Ieri, oggi, domani in early clinical trials

Gustave Roussy experience

DITEP
Drug Development Department

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Disclosure

- I am a medical oncologist and a Phase 1 investigator, ¨raised¨ by Jean-Charles Soria and ¨ perfected¨ (ongoing skill) by Christophe Massard at DITEP (Drug Developement Department)
- Strong believer in Precision medicine programs
- Acquired taste in immunotherapy
- (Star Wars fan… you will understand better later)

- Principal/sub-Investigator of Clinical Trials for Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, Xencor

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Outline

- Changes in the classical drug development paradigm
- Reasons for the current change in Early Clinical Trials :
  - ✓ The advent of precision medicine and molecular targeted agents
  - ✓ Trial enrichment and increased response rates
  - ✓ Immuno-stimulatory antibodies
  - ✓ Open approach of regulators
- Opportunities and challenges related to this new paradigm

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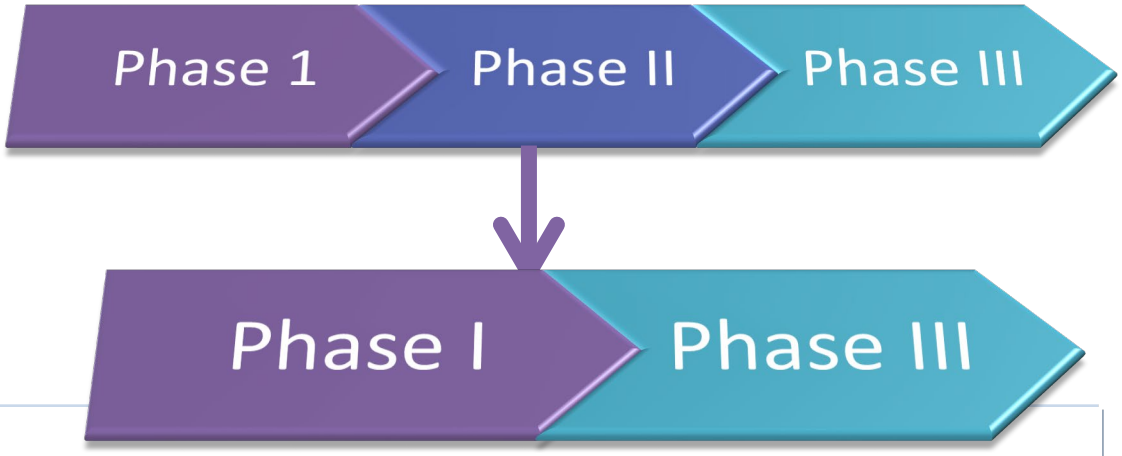
Classical drug development paradigm before 2000

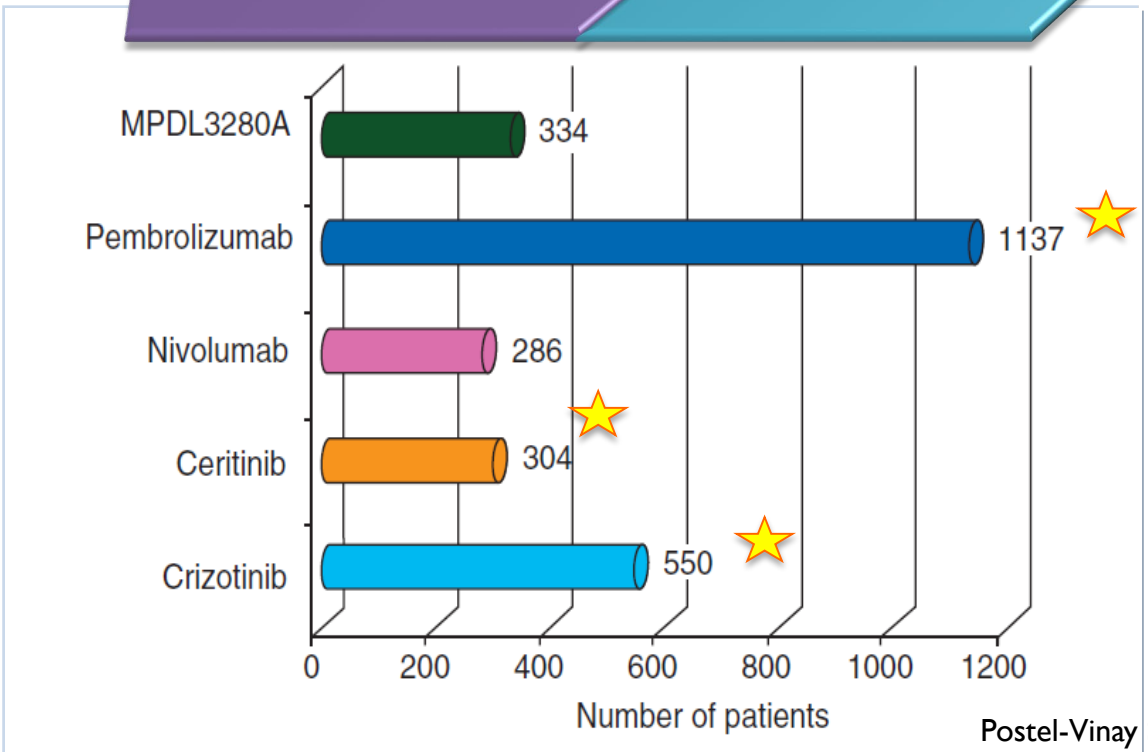
	Phase I	Phase II	Phase III
PURPOSE	Find MTD	Define Activity	Compare with SOC
EMPHASIS	Safety	Activity	Efficacy
ENDPOINT	Toxicity (DLT)	Response (ORR)	Survival (PFS, OS)
N (patients)	20-60	20-200	200-2000
Registration value	Null	Limited	Major

The revolution in drug development is a change in nature and goals of early phases

	Phase I/II	Phase III
PURPOSE	Define MTD and Activity	Compare with SOC
EMPHASIS	Safety & **Activity** & Biomarkers	Efficacy
ENDPOINT	Toxicity & **Response** (all and selected) & Preliminary Survival	Survival (PFS, OS)
N (patients)	100-1000 +	200-2000
Registration value	Real (conditional, breakthrough)	Major (confirmatory)

The new trend in oncology drug development





FDA approval on phase I/II data

Postel-Vinay S et al, Annals of Oncology 2014

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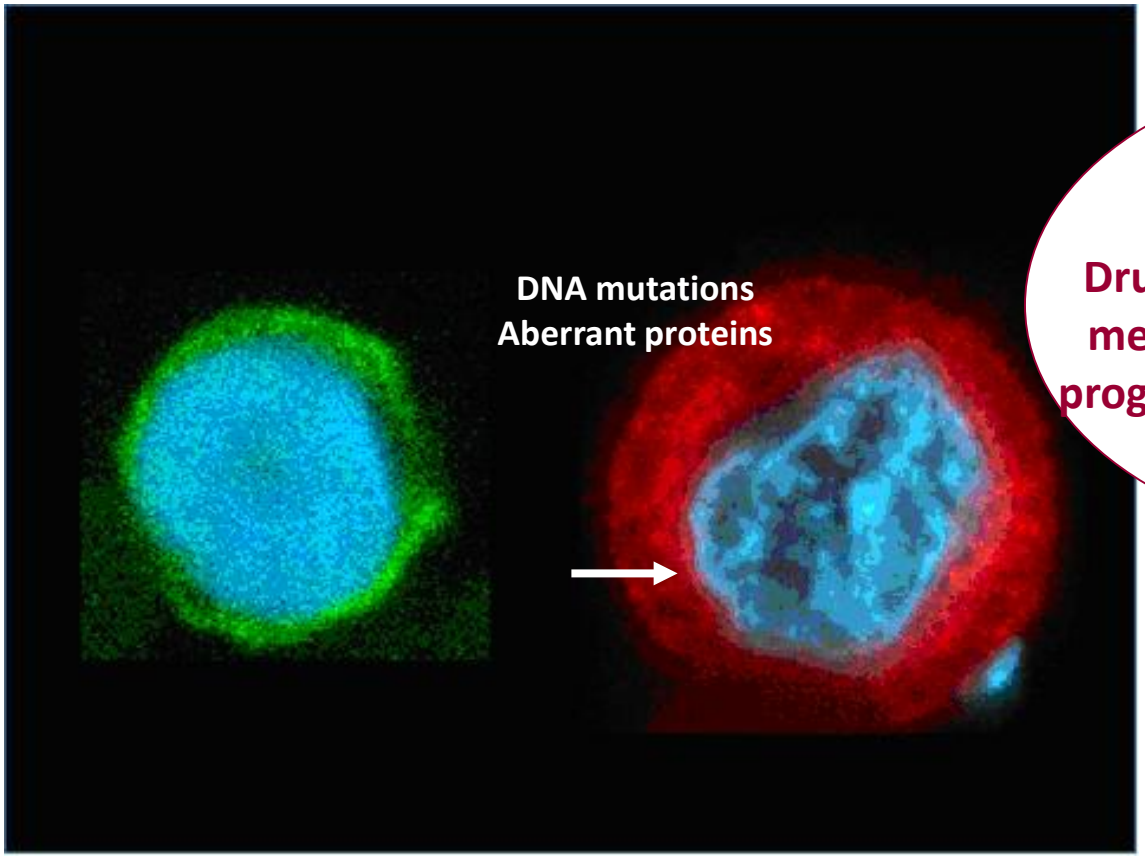
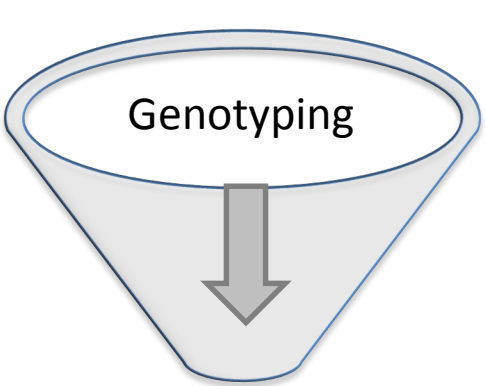
Hypothesis that started it all….



Drugs that target the molecular mechanisms involved in cancer progression can improve outcome

Unselected Phase I population

ORR below 10%

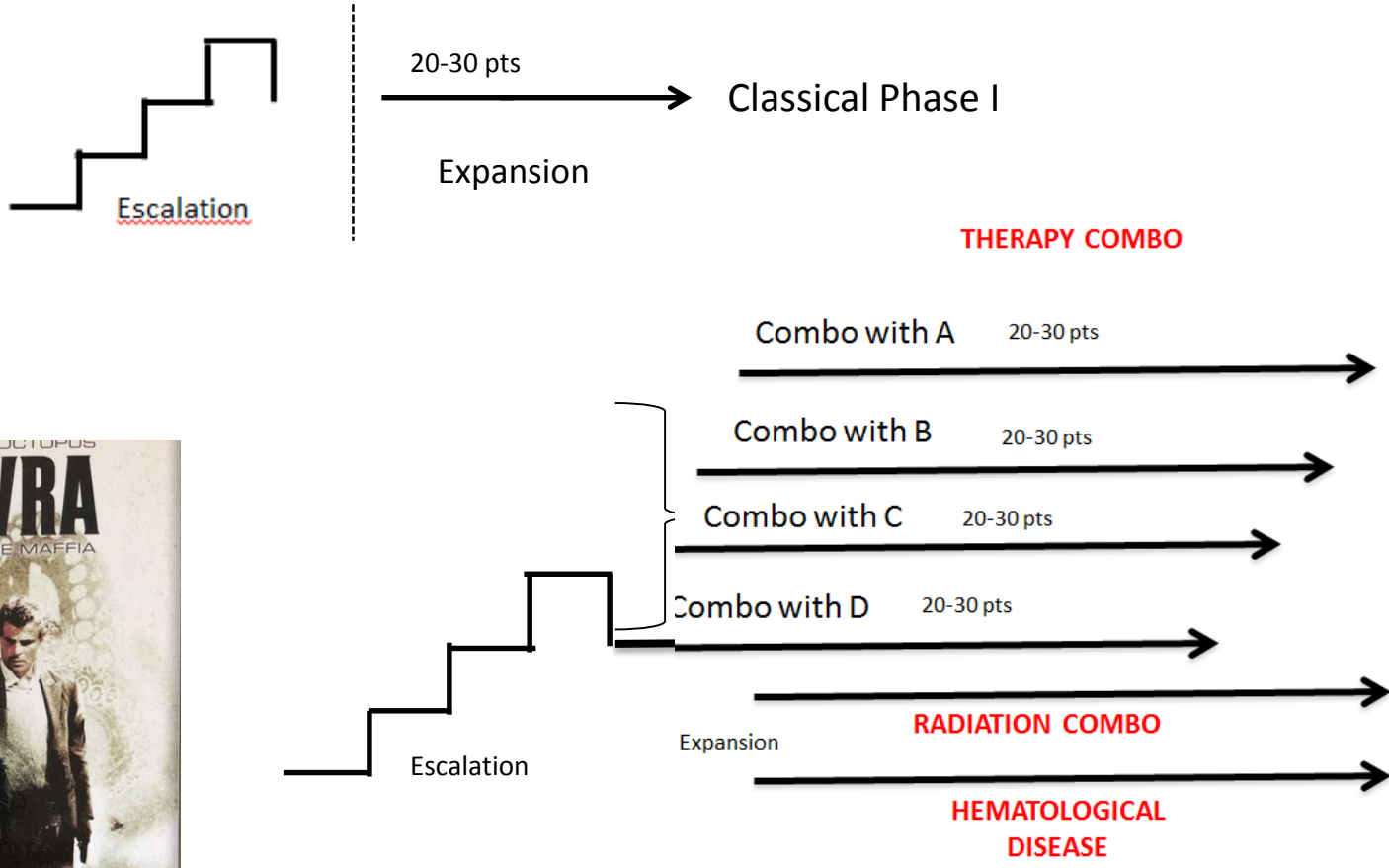


Enriched Phase I population

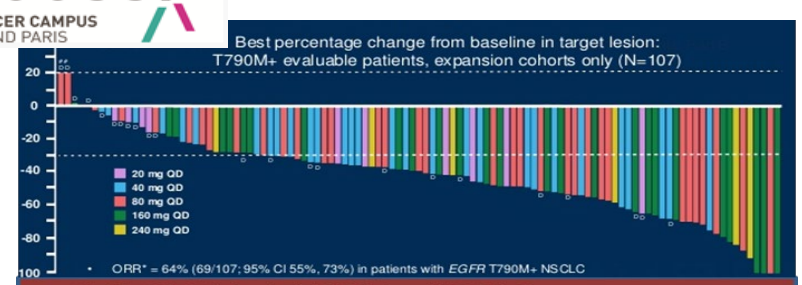
ORR > 30%, and even > 50%

if if true mechanism-based approach
(oncogen de-addiction, synthetic lethality)

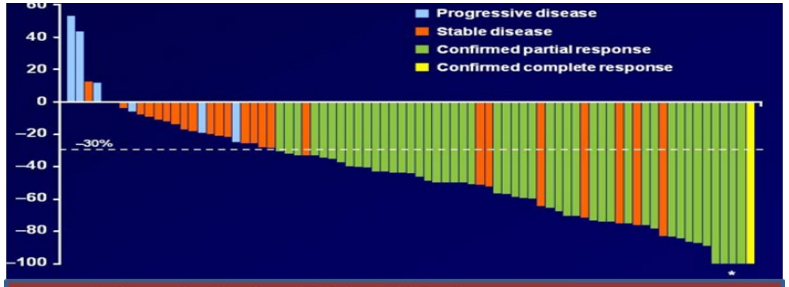
Phase I design modifications



GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

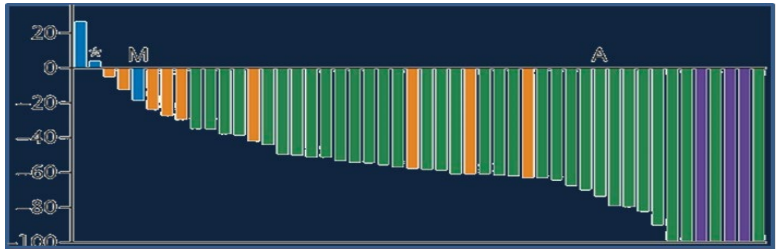


AZD9291 in T790M+ NSCLC. Jänne NEJM2015

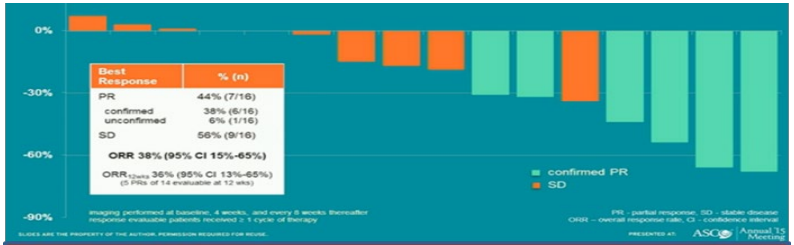


Crizotinib in ALK+ NSCLC. Shaw NEJM 2013

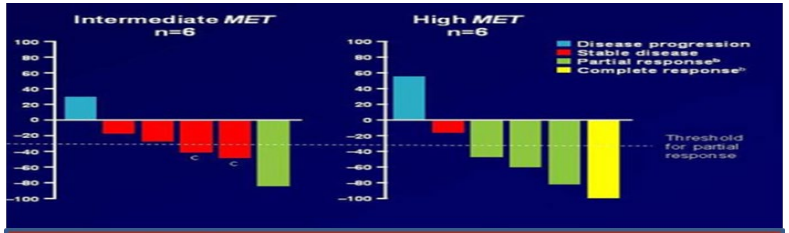
Dabrafenib in BRAF+ NSCLC. Planchard ESMO 2014



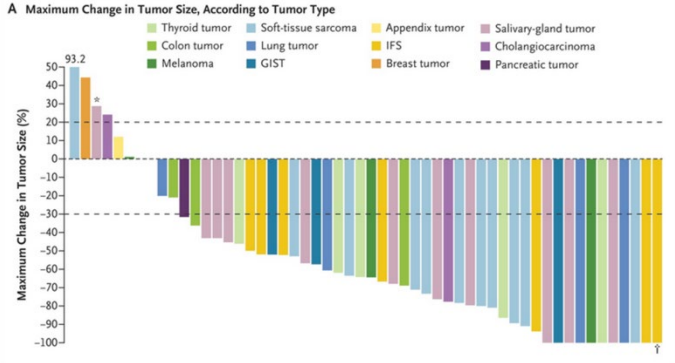
Crizotinib in ROS1+ NSCLC. Shaw NEJM 2014



Cabozantinib in RET+ NSCLC. Drilon ASCO 2015

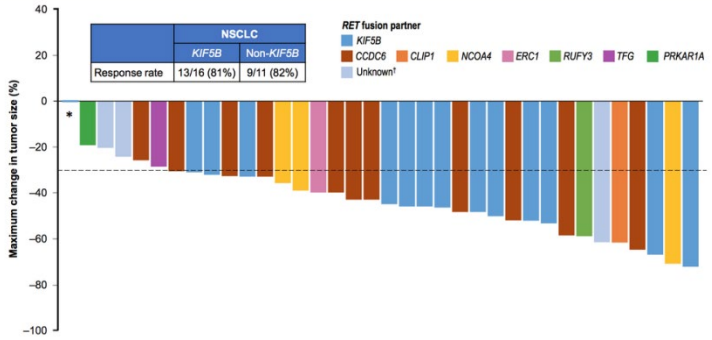


Crizotinib in MET+ NSCLC. Camidge ASCO 2014

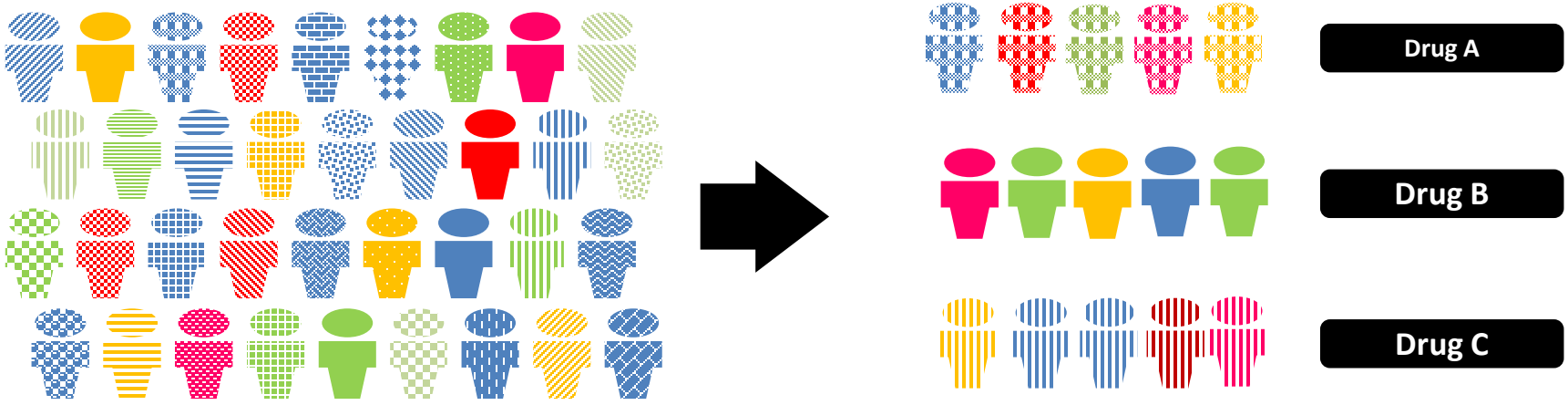


Larotrectinib in TRK Fusion–Positive Cancers

Efficacy of LOXO-292 regardless of *RET* fusion partner



Histology-agnostic, aberration-specific clinical trial design ("basket" of basket trials)



Molecularly profiled patients with different histologies

Histology-independent, aberration-specific clinical trial

Sleijfer S, Bogaerts J, Siu LL, J Clin Oncol 2013

Three cathegories

- **(One drug, several tumor types)**
- **One drug, one molecular alteration, several tumor types**
- **One drug, several molecular alterations, several tumor types**

Importance of Basket Studies

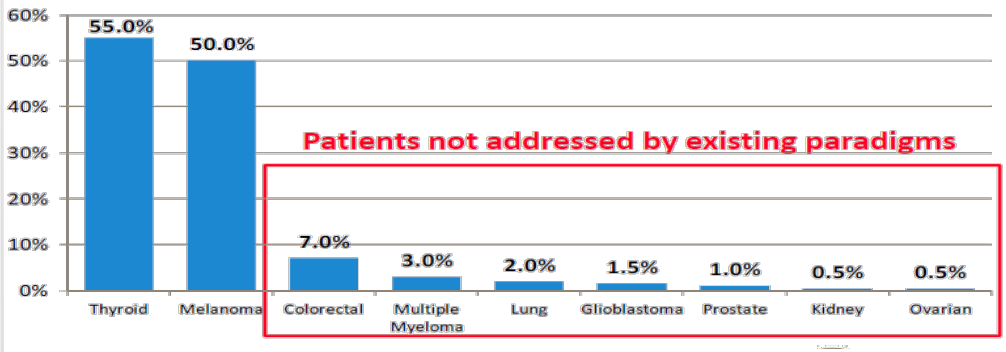
VE-basket trial

- 8 Cohorts *BRAF*^{V600} positive cancers:
  - Metastatic solid tumors
  - Multiple Myeloma
- *BRAF*^{V600} testing
  - All V600 BRAF mutations
  - Tested by local routine methods
  - Retrospective optional evaluation with cobas 4800 BRAF mutation test

NSCLC, Ovarian, Colorectal, Cholangio, Breast, Prostate, Myeloma, Other → vemurafenib (960 mg BID orally)

Hyman D, et al, N Engl J Med 2015; 373:726-736

BRAF Mutations Across Tumors

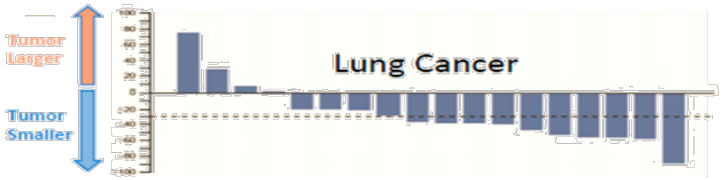


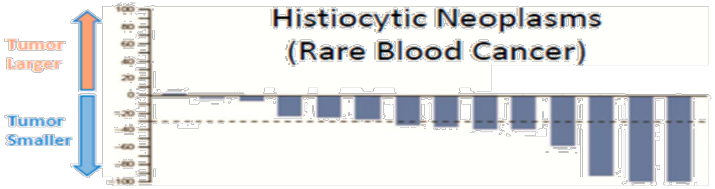
Slide provided by David Hyman

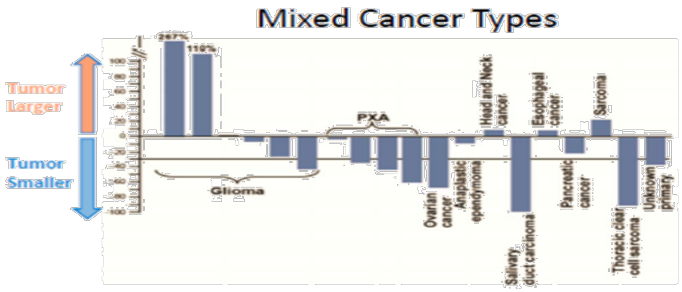
ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

The NEW ENGLAND JOURNAL of MEDICINE







Hyman Di, et al, N Engl J Med 2015; 373:726-736 August 20, 2015

Courtesy J Rodon

Selected Molecular Profiling Initiatives and Genotype-Matching to Clinical Trials

Group	Sample Size	Platform	Fresh Biopsy vs FFPE	Germ-line Control	Number and % of "Matched" Patients in Genotype-Matched Clinical Trials
Gustave Roussy MOSCATO	1,035	40-75 gene panels (Life) + CGH (Agilent) + RNA Seq	Fresh biopsy	Yes	199/1035 = 19%
Institut Curie	741	46 gene panel (Life) + CNA (Affymetrix) +IHC	Fresh biopsy	No	195 randomized/741 = 26%
BCCA	100	Whole genome	Fresh biopsy	Yes	1/100 = 1%
MD Anderson	2,000	11-50 gene panels (Life)	FFPE	No	83/2000 = 4%
Princess Margaret	1,640	23-48 gene panels (Ilumina, Life)	FFPE	Yes	92/1640 = 5.6%

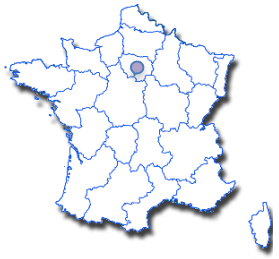
CNA = Copy number alterations; IHC = Immunohistochemistry

Massard et al. Cancer Dis 2017; LeTourneau et al. Lancet Oncol 2015; Laskin et al. Cold Spring Harb Mol Stud 2015; Meric-Bernstam et al. J Clin Oncol 2015; Stockley, Bedard et al. Genome Med 2016.

Gustave Roussy PCM Program

Molecular Screening for Cancer Treatment Optimization: MOSCATO 01(Nov 2011) > MOSCATO 02 (April 2016)

- Monocentric molecular profiling trial
- Total accrual ≈ 1600 patients
- Exploitable molecular portraits : 89%
- Actionable targets: 44%
- Target of oriented/treated = 165 patients



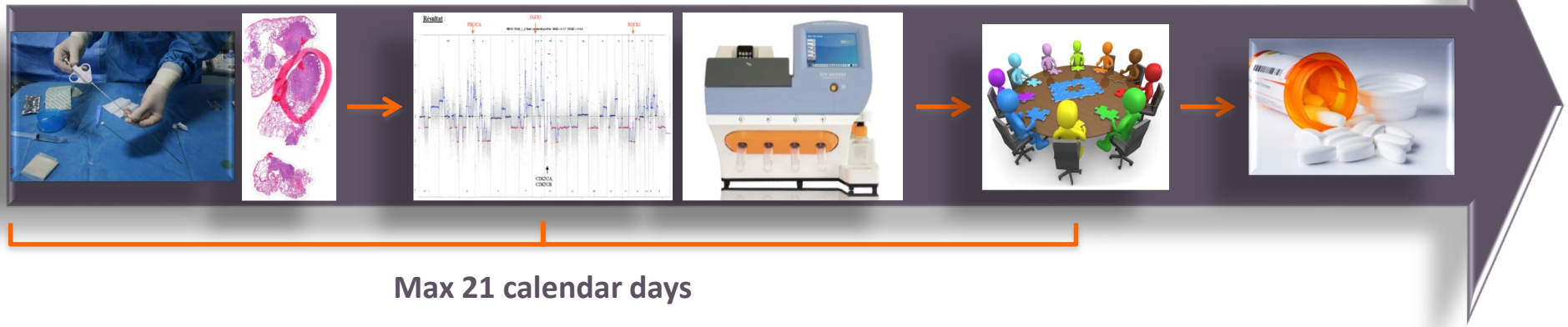
FRESH TUMOR
(on-purpose biopsies)

BIOPSY → PATHOLOGICAL CONTROL

→ **MOLECULAR SCREENING**

CGH Array & NGS+ WES/RNASeq

→ **CLINICAL DECISION** → **TREATMENT**

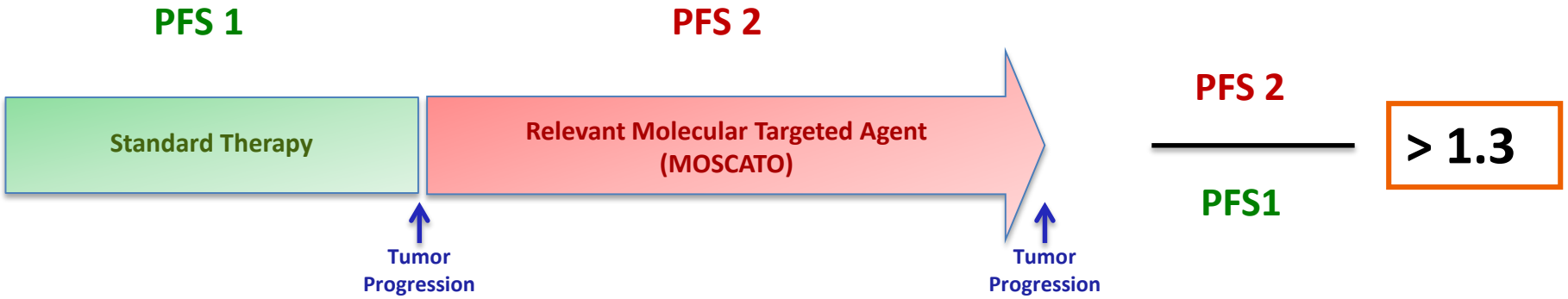


Max 21 calendar days

A Hollebecque et al., ASCO 2013; C Ferte et al, AACR 2014; C Massard, et al, TAT2015
Massard et al, Cancer Discovery 2017

Objectives of MOSCATO

- **Primary Objective: To show that broad molecular screening improves outcome**
  - ✓ **Stastistical hypothesis: ≥ 25%** of patients treated according to their genomic alteration will experience a clinical benefit defined by a **PFS ratio > 1.3**



- **Secondary Objectives**
  - ✓ To assess the feasability of this approach
  - ✓ To improve tumor response
  - ✓ To assess the percentage of patients treated with a selected therapy
  - ✓ To assess the frequency of genomic alterations
  - ✓ To speed-up drug development through enrichment of trials in biomarker-defined patients (stratified medicine)

The molecular portrait performed on material at time of diagnosis

Does not predict for the molecular portrait of the current disease

S Vignot, JC Soria

Gustave Roussy PCM Program

profeel
Cancer du sein métastatique

LIQUID BIOPSY
(CTC, ctDNA)

IF=6,029

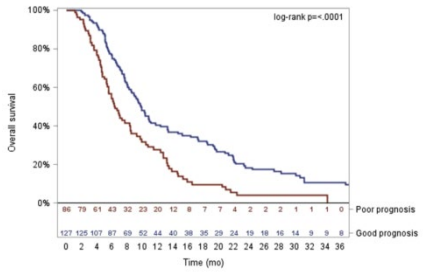
Original Research

RECIST response and variation of circulating tumour cells in phase 1 trials: A prospective multicentric sti

Christophe Massard [a,*,1], Isabelle Borget [b,c,1], Françoise Farace [d,e,]
Sandrine Aspeslagh [a], Marie-Cécile Le Deley [b,c],
Christophe Le Tourneau [g,h], François-Clement Bidard [g,i],
Jean-Yves Pierga [g,i,j], Veronique Dieras [g], Paul Hofman [k],
Jean-Philippe Spano [l], Charles Ferte [a], Ludovic Lacroix [m,2],
Jean-Charles Soria [n,o,2]

European Journal of Cancer 83 (2017) 185–193

C. Massard et al. / European Journal of Cancer 83 (2017) 185–193

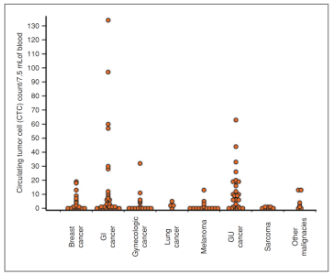


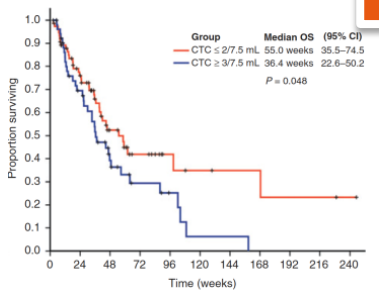
IF=9,619

Predictive Biomarkers and Personalized Medicine

Baseline Circulating Tumor Cell Counts Significantly Enhance a Prognostic Score for Patients Participating in Phase I Oncology Trials

David Olmos[1,2], Richard D. Baird[1,2], Timothy A. Yap[1,2], Christophe Massard[1,2], Lorna Pope[2], Shahneen K. Sandhu[1,2], Gerhardt Attard[1,2], Juliet Dukes[2], Dionysis Papadatos-Pastos[1], Philippa Grainger[2], Stan B. Kaye[1,2], and Johann S. de Bono[1,2]





PLOS ONE

RESEARCH ARTICLE

Whole exome sequencing for determination of tumor mutation load in liquid biopsy from advanced cancer patients

Florence Koeppel[1], Steven Blanchard[2], Cécile Jovelet[1], Bérengère Genin[2], Charles Marcaillou[2], Emmanuel Martin[2], Etienne Rouleau[1,3], Eric Solary[4,5], Jean-Charles Soria[6,7,8], Fabrice André[7,8], Ludovic Lacroix[1,3]*

Personalized Medicine and Imaging

Circulating Cell-Free Tumor DNA Analysis of 50 Genes by Next-Generation Sequencing in the Prospective MOSCATO Trial

Cécile Jovelet[1], Ecaterina Ileana[1,2], Marie-Cécile Le Deley[3,4,5], Nelly Motté[1], Silvia Rosellini[3], Alfredo Romero[1], Celine Lefebvre[6], Marion Pedrero[6], Noémie Pata-Merci[7], Nathalie Droin[7], Marc Deloger[8], Christophe Massard[2], Antoine Hollebecque[2], Charles Ferté[9], Amélie Boichard[1], Sophie Postel-Vinay[2,6], Maud Ngo-Camus[2], Thierry De Baere[10], Philippe Vielh[11], Jean-Yves Scoazec[1,5,11], Gilles Vassal[12], Alexander Eggermont[5,9], Fabrice André[5,6,9], Jean-Charles Soria[2,5,6], and Ludovic Lacroix[1,6,11,13]

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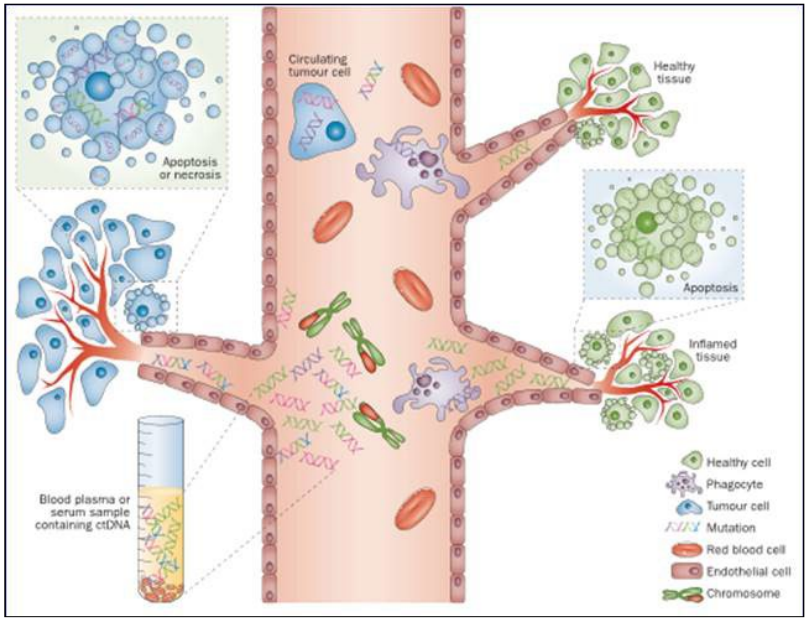
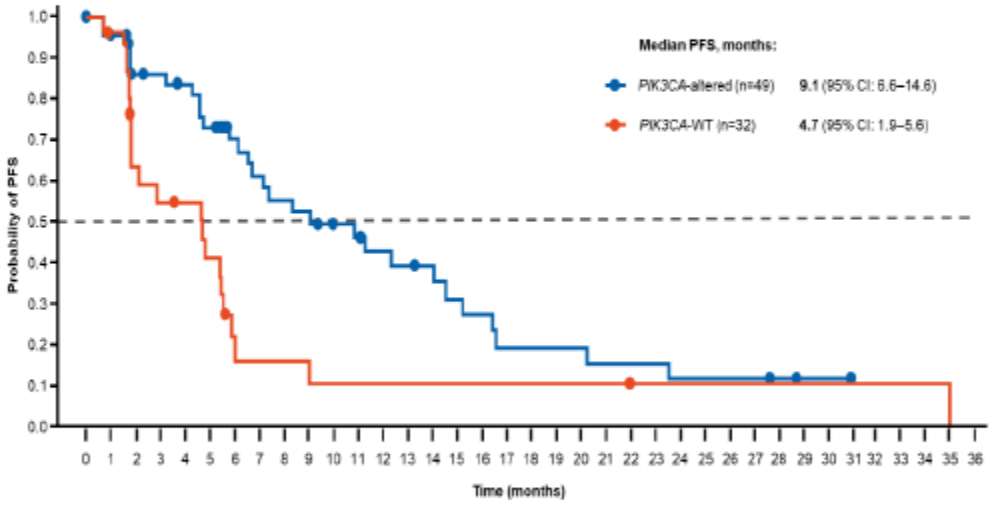


Phase Ib: Preliminary clinical activity with alpelisib + fulvestrant

- In a Phase Ib trial, alpelisib + fulvestrant was administered in heavily pretreated patients with ER+ ABC and known *PIK3CA* mutation status[1]
- In patients with *PIK3CA*-altered disease, alpelisib + fulvestrant led to a median PFS of 9.1 months[1]
- For patients with *PIK3CA*-wild-type disease, alpelisib + fulvestrant led to a median PFS of 4.7 months[1]

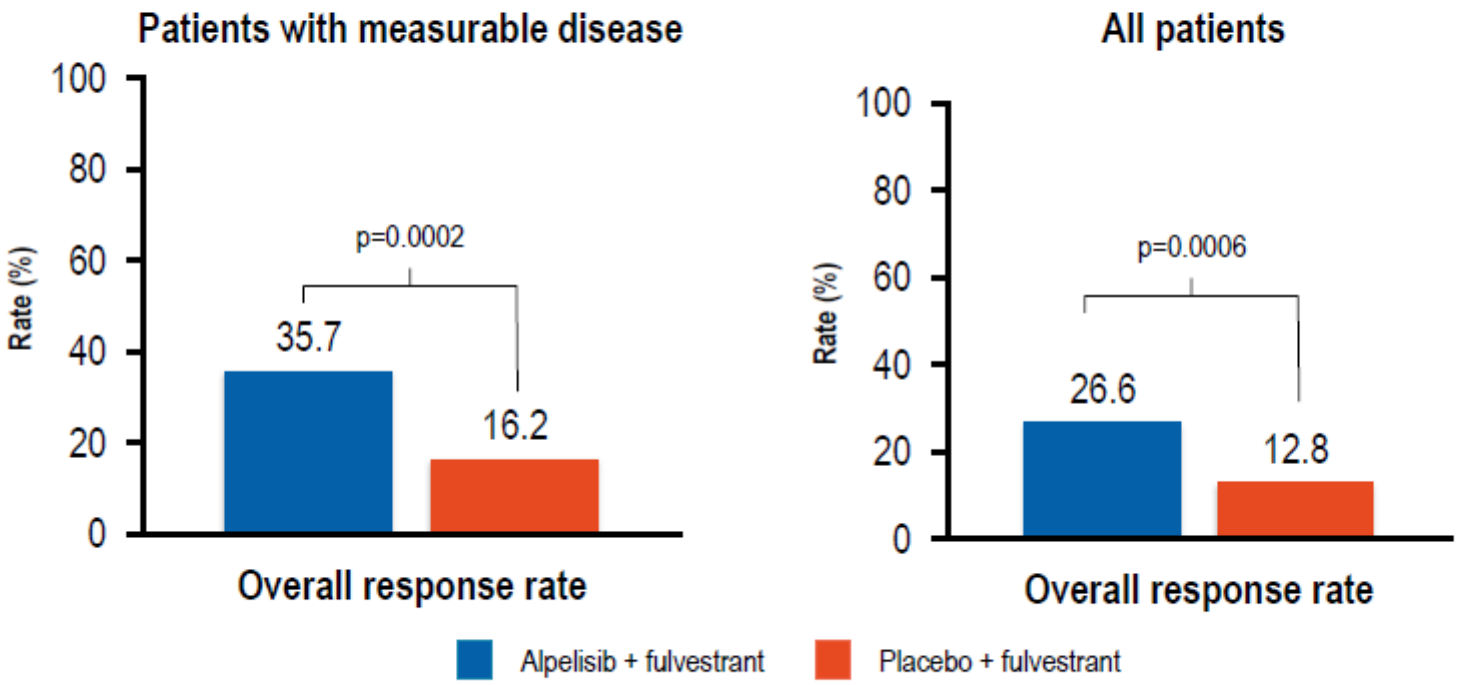
Phase Ib: PFS with alpelisib + fulvestrant[1]



There is a strong rationale for a Phase III trial to evaluate efficacy of alpelisib in patients with *PIK3CA*-mutant ABC, while further exploring potential activity in *PIK3CA*-non-mutant disease

1. Juric D, et al. *JAMA Oncol* 2018;In press.

Overall response rate in the *PIK3CA*-mutant cohort



ORR = complete response + partial response.

Open approach of regulators (FDA…and EMA?)

- **Food and Drug Administration (FDA) breakthrough designations based on phase I trials results:**
  - AZD9291 for EGFR T790M NSCLC (May 2014, based on less than 100 patients)
  - Atezolizumab and bladder cancer (Feb 2014, based on less than 70 patients)
- **FDA conditional approvals based on phase I/II data**
  - accelerated approval by the FDA in August 2011 for crizotinib and in April 2014 for ceritinib (N=246)
  - accelerated approval by the FDA in November 2015 for osimertinib (less than 3 years after 1st patient dosed in phase I)

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  - ✓ Open approach of regulators

- **Opportunities and challenges related to this new paradigm**

General goals of tumour molecular profiling

- Tumour molecular profiling can help decipher cancer biology at the individual level and identify:
  - Oncogenic drivers and predictors of efficacy
  - Resistance molecular mechanisms
  - Lethal subclones & intratumor heterogeneity
  - Mutagenesis processes & DNA repair defects
  - Dialogue between cancer cells and immune system

Broad prescreening ("Finding trials for patients")

✓ preferred by patients and by investigators

✓ ok for large sites/large portfolios/cooperative groups.

Challenges of tumour molecular profiling

- Various models of implementation in the clinical setting
- The optimal technology is yet to be universally adopted
- An urgent need to develop non invasive biomarkers
- The optimal setting for analysis (metastatic vs locoregional vs resected) is still debated
- Best patient population to enroll (refractory, sensitive…) TBD
- Access to therapies (and notably combinations) is a problem

IN THE REAL WORLD….

- Interventional radiologist is your best friend

IN THE REAL WORLD….

- Molecular pathologist is your best friend

IN THE REAL WORLD….

- Refferal oncologist is your best friend

IN THE REAL WORLD, everybody is your best friend….

Grazie per l'attenzione