Phase I studies in NSCLC

Challenges of targeted drugs development

Sophie POSTEL-VINAY, M.D., Ph.D

ELCC, March 27, 2014

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Disclosures

- No personal financial disclosures

Overview

- Enrichment strategies and development of companion biomarker
  - Context & rationale for enrichment strategies
  - Examples of success
    - Molecular screening
    - Specific clinical entities
  - Challenges
- MTD and RP2D customization?
- Future directions

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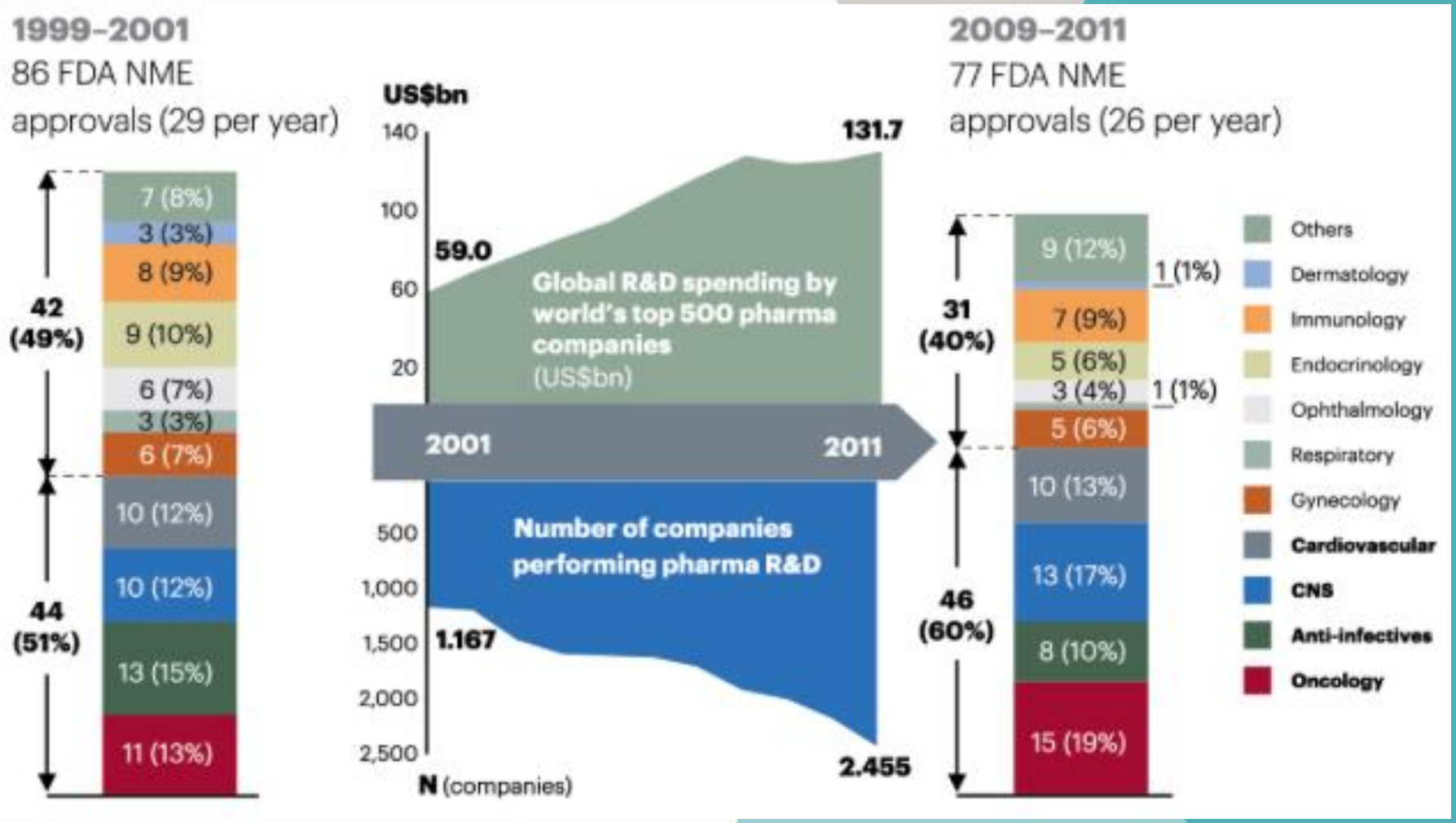
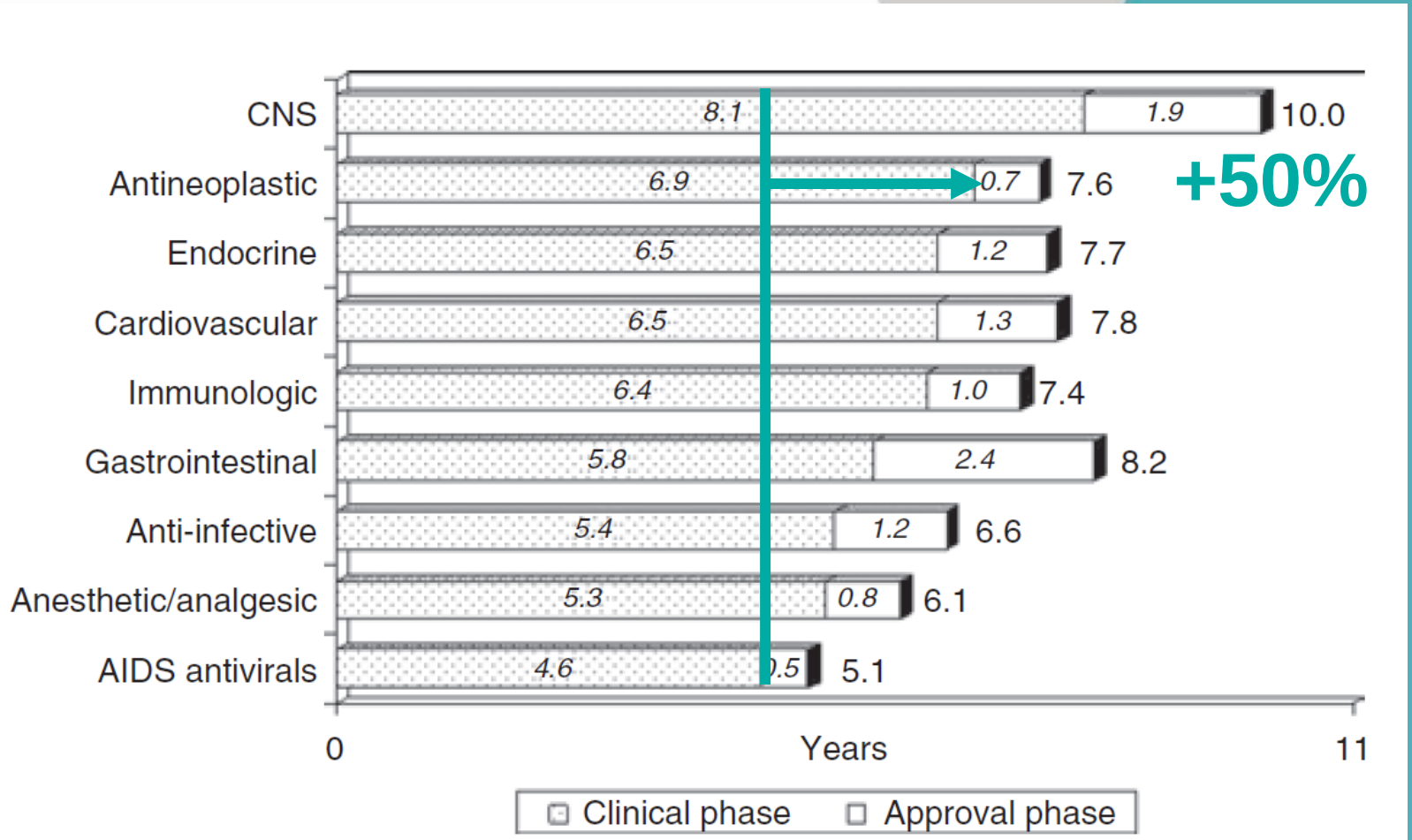
Costs and success of drug development

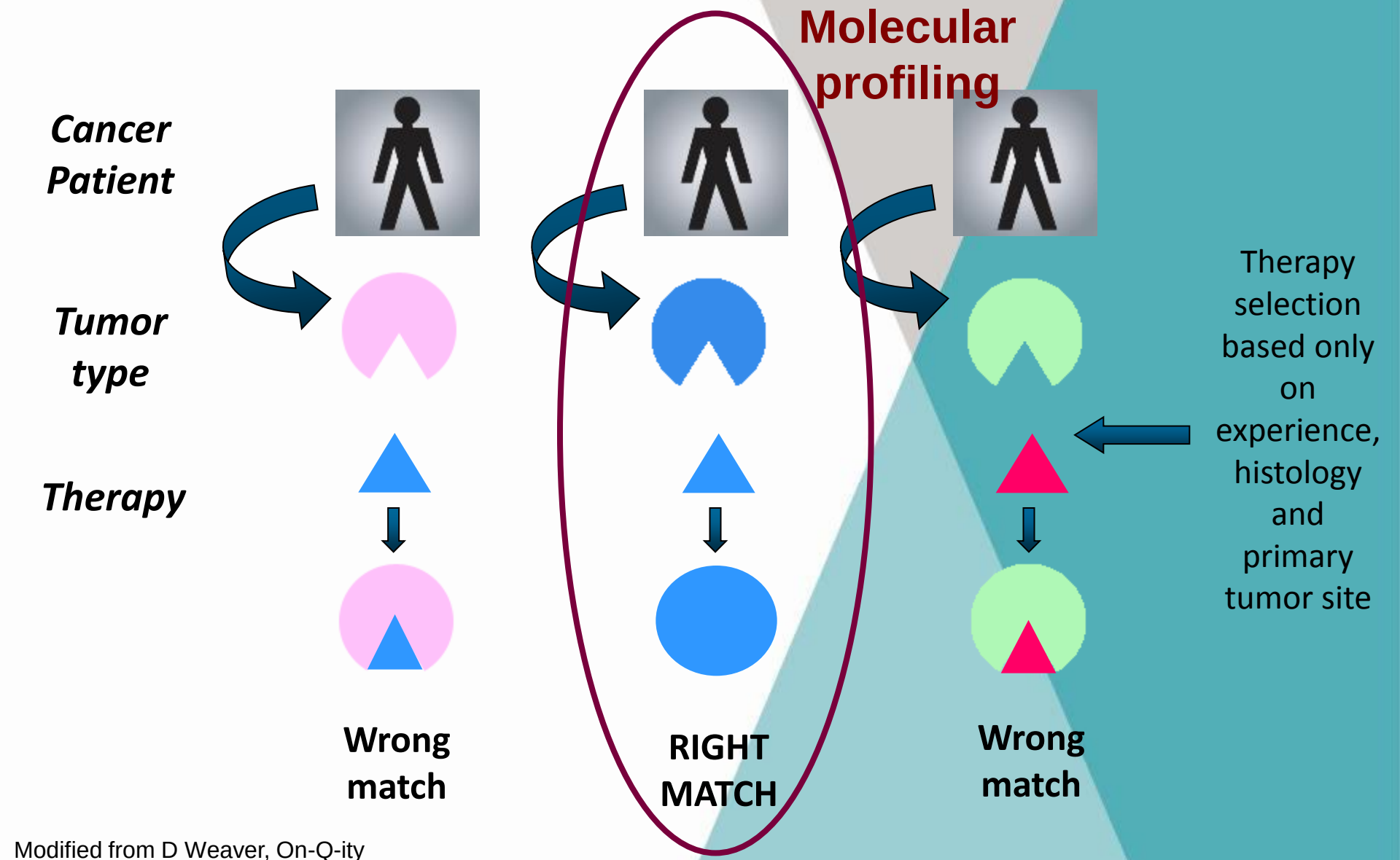


Parexel Sourcebook Biopharmaceutical R&D Statistical source book 2011/2012

Time of successful drug development

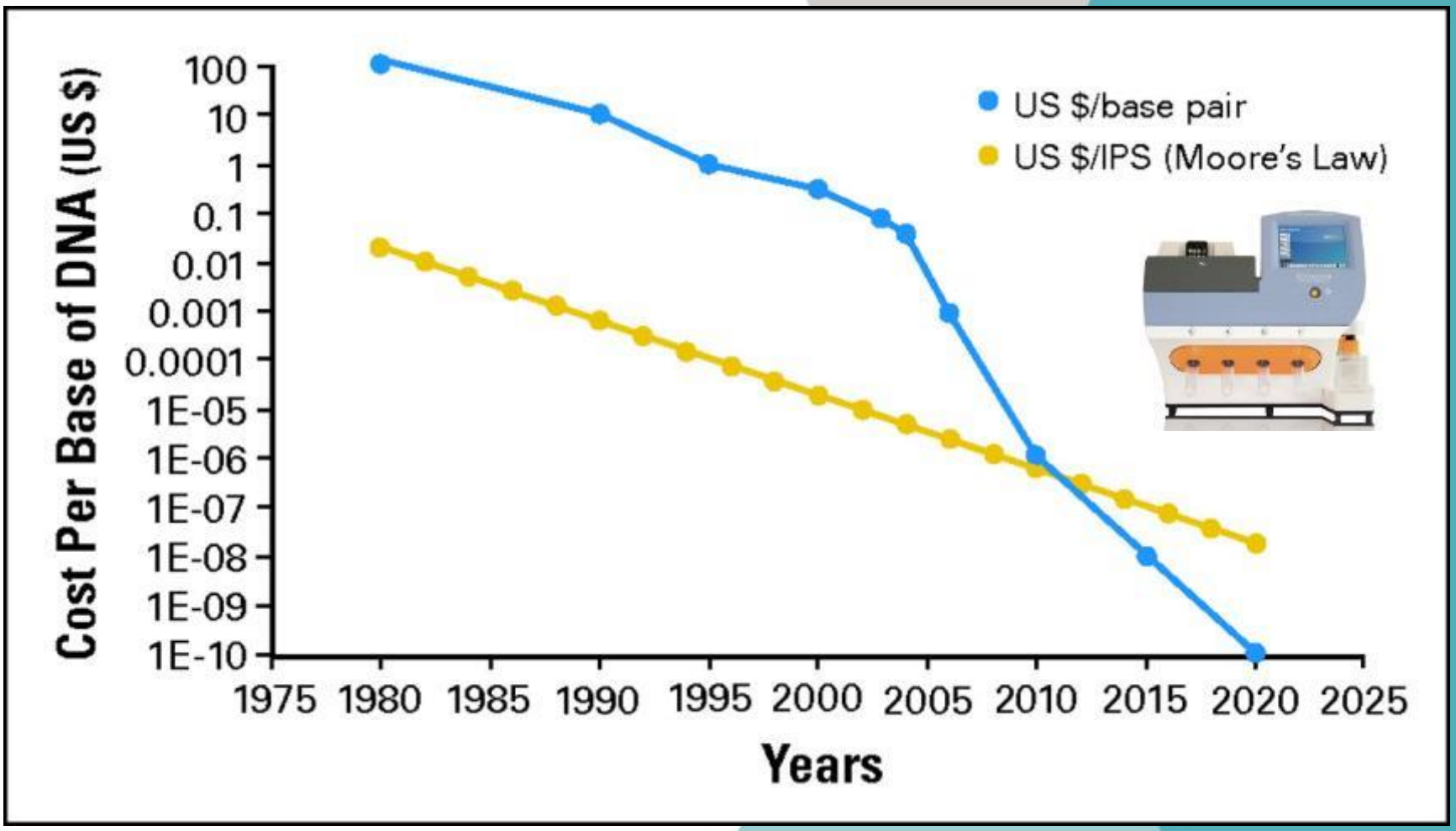


Customizing & matching therapy



Modified from D Weaver, On-Q-ity

Dropping costs of NGS



MacConaill L E , Garraway L A JCO 2010;28:5219-5228

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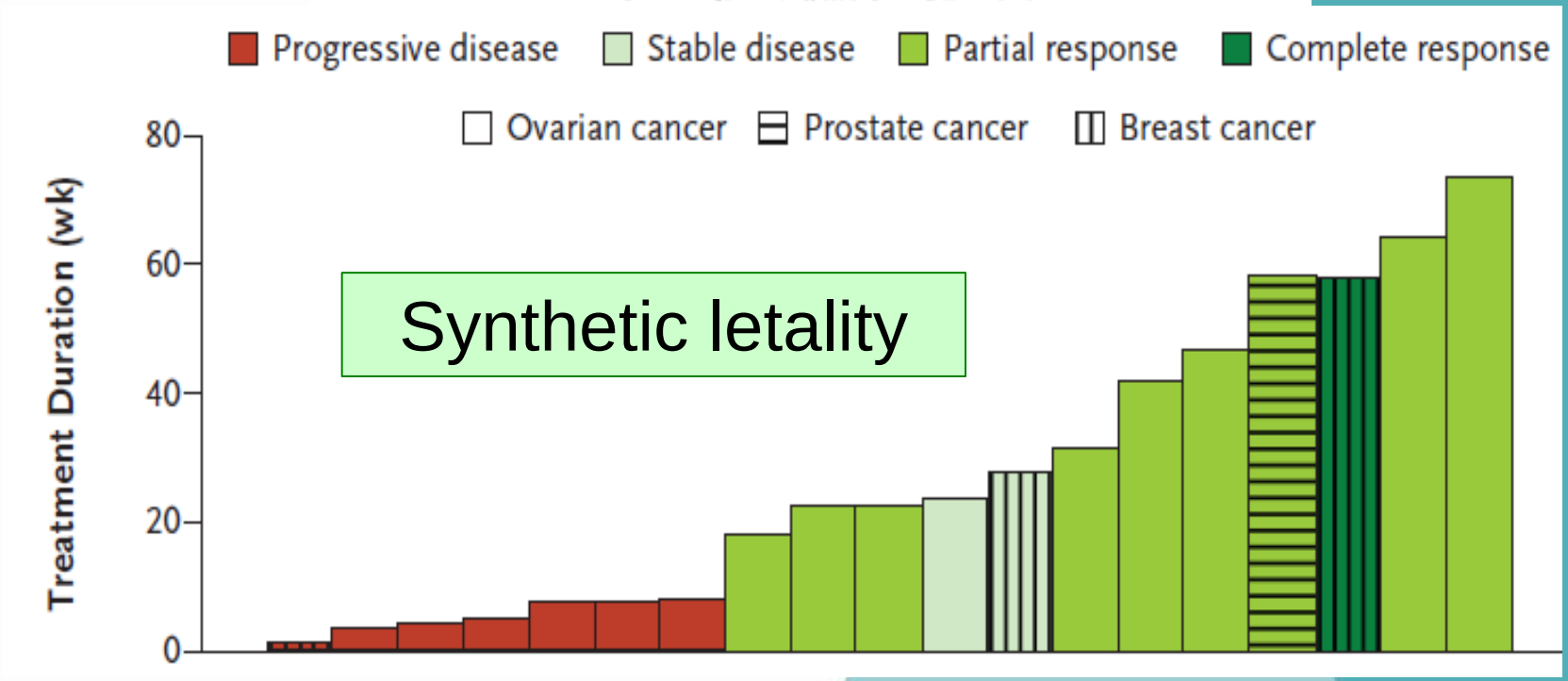
Molecular screening: first success…

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

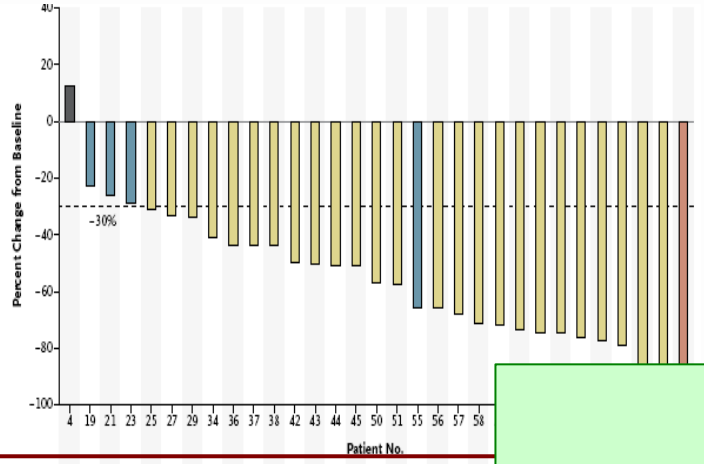
Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers



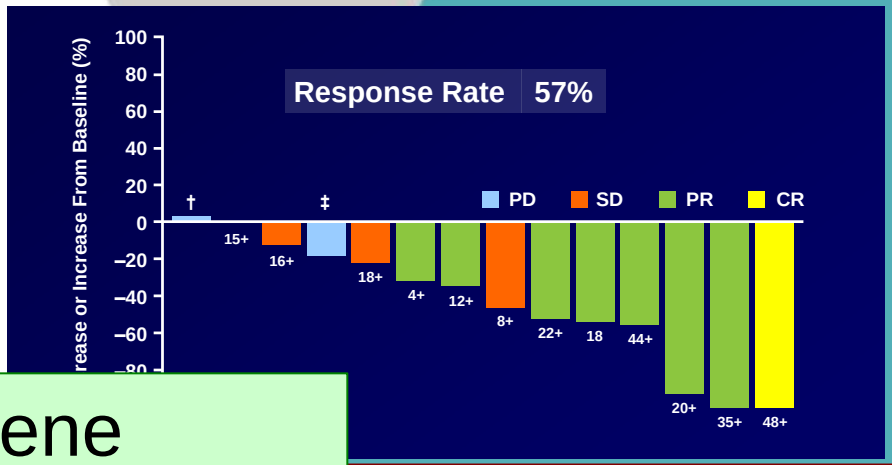
Ashworth A, JCO 2008; Fong et al, NEJM 2009

… followed by several victories

ALK inhibitor in NSCLC
(ALK translocation) *NEJM 2010*

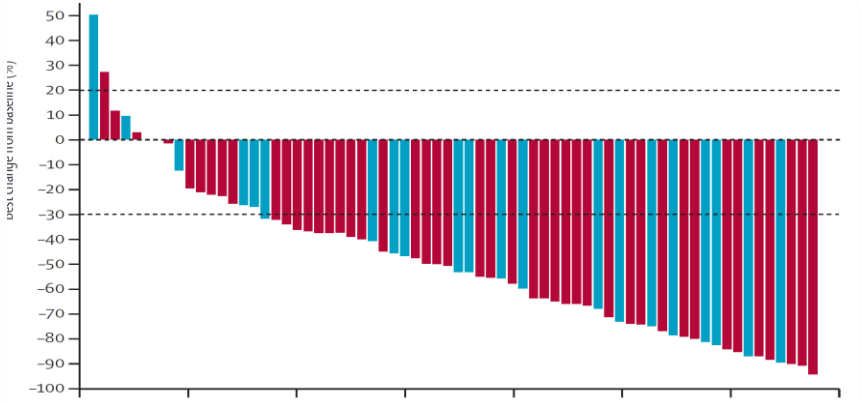


ROS1 inhibitor in NSCLC
(ROS1 rearrangment) *ASCO 2012*

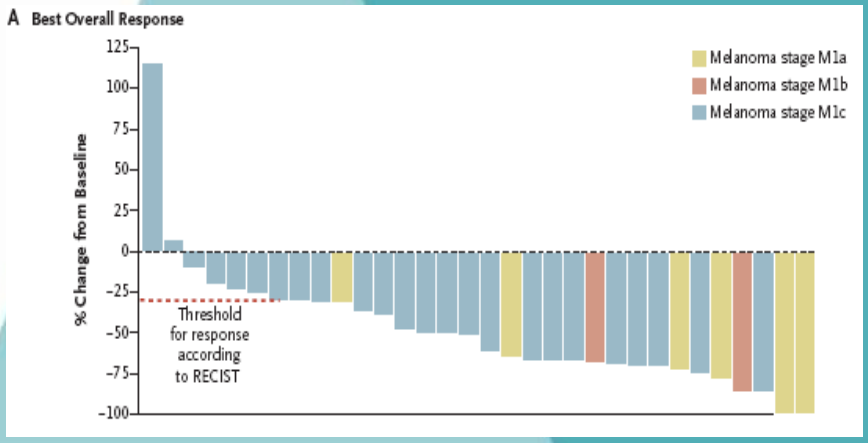


Oncogene addiction

EGFR inhibitor in N
(EGFR mutation) *Lancet Oncol 2012*

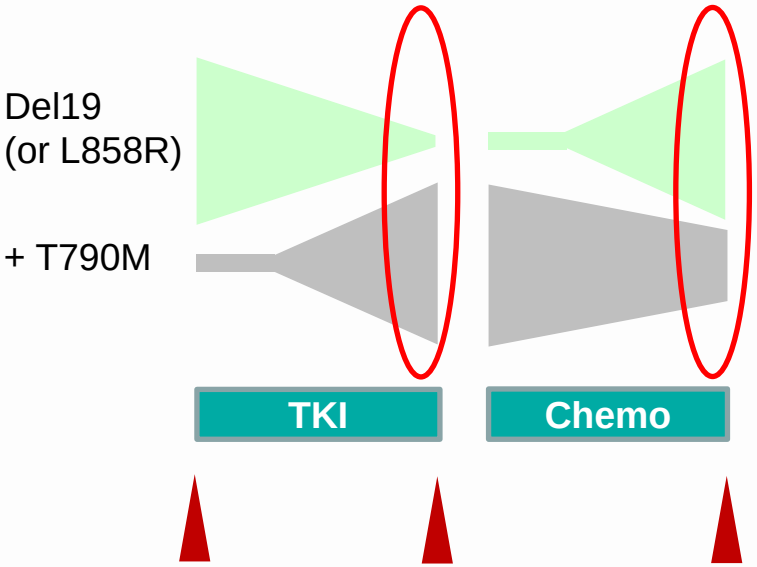


or in melanoma
(V600E BRAF mutation) *NEJM 2010*



CO-1686

"Clonal Warfare"



Diagnosis

Del19 dominates because clone is fitter

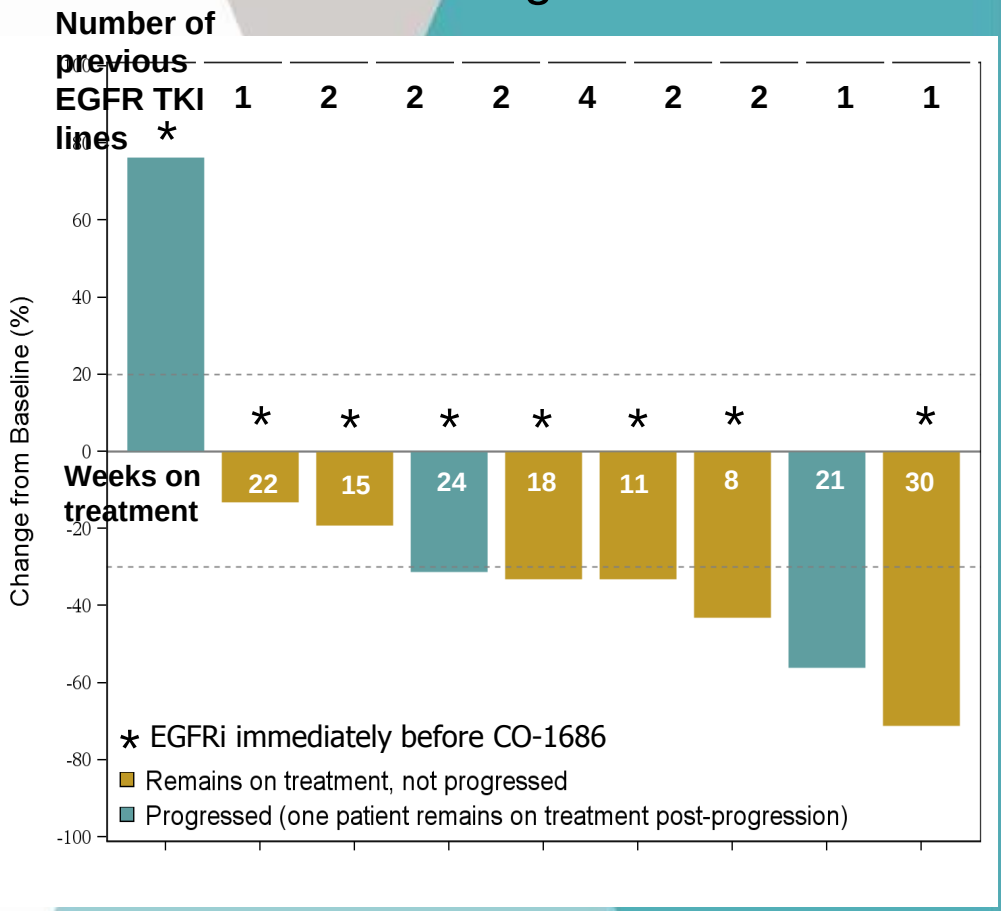
Progression #1

Driven by T790M in 60% because of TKI selection pressure

Progression #2

Heterogeneity of resistance: Del19 fitter than T790M under chemo selection

67% RECIST response rate in evaluable T790M+ patients treated at 900mg BID



JC Soria et al, IASLC 2013

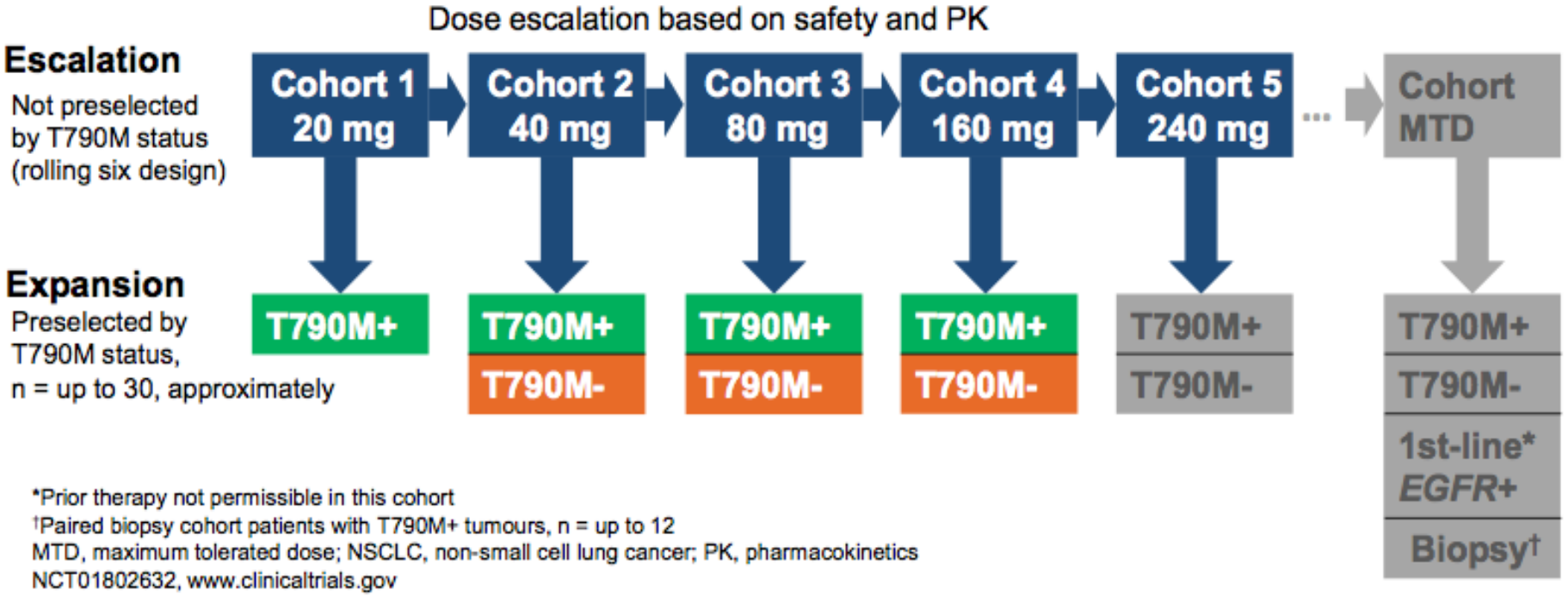
AZD9291 – Study design

Phase I, open-label, multicentre study of AZD9291 in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI

Objectives

1°: safety and tolerability in EGFR-TKI-refractory patients

2° include: define MTD, safety and tolerability as 1st-line therapy,* PK, preliminary efficacy



*Prior therapy not permissible in this cohort

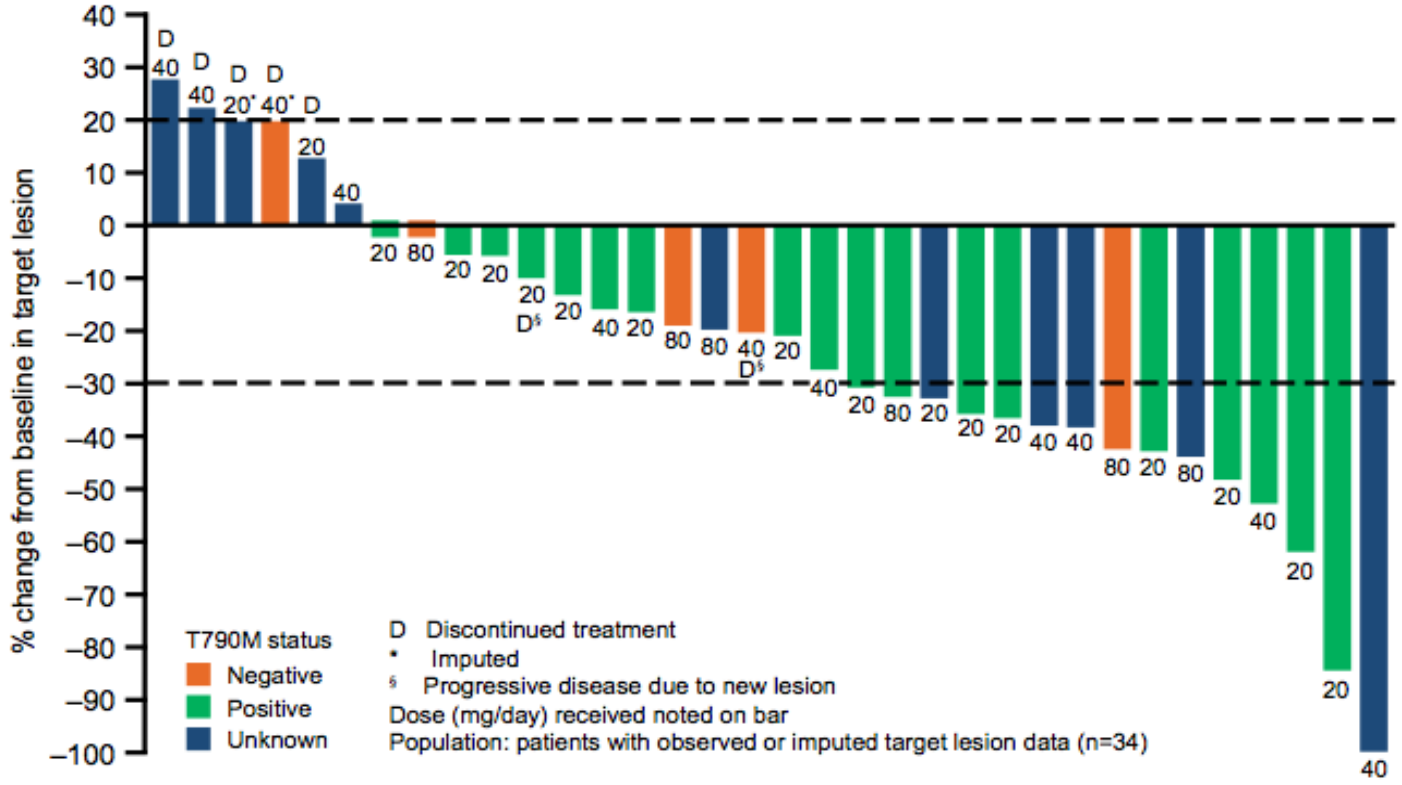
†Paired biopsy cohort patients with T790M+ tumours, n = up to 12

MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics

NCT01802632, www.clinicaltrials.gov

Ranson et al, IASLC 2013

AZD 9291 – Efficacy data



Best overall response#

- 15/35 patients evaluated had a partial response (confirmed + unconfirmed)
- 9/18 patients with T790M+ tumours achieved a partial response (confirmed + unconfirmed)

#Response Evaluation Criteria in Solid Tumors v1.1, programmatically calculated from investigator-recorded tumour measurements
T790M result from local testing except for some expansion patients where local testing result unknown (central test result used)

Preliminary data, cut-off 27 September 2013

Ranson et al, IASLC 2013

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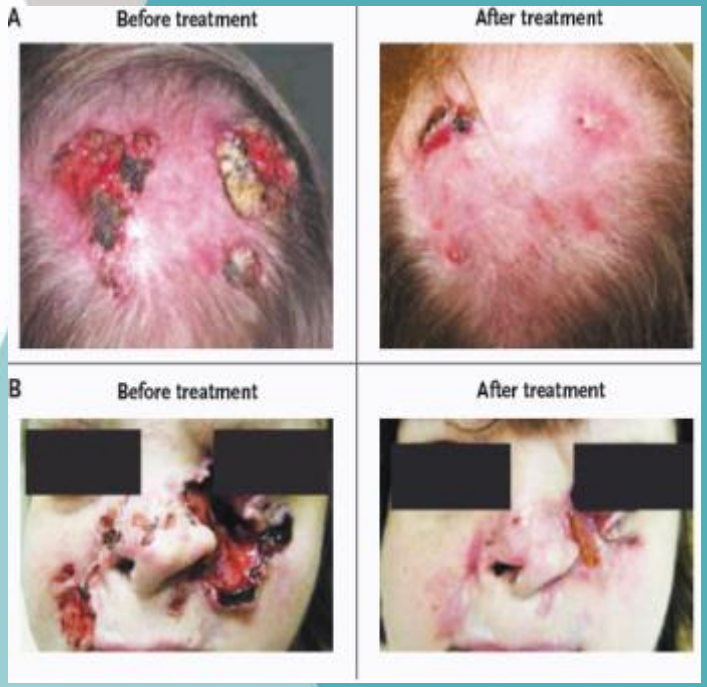
Surrogates for molecular enrichment

- Some specific clinical entities can represent per se a surrogate for a specific molecular context
  - Basal cell carcinoma and PTCH mutations in the HH pathway
  - Liposarcome and MDM2 amplif
  - Prostate cancer and AR dependency
- Previous response to CT

Relevance for NSCLC?



Von Hoff D, NEJM 2009
Rodon J et al, NRCO 2012

Conclusion 1: advantages of enrichment strategies

- **Accelerated timelines for approval (~ 5 years)**
  - Crizotinib: FIM April 2006 => FDA approval August 2011
  - Vismodegib: Ph1 January 2007 => FDA approval January 2012
- **Limited number of pts needed for efficacy read-out**
  - Crizotinib registered by the FDA on the basis of single arm phase I and II trials (n= 119 and n=136) and more recently by EMA (phase III trial, n = 347)
  - Vismodegib registered on the basis of phase II single arm trial (n= 96 patients)

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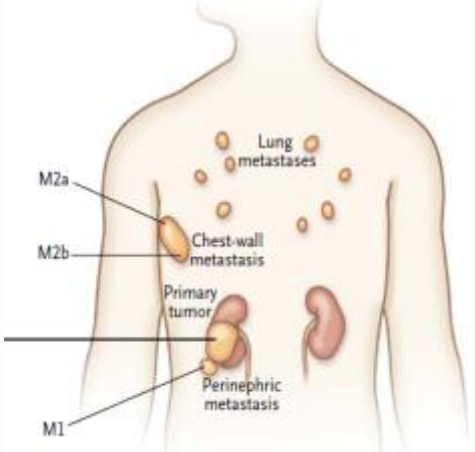
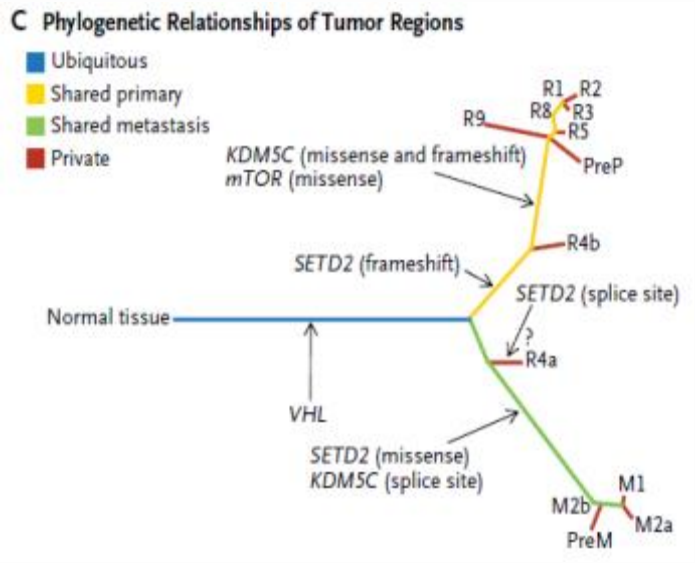
Tumoral heterogeneity

Spatial heterogeneity



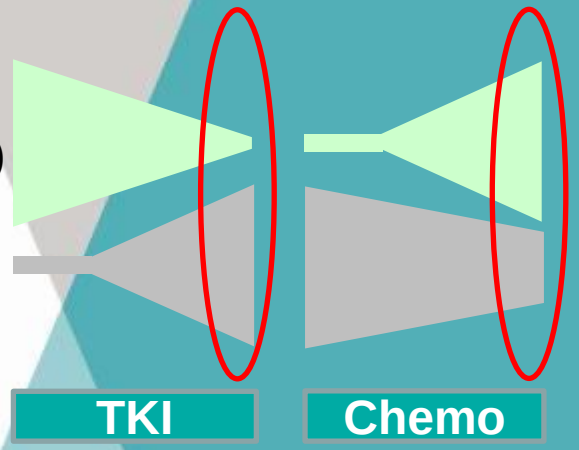


Gerlinger et al, NEJM 2010

Temporal heterogeneity

Del19
(or L858R)

+ T790M



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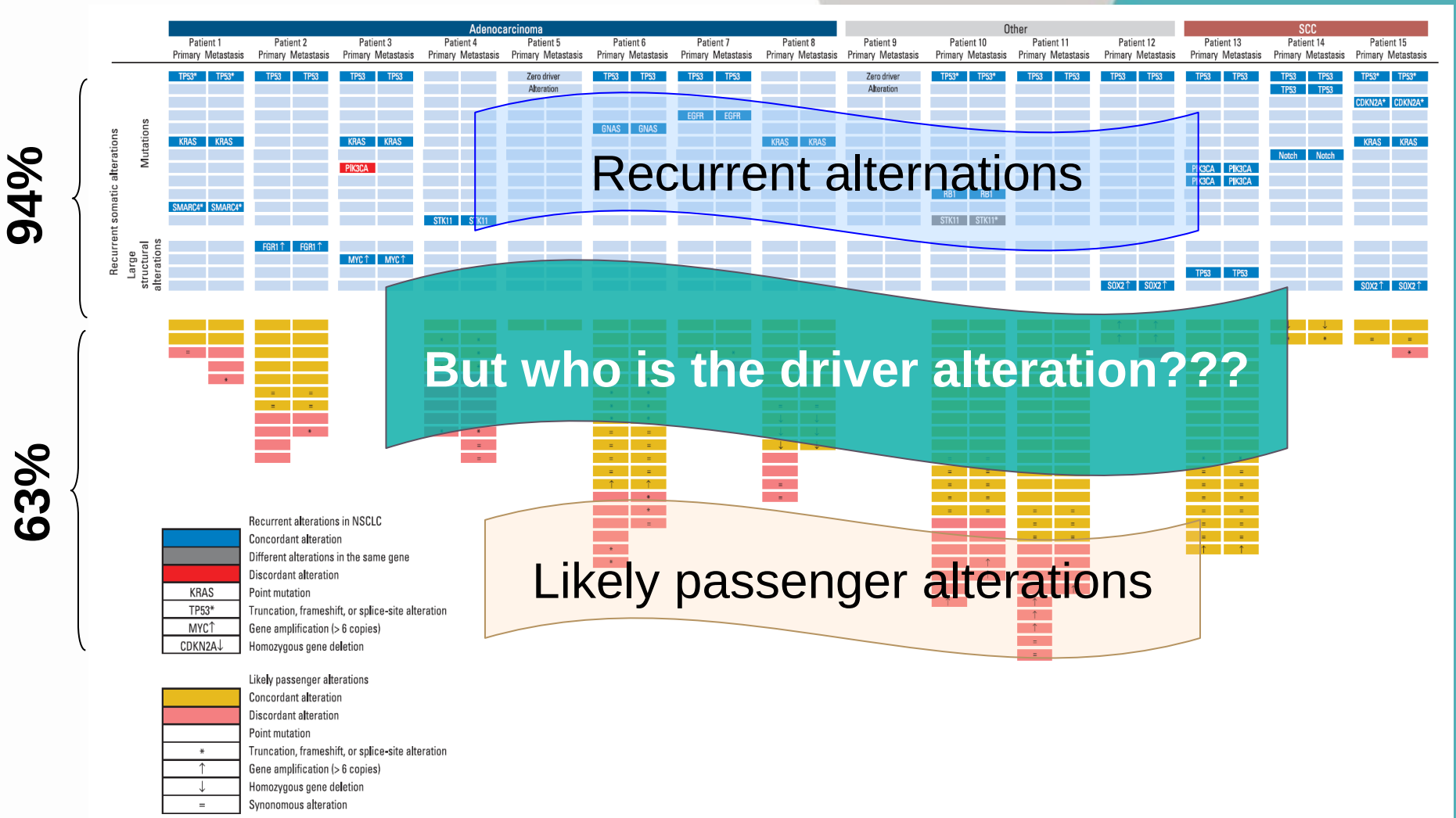
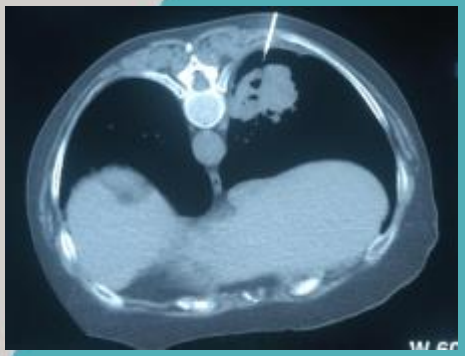


Vignot et al JCO 2013

Technical challenge & feasibility

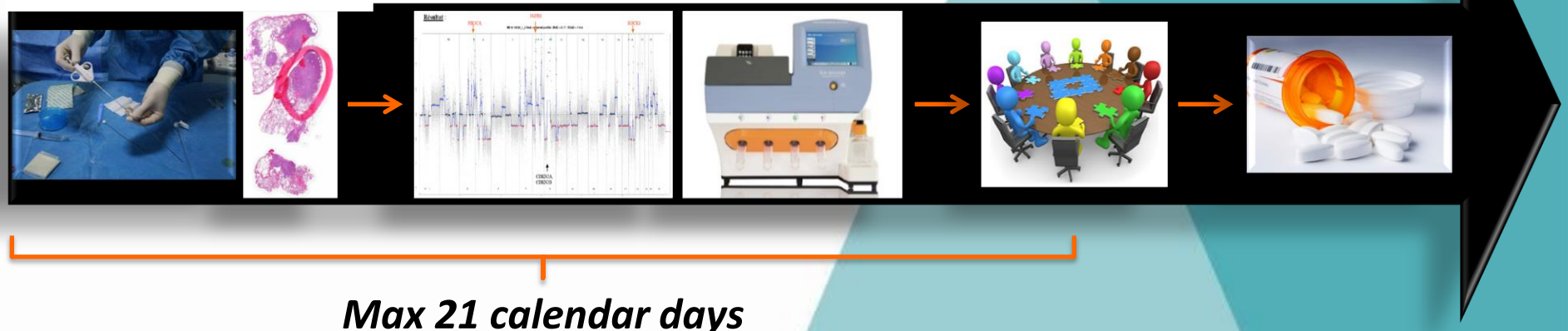
MOSCATO: MOlecular **S**creening
for **CA**ncer **T**reatment **O**ptimization



FRESH TUMOR → **MOLECULAR SCREENING** → **CLINICAL DECISION** → **TREATMENT**

BIOPSY → **PATHOLOGICAL CONTROL**

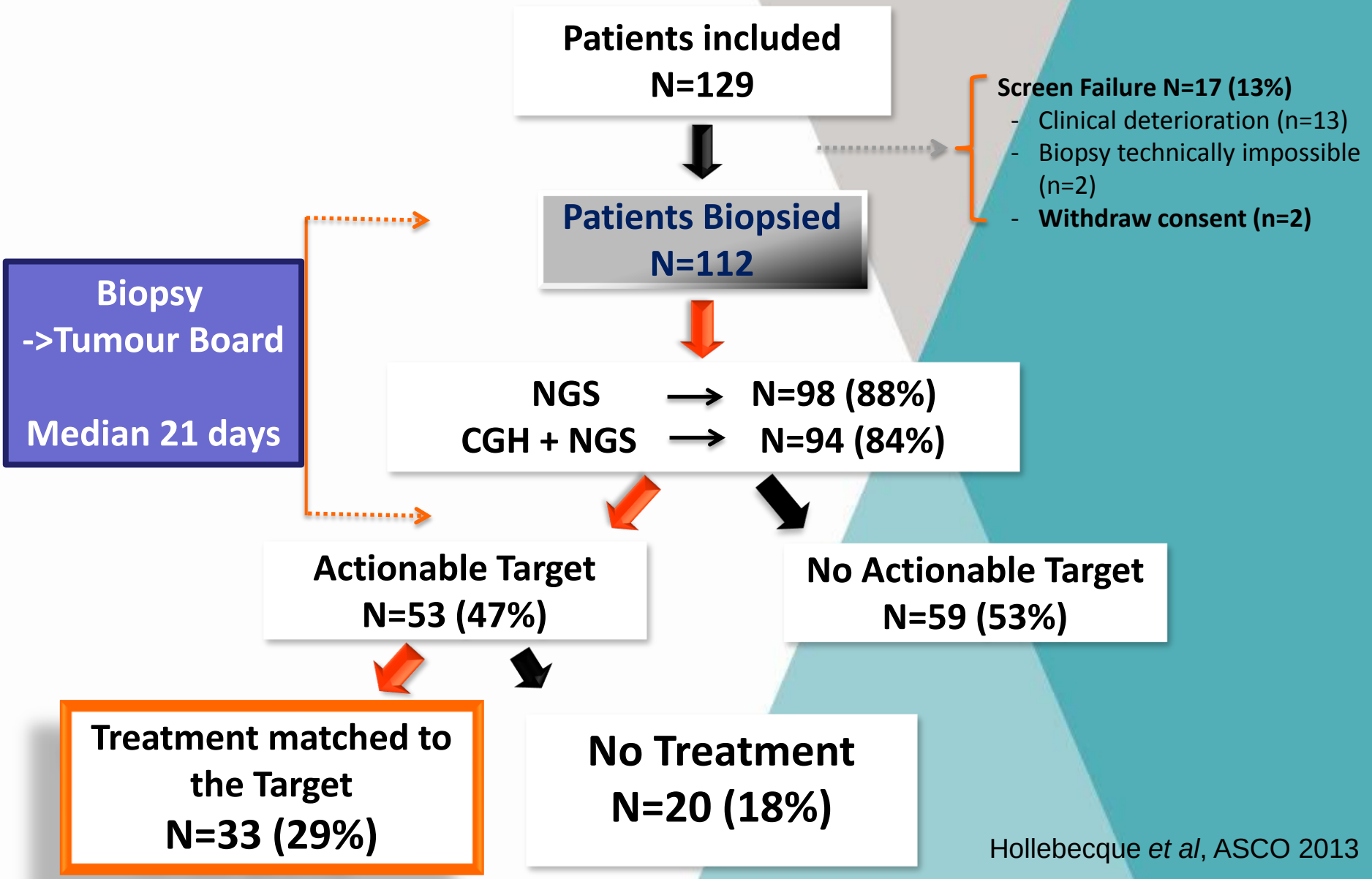
CGH Array & NGS



Max 21 calendar days

Hollebecque *et al*, ASCO 2013

MOSCATO - Results 2013

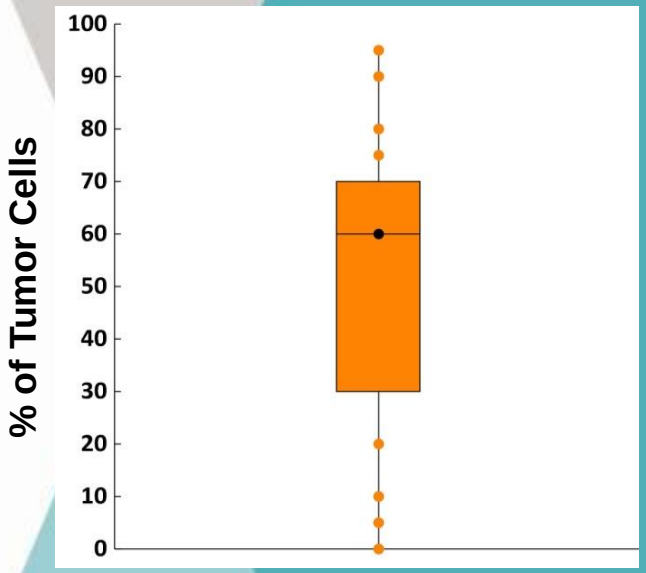


Hollebecque *et al*, ASCO 2013

MOSCATO – Results 2013

Biopsies characteristics

Site of biopsy	N	%
Lung	33	29,5%
Liver	32	28,6%
Lymph Node	23	20,5%
Skin/Sub-cut	10	8,9%
Surgical biopsy (H&N)	5	4,5%
Bone	2	1,8%
Other	7	6,3%



Complications

Pneumothorax grade 2 (n=1)
Liver Hematoma grade 2 (n=1)

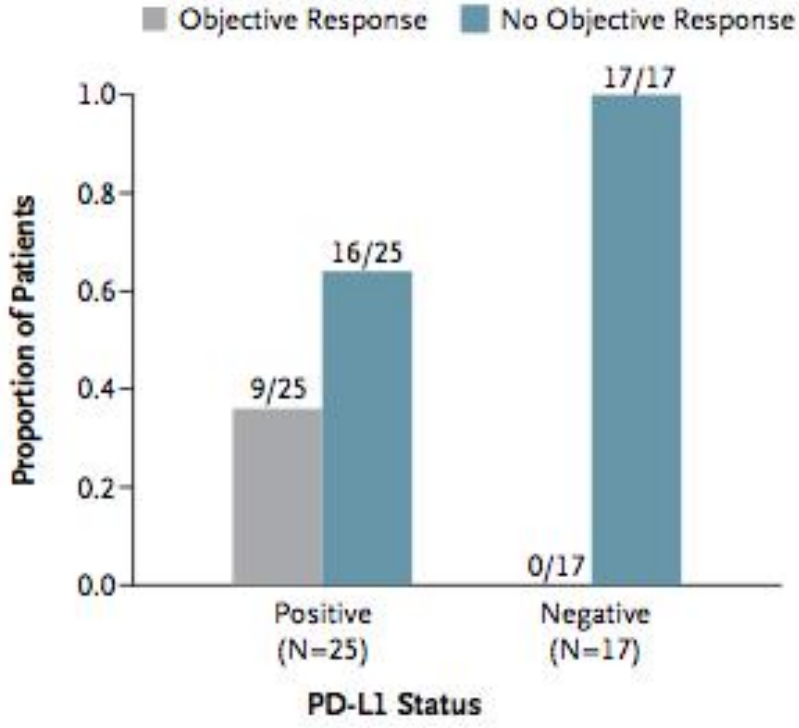
FEASIBLE

> 90 % of pts with >10% Tumor cells

USEFUL

Hollebecque, ASCO 2013

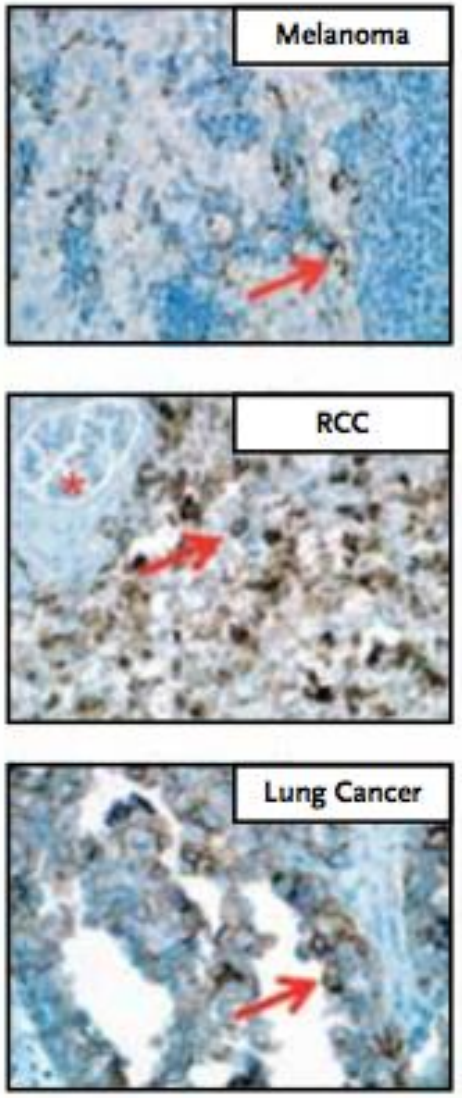
Immune checkpoints - Nivolumab



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

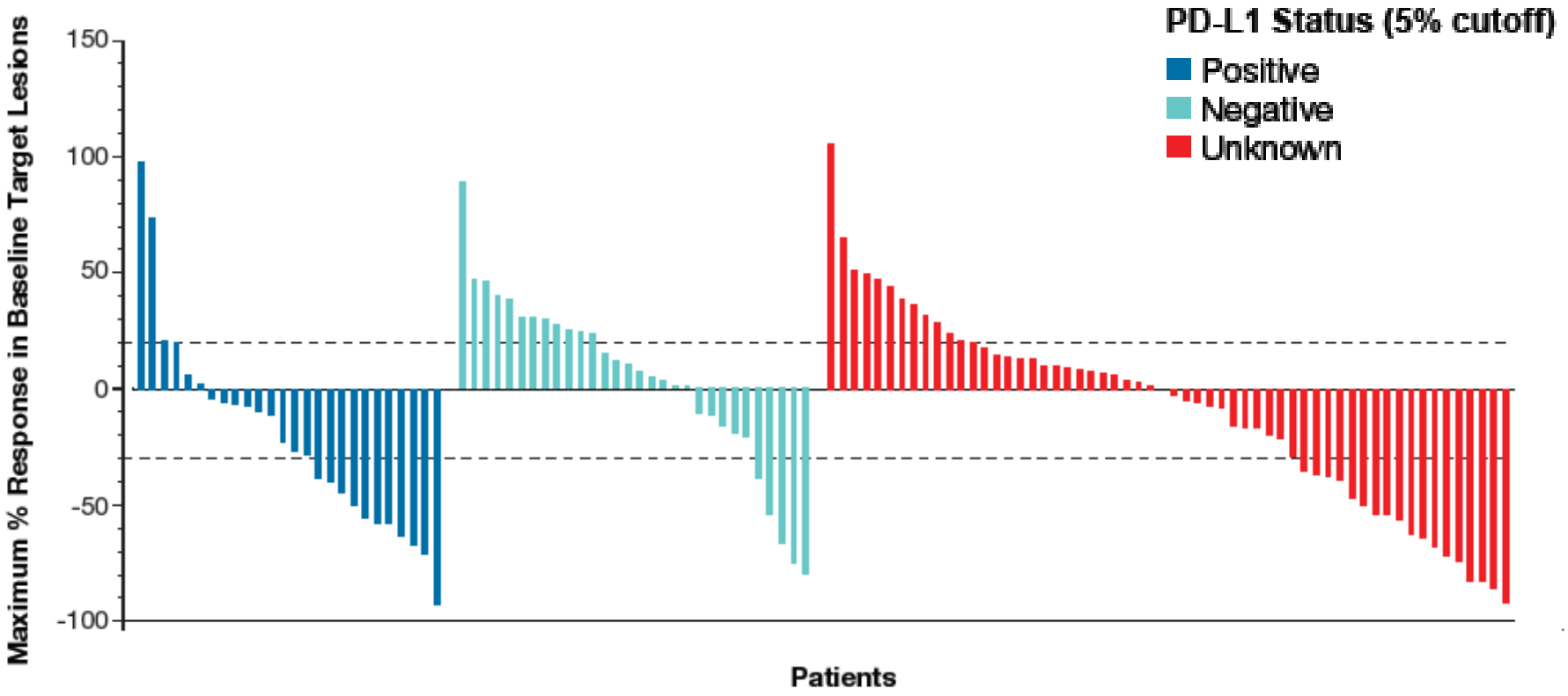
Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



Topalian S. *et al*, NEJM 2012

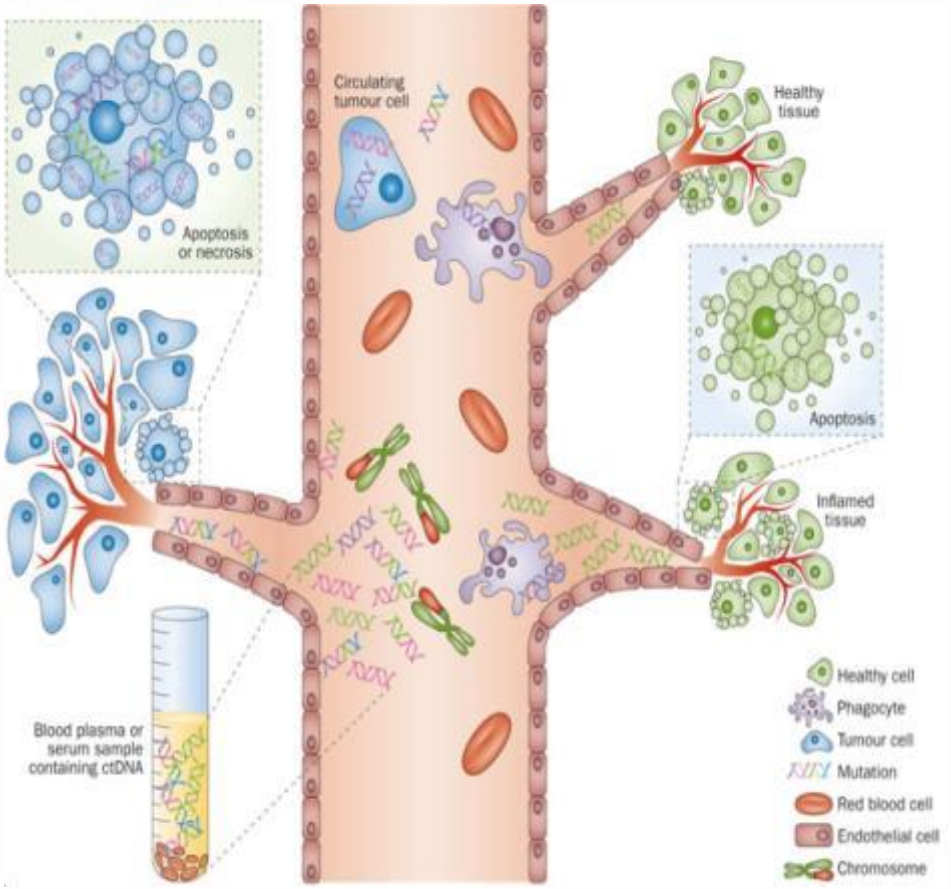
Biomarker assesment method and threshold?



P2.11-035, Antonia et al, WCLC 2013

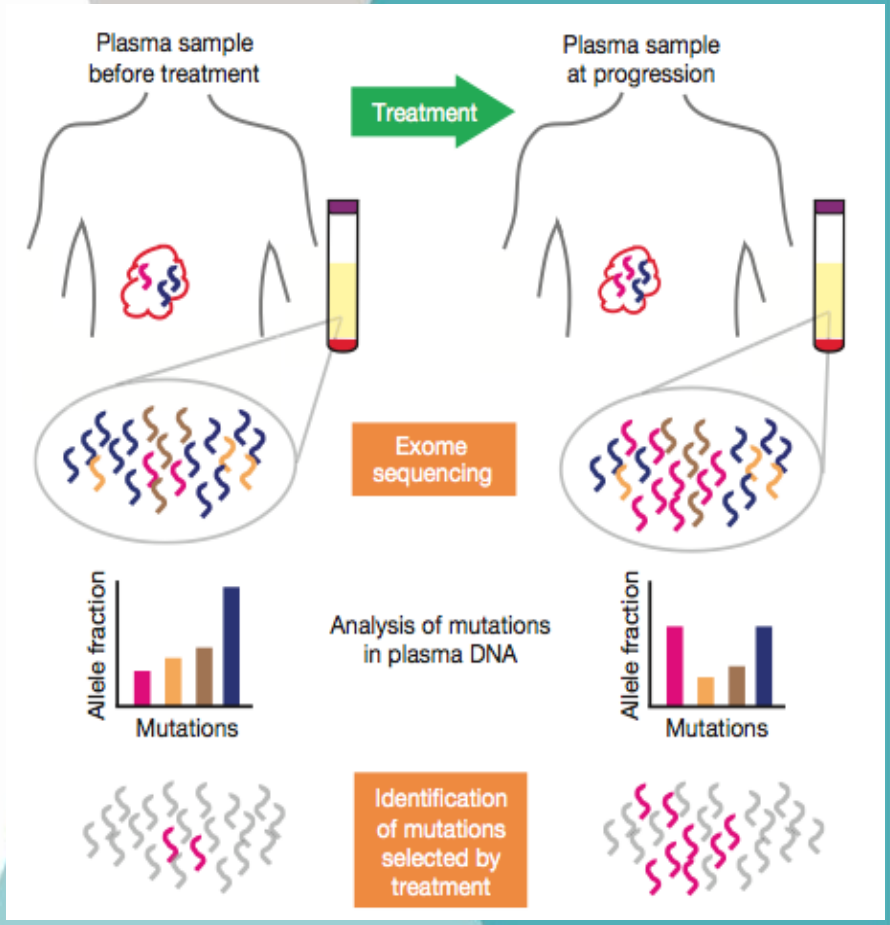
Liquid biopsy

Diagnosis



Crowley E *et al,* NRCO 2013

Resistance



Murtaza M. *et al*, Nature 2013

Intrinsic Challenges of an Enrichment strategy

- **Success is contingent on the following assumptions:**
  - Effective drug
  - Mutation = driver
  - Clinical feasibility
  - Long-term onset of resistance

- **Challenges:**
  - Flexibility of phase I inclusion criteria (timing, dose level known to be safe, tumour type)
  - Rare mutations
  - Multiple drivers

Courtesy B Besse

Risk to discard active compounds

- **Incorrect understanding of the MOA of the compound**
  - Sorafenib a lousy RAF inhibitor but a good anti-angiogenic compound
- **Inadequate molecular test to predict for efficacy**
  - PI3K mutation without accounting for concomitant mutations

-> Strategies to decrease that risk

  - Perform dose escalation in all comers
  - Restrict expansion cohort to molecularly selected patients

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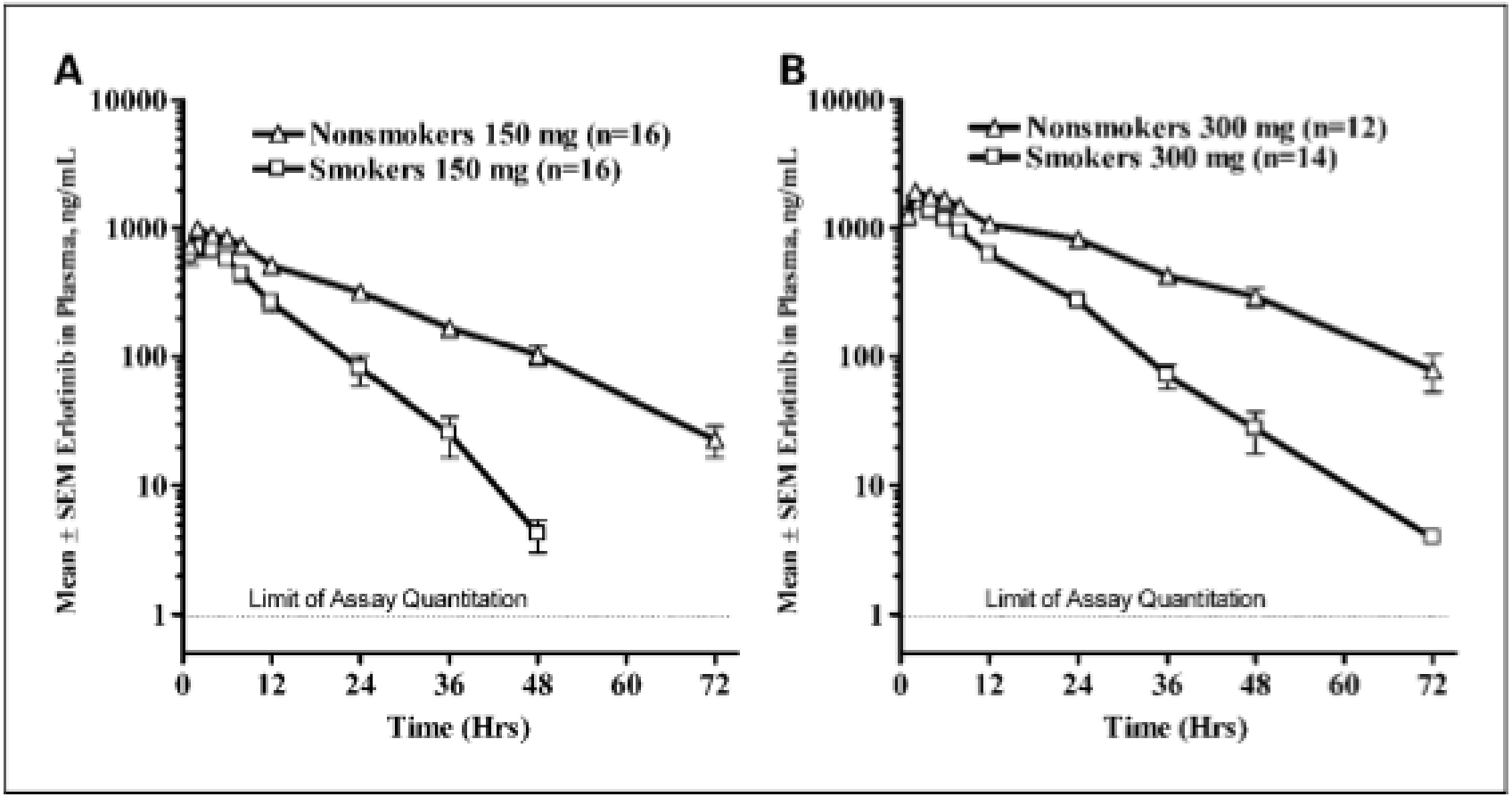
MTD and RP2D

Drugs		MTD	Clinical dose
Trade name	Generic name		
Glivec	Imatinib	>1000 mg, b.i.d.	400 mg, q.d.
Iressa	Gefitinib	700 mg, q.d.	250 mg, q.d.
Tarceva	Erlotinib	150 mg, q.d.	150 mg, q.d.
Nexavar	Sorafenib	600 mg, b.i.d.	400 mg, b.i.d.
Sutent	Sunitinib	50 mg, q.d.	50 mg, q.d.

One dose fits all?

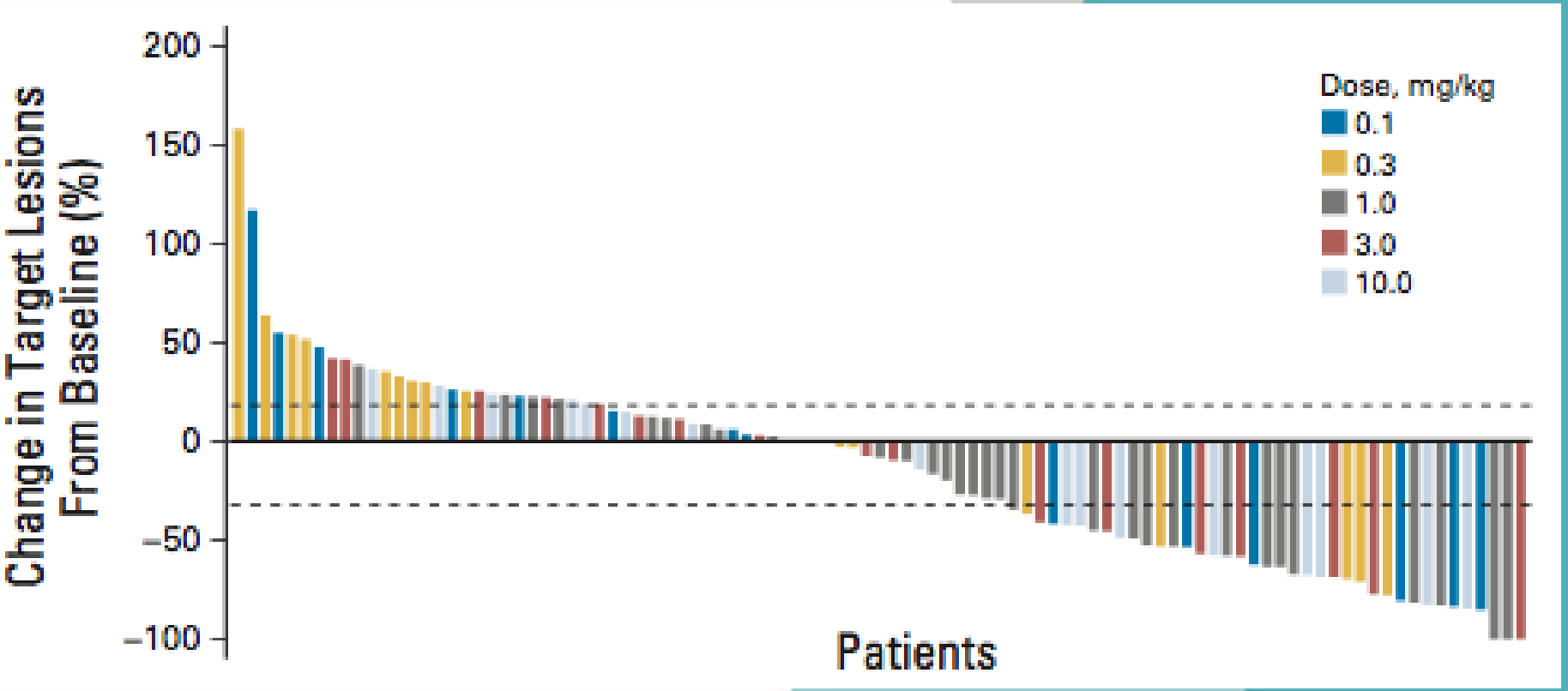
The well-known example of erlotinb…



Hamilton *et al*, CCR 2006

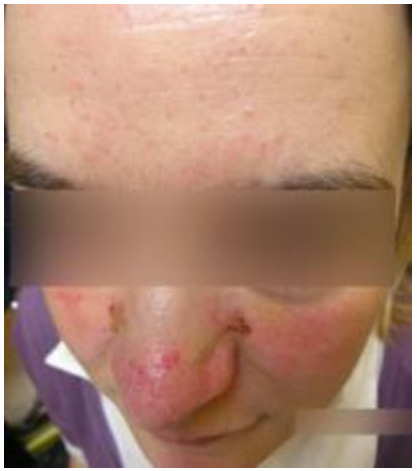
MTD and RP2D determination for Ab and immune checkpoints

Nivolumab phase I (NEJM 2012): no recommendation of the phase II dose

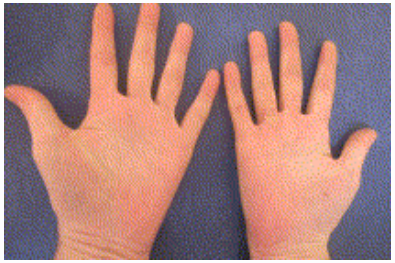


Topalian S. *et al,* JCO 2014

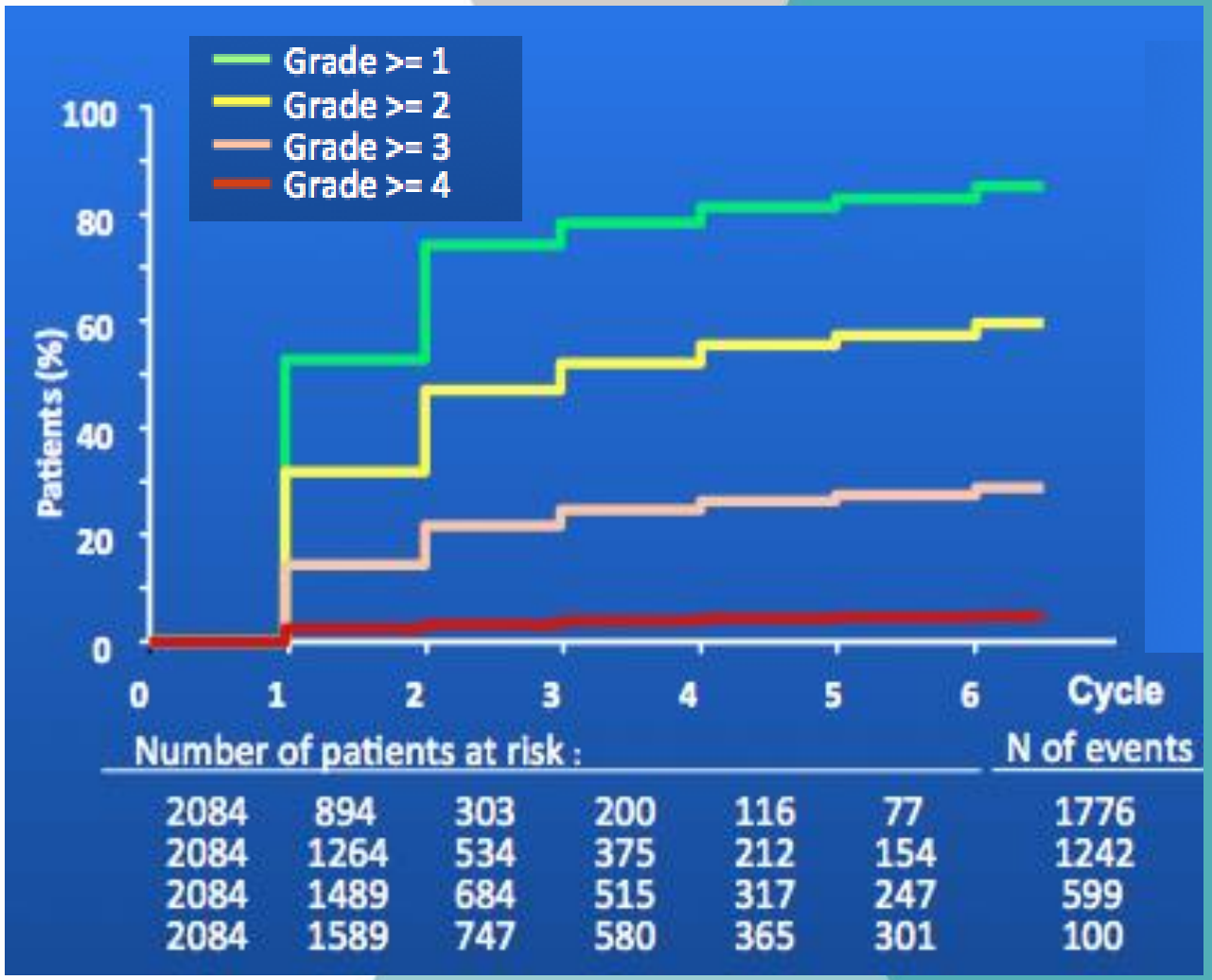
Late & moderate toxicities



Grade 2 folliculitis with EGFR-inhibitors



Grade 1 HFSR with sorafenib



Robert C, Semin Oncol 2012

Postel-Vinay *et al*, ESMO 2013

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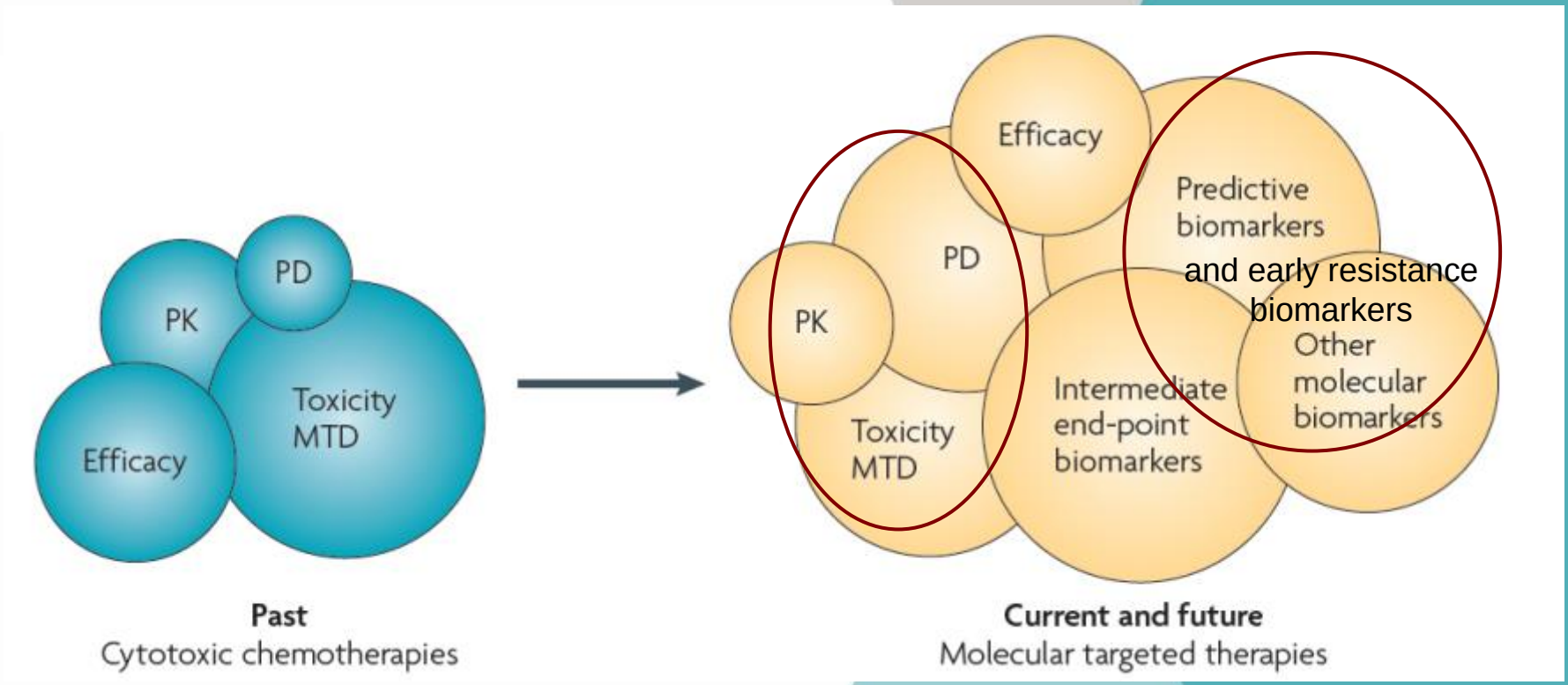
Conclusions

- **Enrichment strategies for patient selection in early drug development**
  - Are sound + Can lead to accelerated approval with a reduced number of patients to be treated

  ONLY IF: (i) target is true driver, (ii) drug really effective in modulating the target, and (iii) companion diagnostic test reliable

  - Organisational, logistical and ethical challenges are diverse
- **Academic centers aiming at developing molecularly-driven early clinical trial programs:**
  - Need to invest on ad hoc multiplexing platforms and related personnel
  - **Need a very large panel of readily available phase I/II trials to deal with the diversity of available targets**
- **Customize the MTD and RP2Dfor MTAs**

Future directions



Yap T. *et al*, NRCO 2010

Acknowledgements

- Pr Jean-Charles Soria
- Dr Benjamin Besse

Thanks a lot for your attention