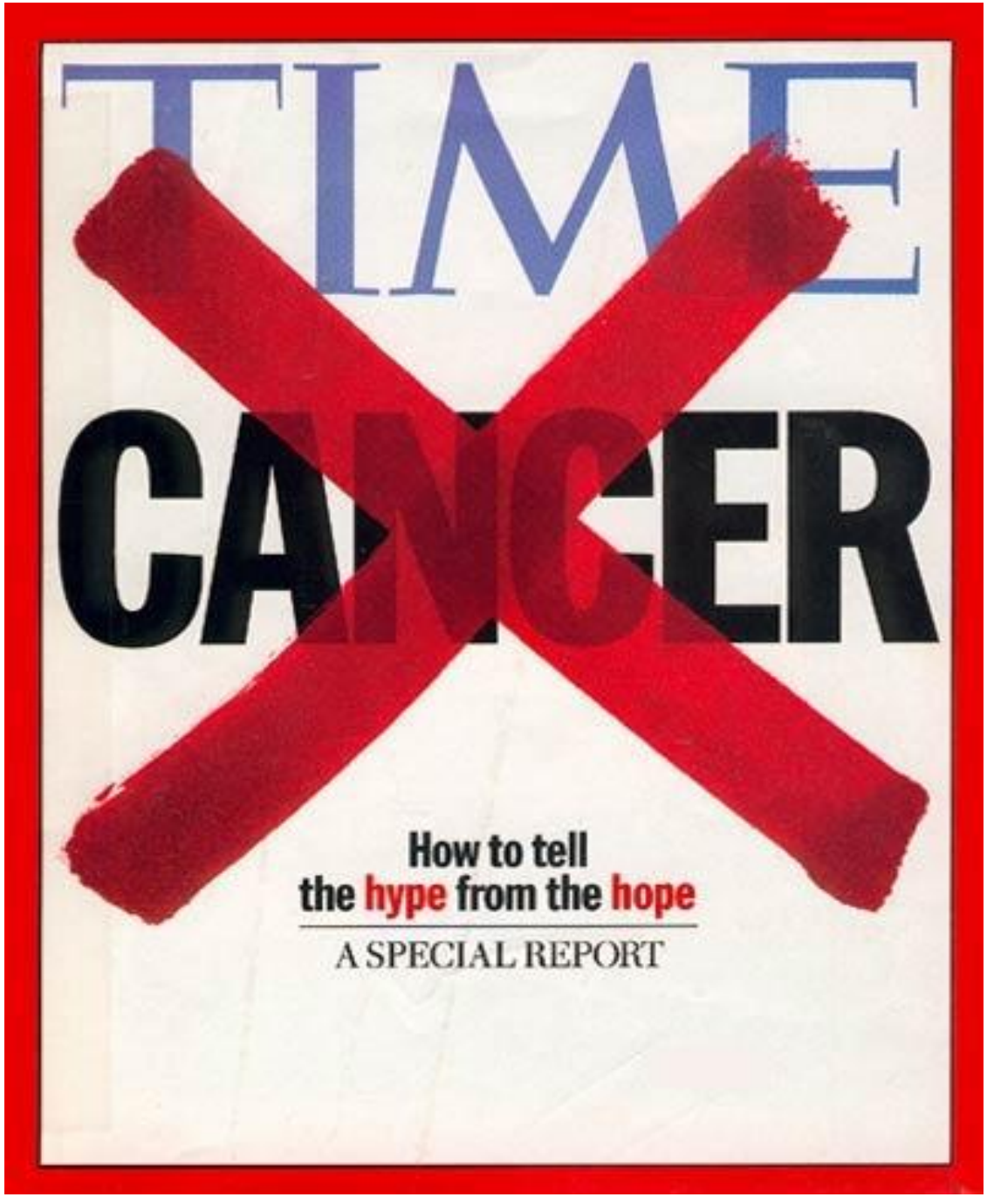
No. of patients in follow up

Dacarbazine	336	283	192	137	98	64	39	20	9	1	1
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1

N Engl J Med 2011;364:2507-16.

Personalized Healthcare and Fighting Cancer – a joint responsibility




TIME
CANCER
How to tell
the hype from the hope
A SPECIAL REPORT

Summary: Personalised Healthcare (PHC)

PHC is reality and here to stay

Patient benefits from PHC are evident today

PHC is a core element of successful R&D strategies

Summary

Roche is pioneering Personalised Healthcare

Developing the targeted therapies of tomorrow

We Innovate Healthcare