Evolution de la méthodologie des essais cliniques

David Planchard (MD, PhD)
Department of Cancer Medicine
Thoracic Unit
Gustave Roussy – Villejuif (France)

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

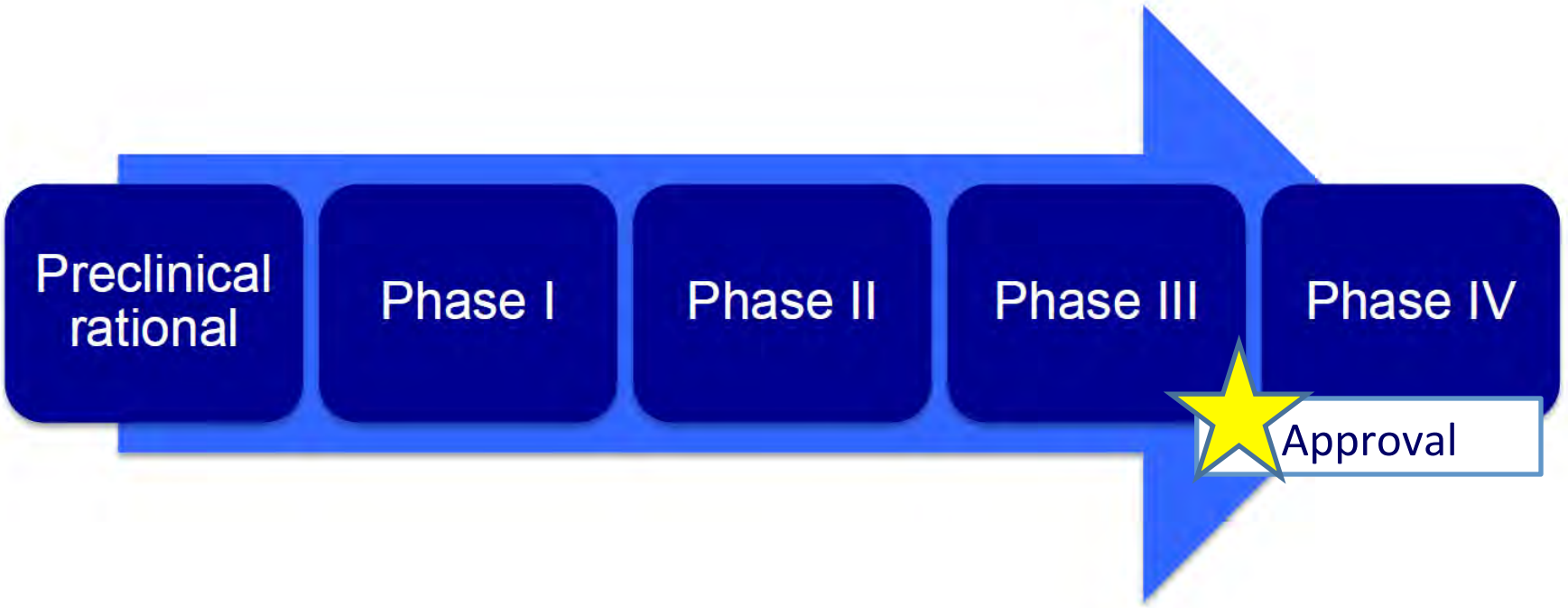
IOT
institut-oncologie-thoracique.com

Disclosure Slide

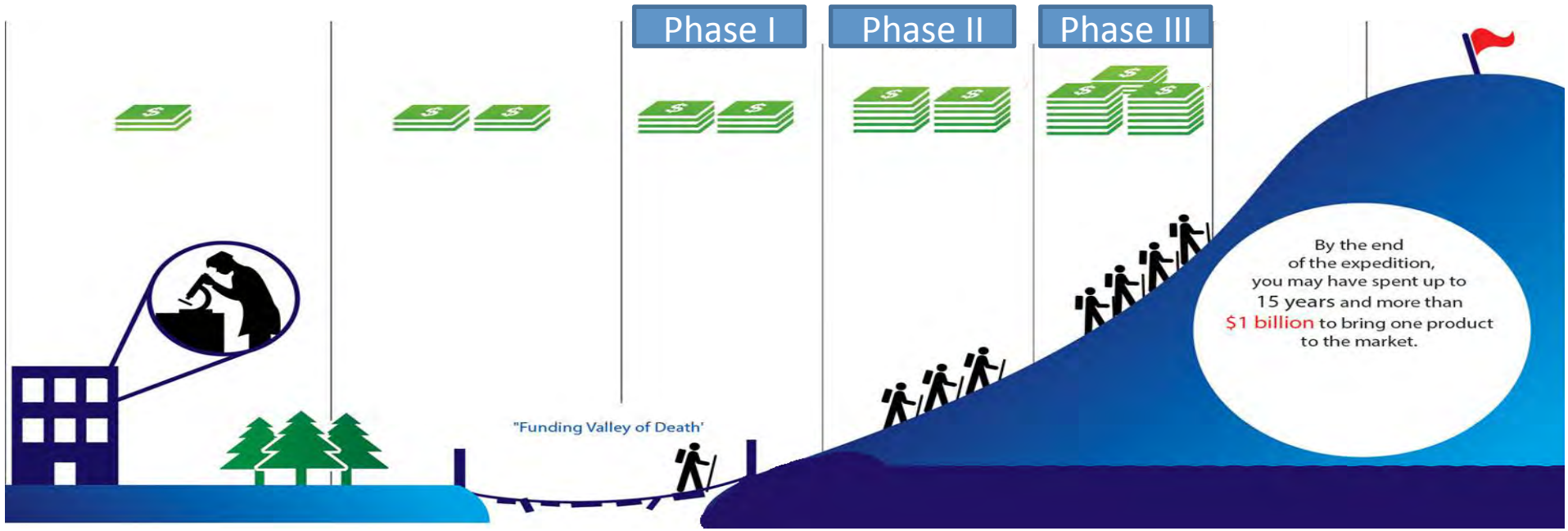
Consultancy fees from

- **AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Novartis**

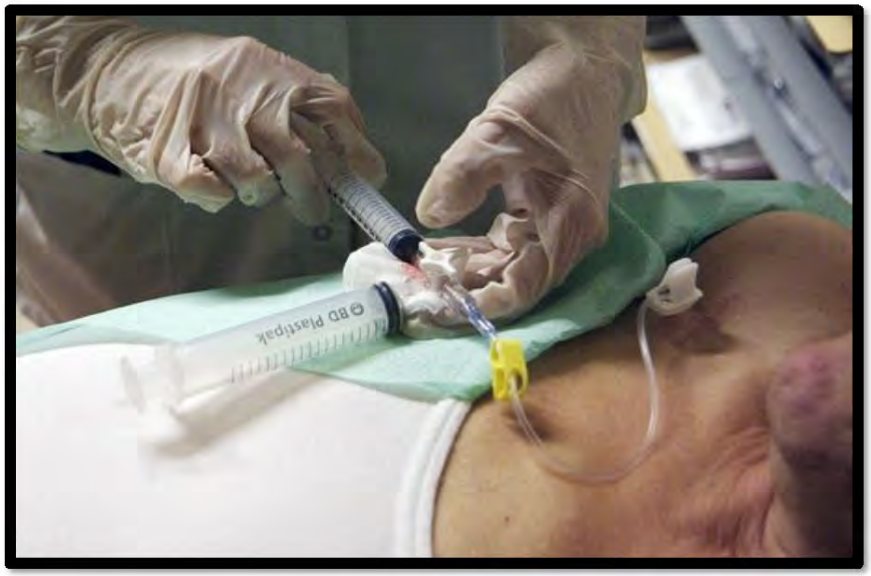
Traditional clinical development



From phase I trials to regulatory approval: climbing the Everest



Phase I cancer studies
« the most critical step from bench to bedside »



Objectives of a typical phase I trial

- **Primary objective**
  - Define the recommended phase II dose (RP2D)
- **Primary endpoint**
  - Identify the presence of dose-limiting toxicities (DLTs)

Dose-limiting toxicity (DLT)

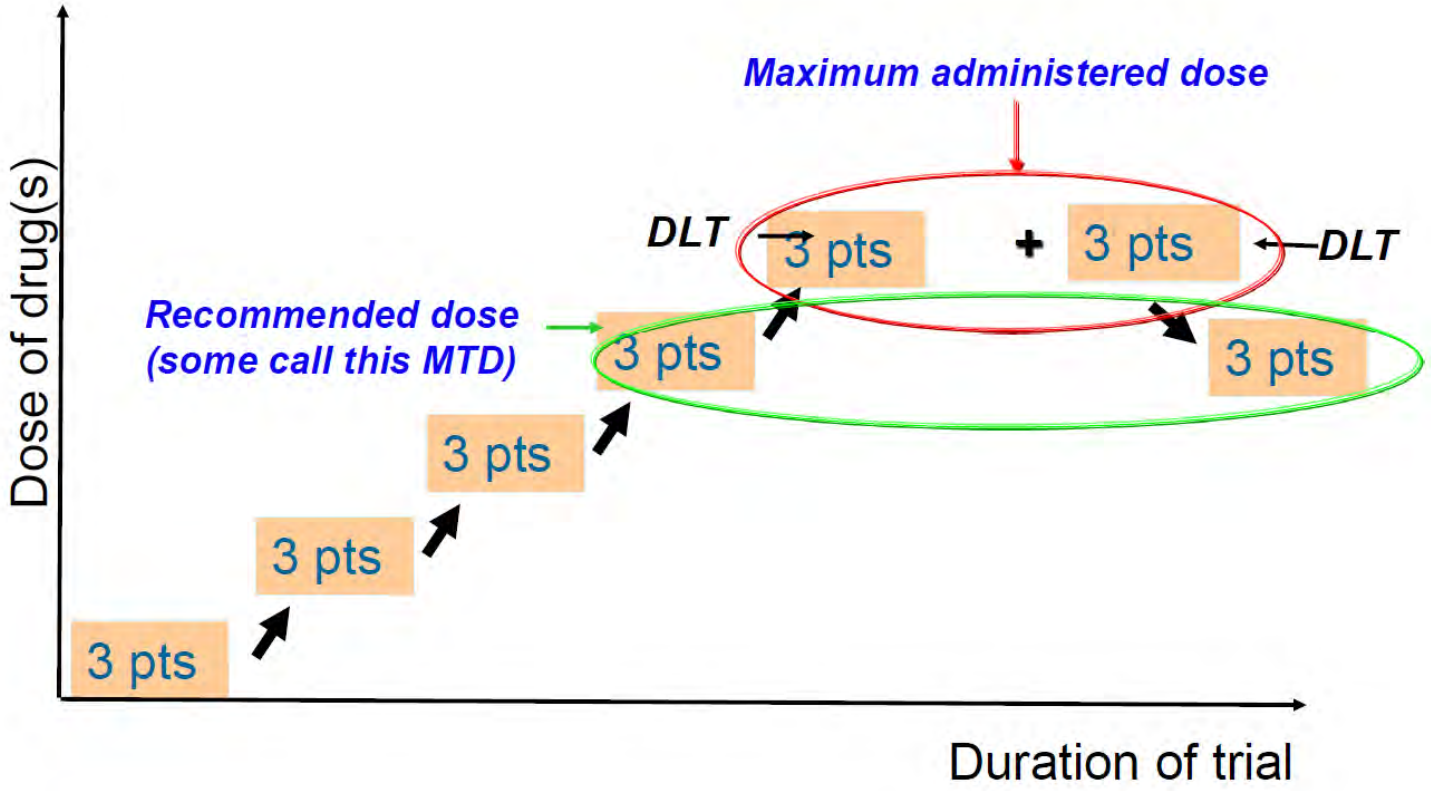
- "Toxicity that is considered unacceptable due to severity and/or irreversibility or because it limits further dose escalation"
- Specified using standardized grading criteria, e.g. Common Terminology Criteria for Adverse Events (CTC-AE, multiple versions)

- DLT is defined in advance prior to beginning the trial and is highly protocol-specific
- Typically defined based on drug-related adverse events seen in the first treatment period (= 1 cycle)

CTC-AE: standard methodology for assessement of adverse events and DLT

BLOOD/BONE MARROW						Page 1 of 1
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow	RAEB or RAEB-T	Death

Phase I trial design: standard 3+3 design

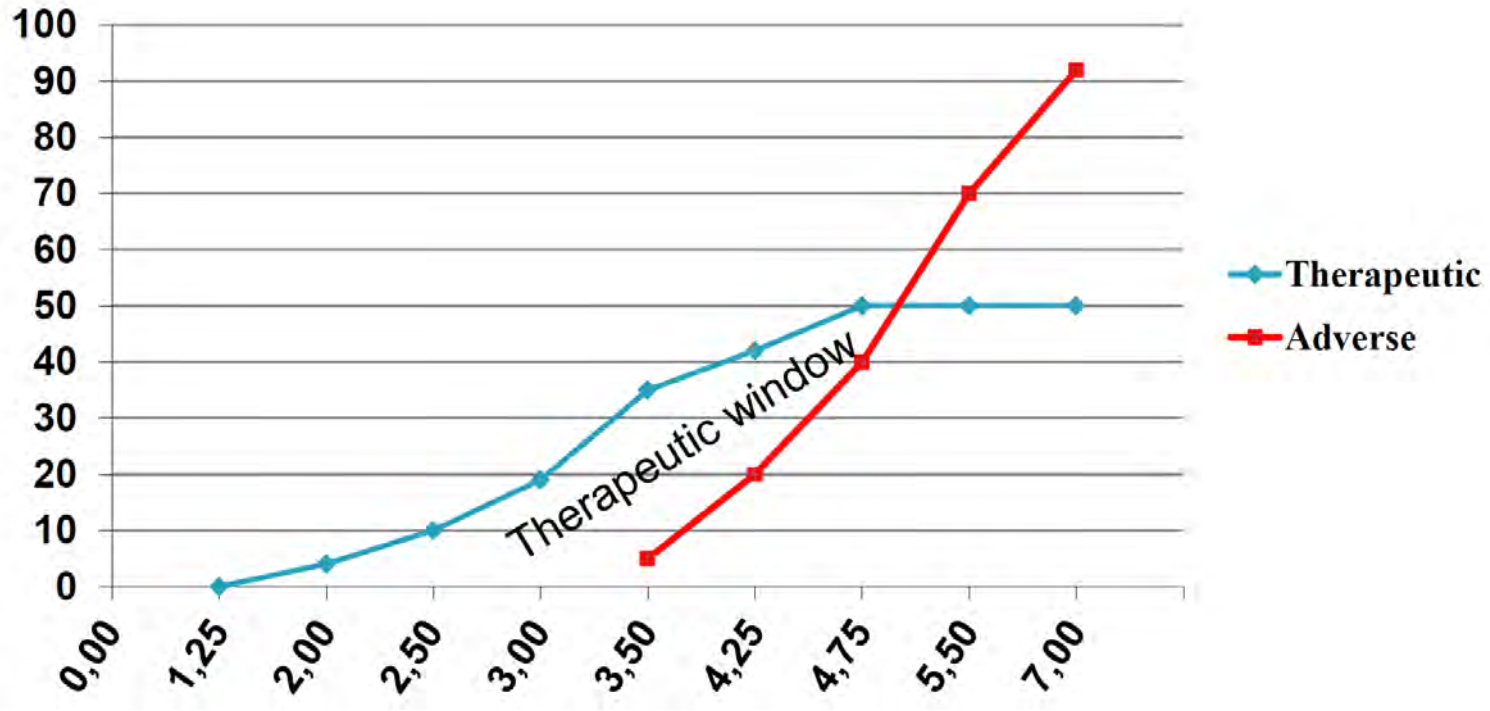


Traditional phase I trial assumption

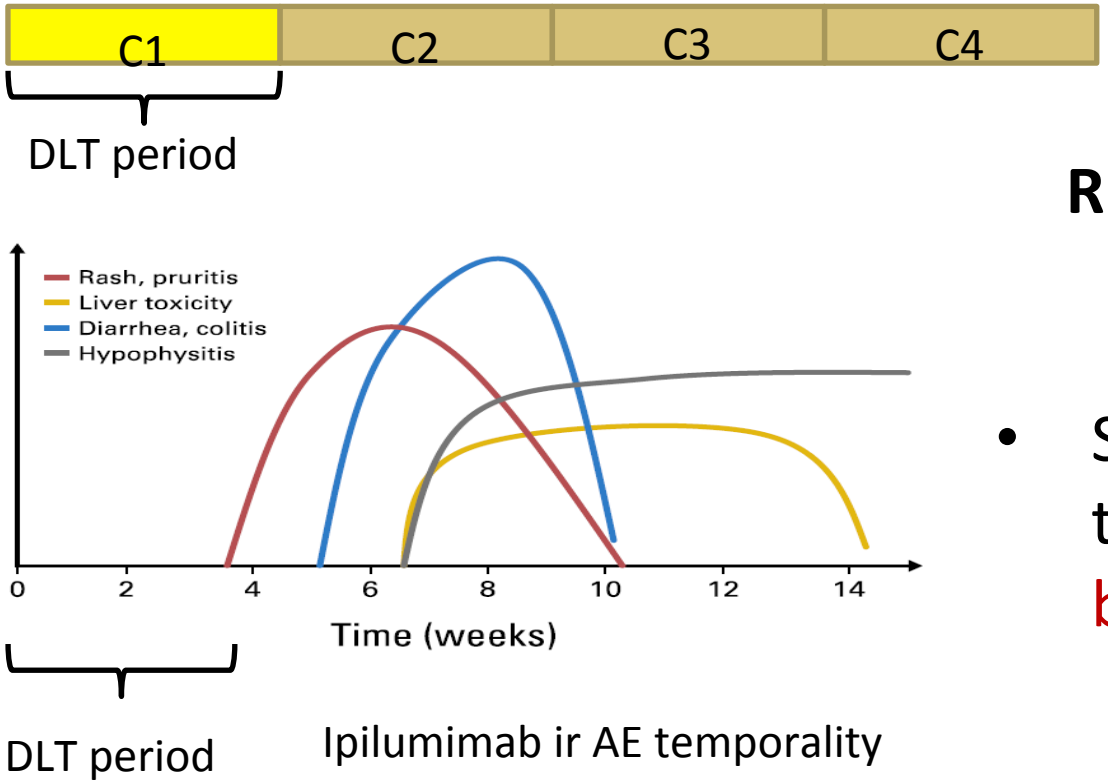
- Assumes increased dose associated with increased chance of efficacy: **"The higher the dose, the greater the likelihood of efficacy"**
  - Dose-related acute toxicity is regarded as a surrogate for efficacy
  - The highest safe dose is the dose most likely to be efficacious

- This dose-effect assumption is primarily valid for cytotoxic agents
- May not apply to (all) molecularly targeted agents

Dose-response: relation between efficacy and toxicity



Kinetics of irAE with imAbs



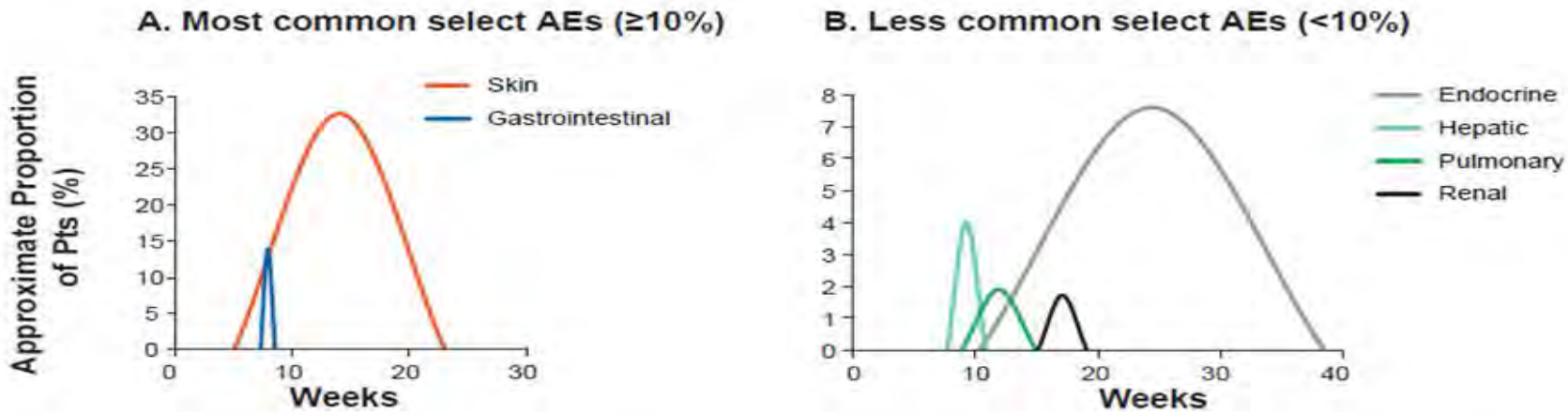
Ipilumimab ir AE temporality

RP2D: RECOMMENDED PHASE 2 DOSE

- Should encompass toxicities observed beyond cycle 1

Postel-Vinay S et al, EJC 2014
Kaehler, KC et al Semin Oncol 2010

Kinetics of Onset and Resolution of Select Nivolumab Treatment-related AEs (Any Grade)



- Select AEs generally resolved within several weeks, apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Presented By Michael Postow at 2015 ASCO Annual Meeting

Special situation: Phase I trials with targeted agents

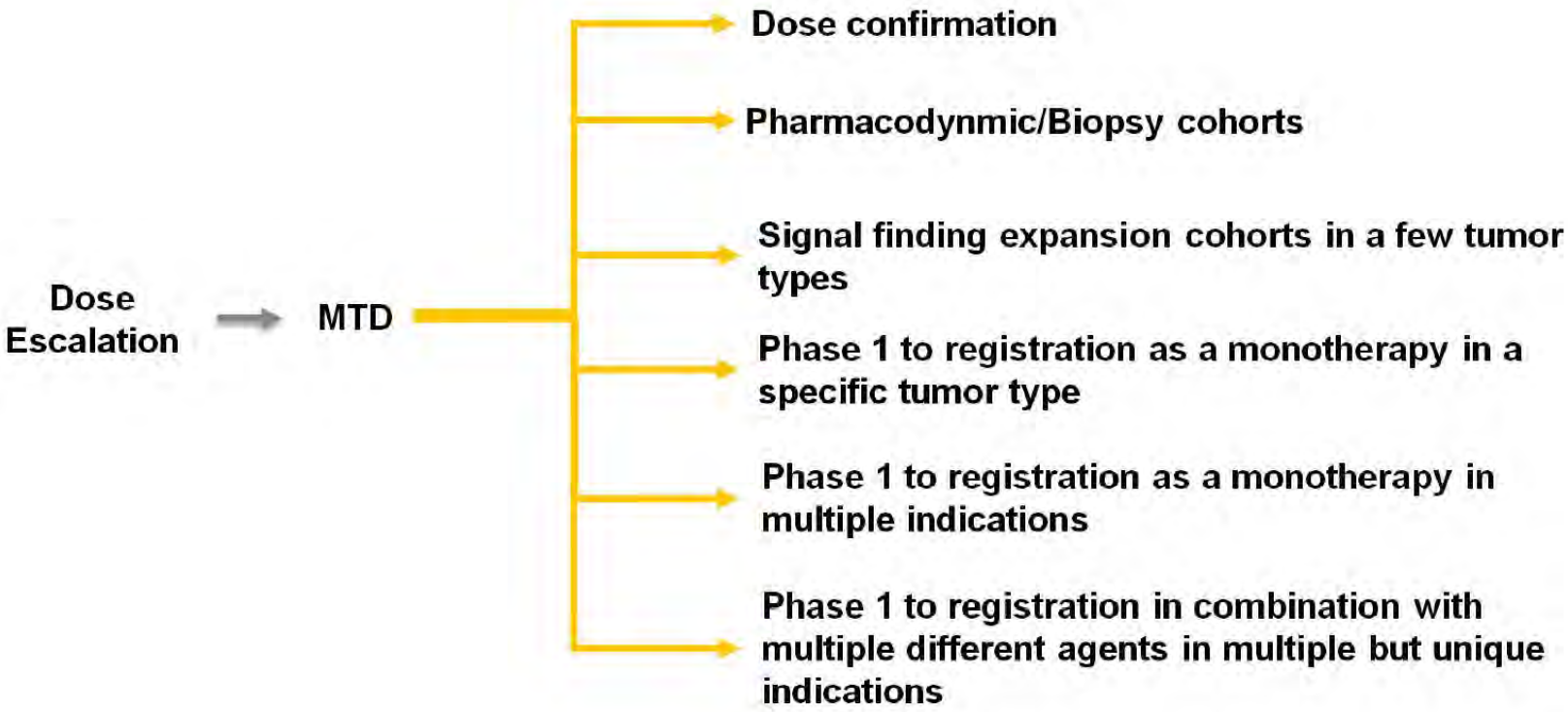
- **Targeted agents differ from cytotoxic agents, as they can be therapeutically active below toxic doses**
  - Conventional Phase I trial design, based on dose escalation until toxicity reached, is likely inappropriate
  - Reaching MTD may not be the goal of such Phase I since the specificity of effect may be lost at MTD

- **Another potencial goal: identify "biologically effective" or "optimal biologically dose"**
  - Paradox: requires early development and integration of (frequently unvalidated) measures of biologic effect into Phase I trial (the so-called "surrogate endpoints")

Responses in phase I trials

- **Classic cytotoxic agents: response rates in studies from the 80's and 90's ranged from 2 – 9% (overall <5%)**
  - Activity in those Phase I trials in that period suggested that the agent might find a role in oncology
- **Currently, clinical benefit rates, including prolonged stabilizations of disease, occur in aprox 1 out of 3 patients in ph1 studies**
  - Activity in these Phase I trials might lead to regulatory approval or fast track designation

Evolution of phase I study designs, after MTD achieved



Early phase trials are getting larger !

Fast-track designation or even regulatory approval might be a potential goal!!

Jeffrey Infante at 2016 ASCO Annual Meeting

Anaplastic Lymphoma Kinase (ALK) Inhibition

Phase I

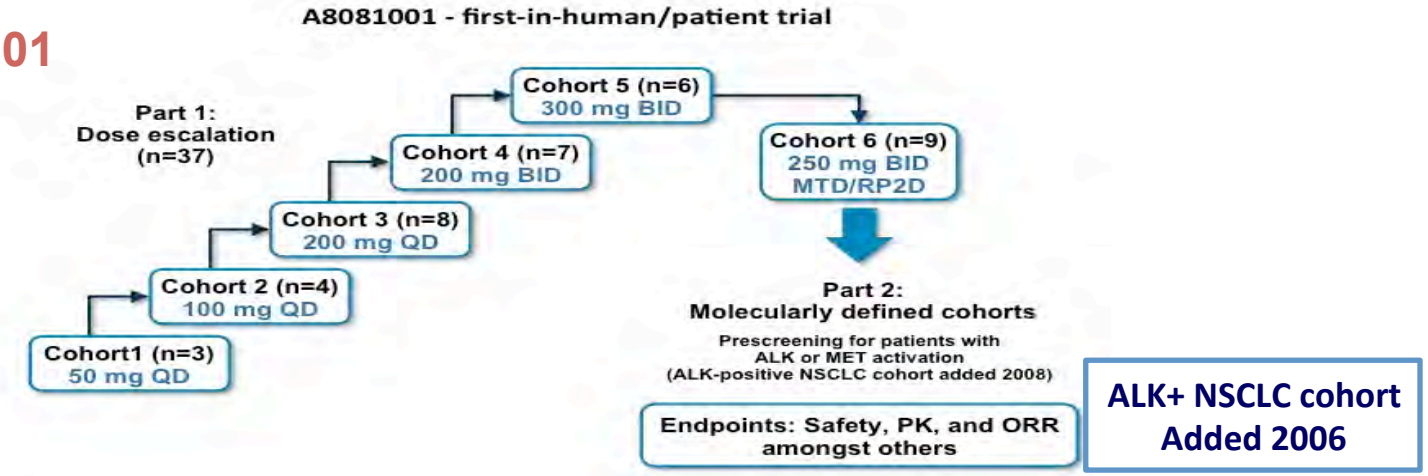
Part 1: toxicity, MTD, PK in non-enriched patient cohort
250mg crizotinib b.i.d., 28-day cycles
2 *ALK* rearranged patients reached PR
(1 myofibroblastic tumor, 1 NSCLC)

Part 2: Original plan
to assess clinical activity at the dose recommended for phase II in the molecularly enriched cohort of *MET* amplified tumors

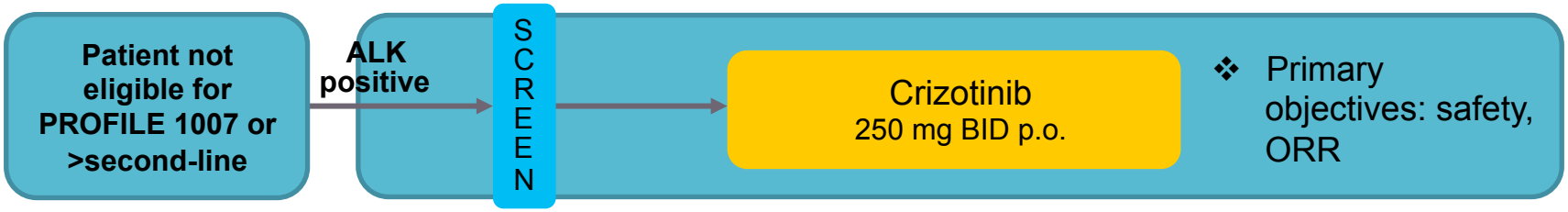
Clinical reality
additional cohort of *ALK* rearranged NSCLC patients

A8081001 and PROFILE 1005 trials for patients with advanced ALK-positive NSCLC

Phase I: A8081001

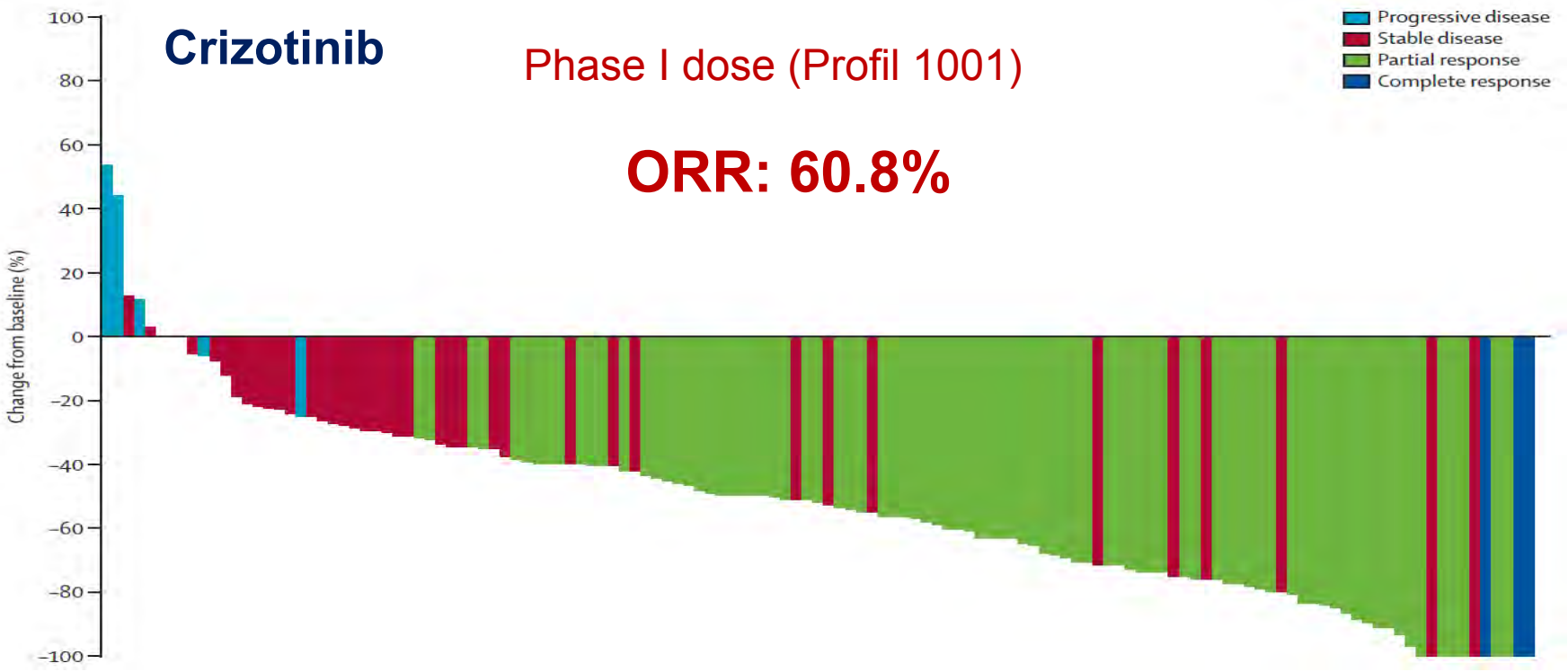


Phase II: PROFILE 1005



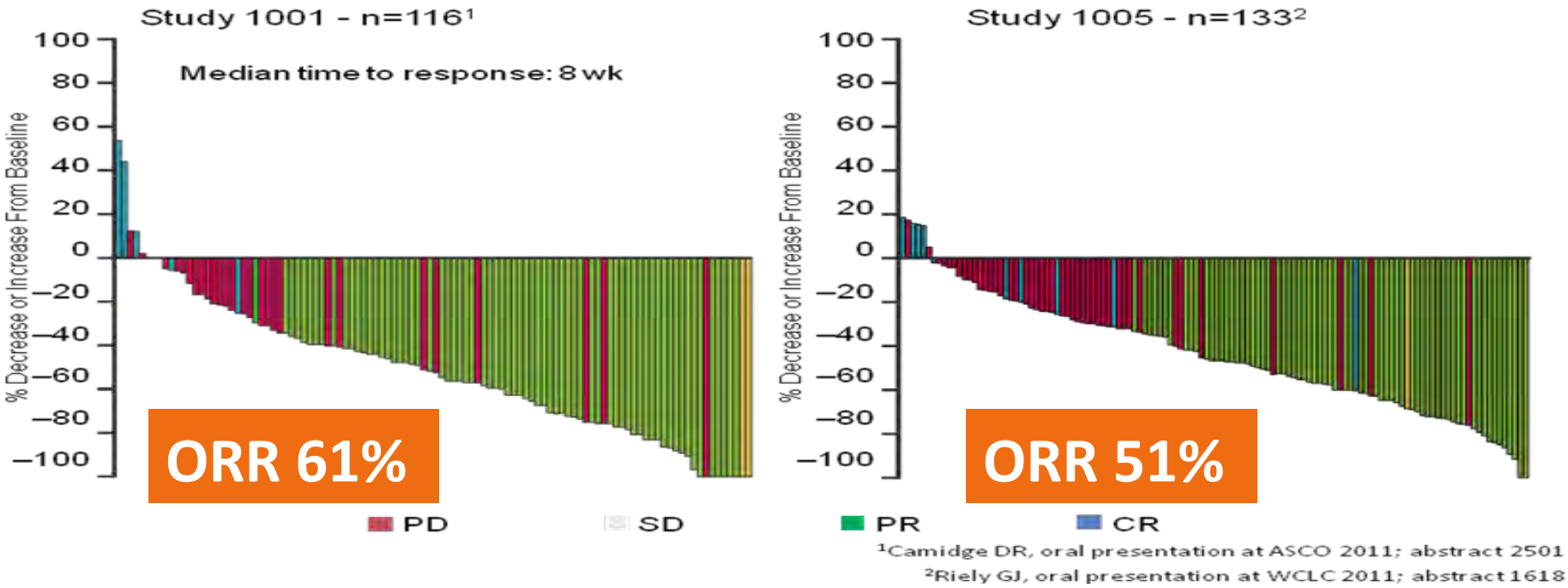
PROFILE 1001: NCT00585195; PROFILE 1005:NCT00932451

Waterfall plot of best percent change in target lesions from baseline for 133 patients on the basis of investigator assessment



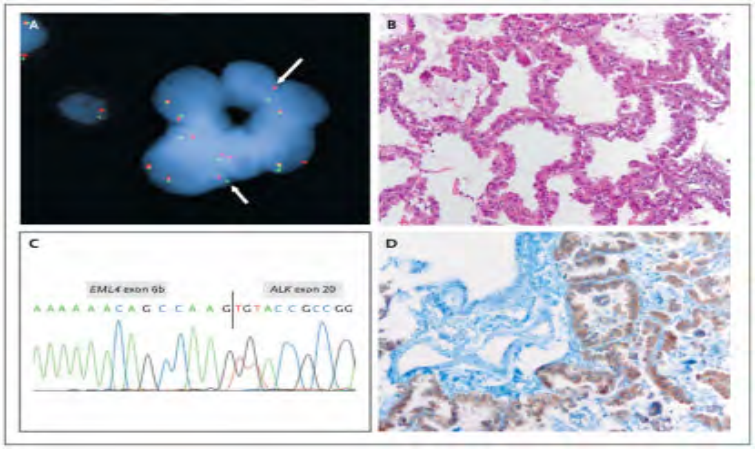
D Ross Camidge et al, lancet onco 2012

Response rates to ALKi crizotinib in ALK+ NSCLC patients (phase I&II)

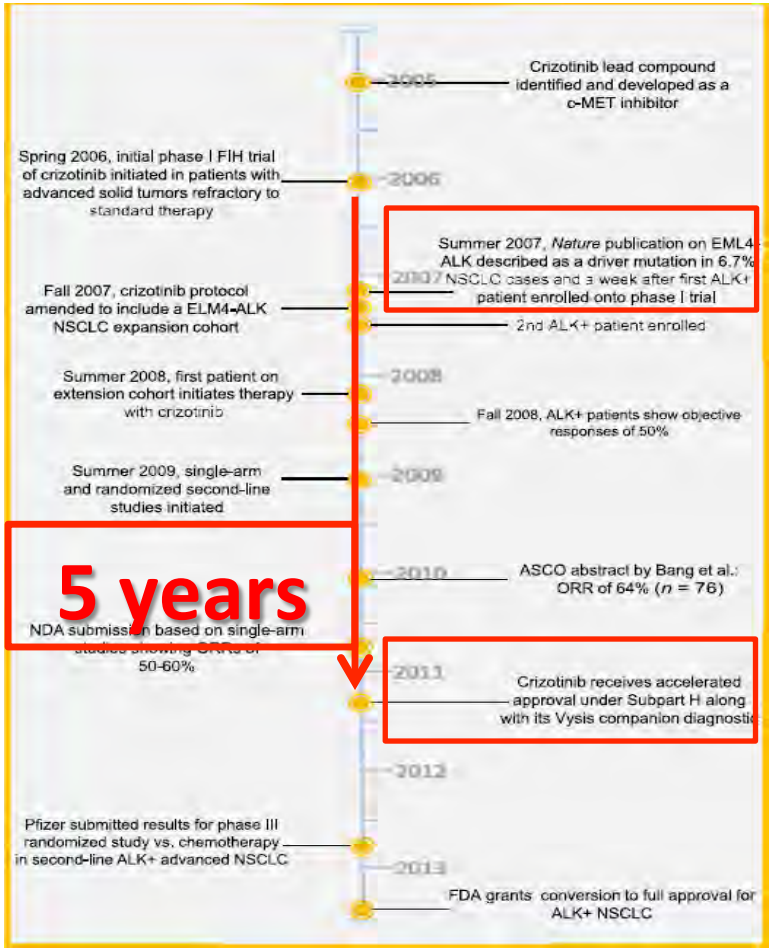


Eunice L. Kwak et al, NEJM 2010

The crizotinib example

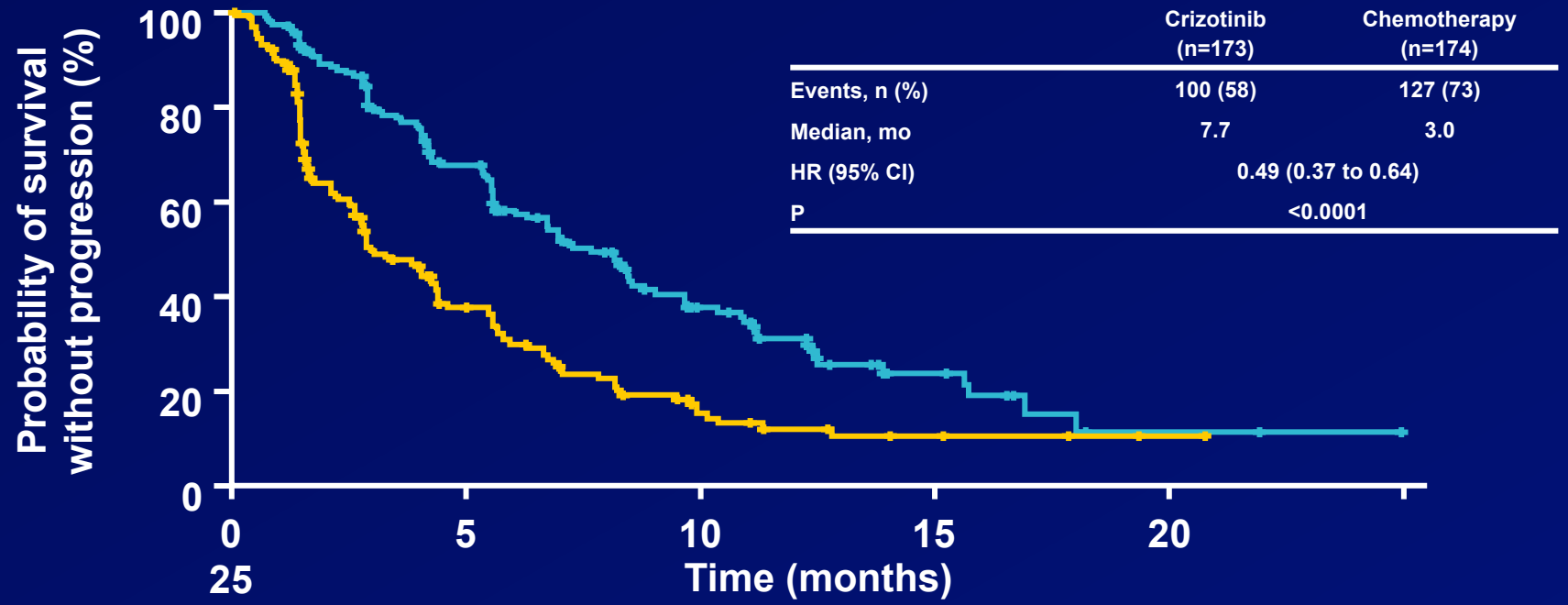


→ Crizotinib registered on the basis of phase I and II single arm data by FDA (n= 119 and n=136)



Courtesy Jessica Menis

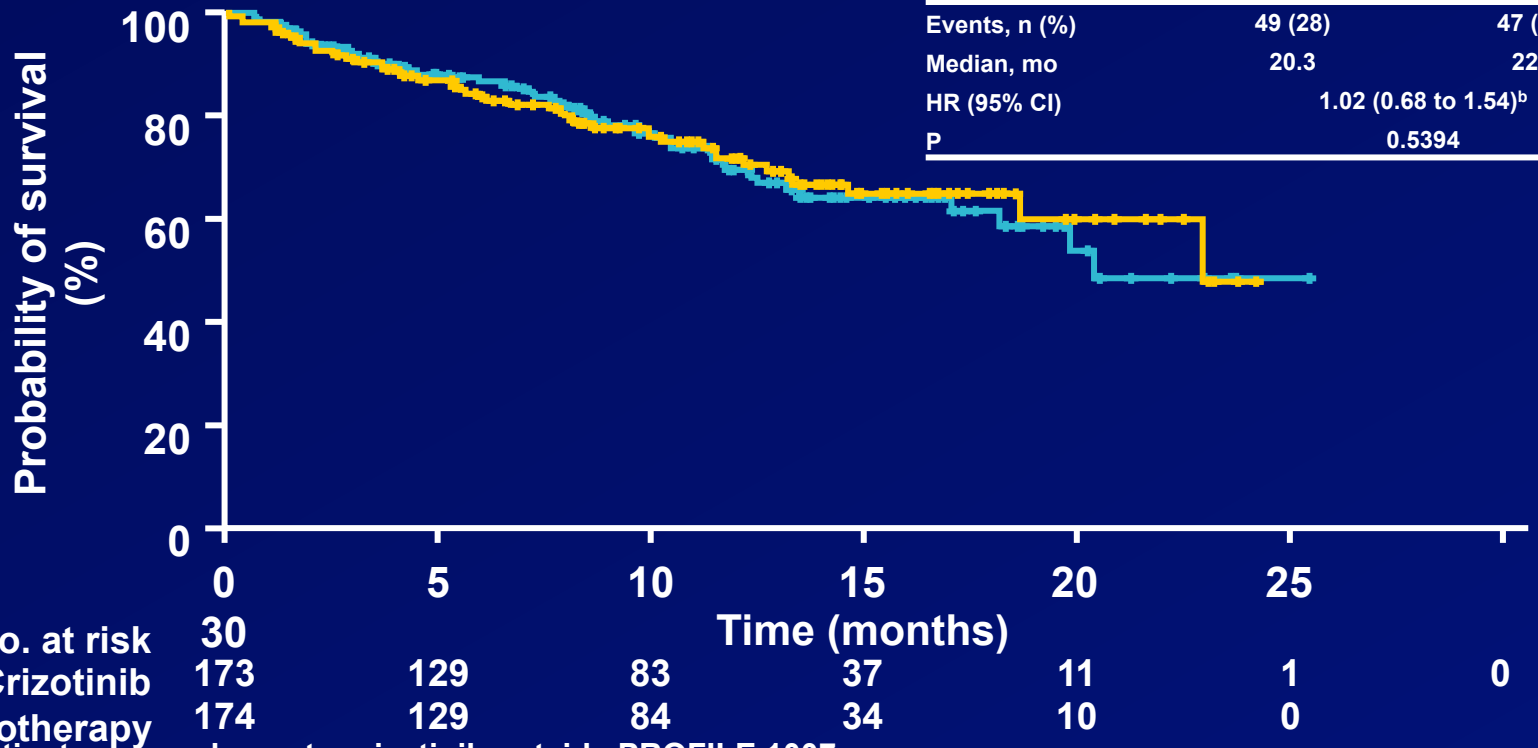
Beyong first line
Progression free survival (Profil 1007)



	Crizotinib (n=173)	Chemotherapy (n=174)
Events, n (%)	100 (58)	127 (73)
Median, mo	7.7	3.0
HR (95% CI)	0.49 (0.37 to 0.64)	
P	<0.0001	

Shaw, et al. N Engl J Med 2013

Interim Analysis of OS (Profil 1007)



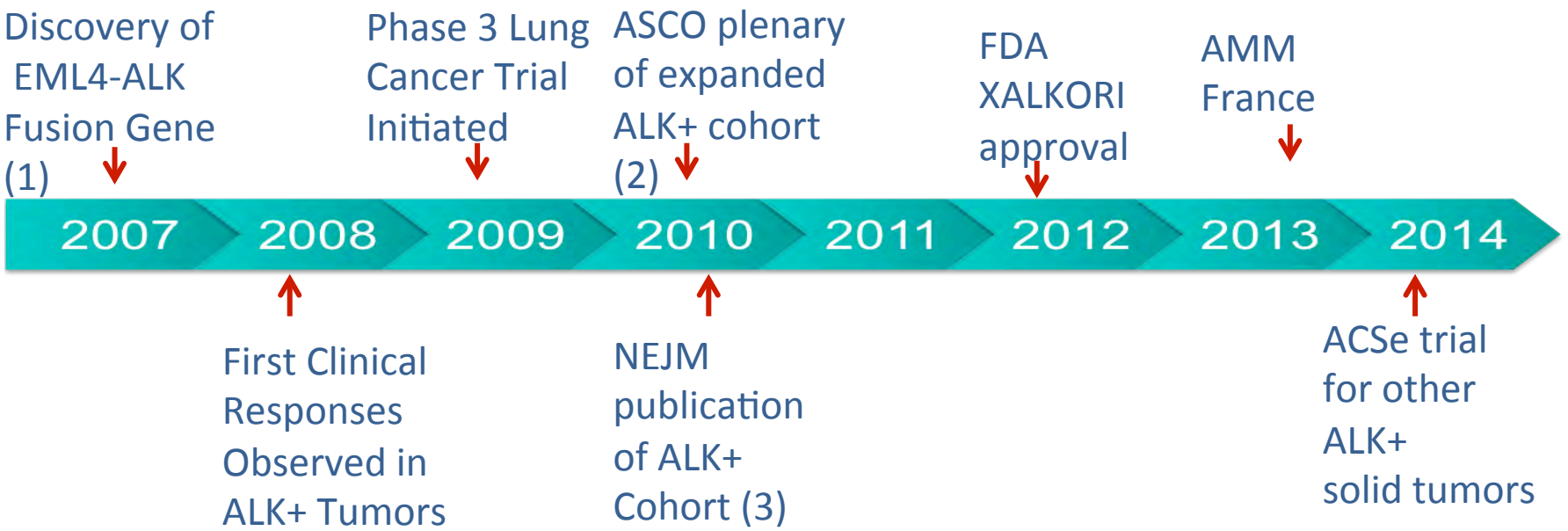
	Crizotinib (n=173)	Chemotherapy[a] (n=174)
Events, n (%)	49 (28)	47 (27)
Median, mo	20.3	22.8
HR (95% CI)	1.02 (0.68 to 1.54)[b]	
P	0.5394	

[a]111 patients crossed over to crizotinib outside PROFILE 1007

[b]HR adjusted for crossover using rank-preserving structural failure time method: 0.83 (0.36 to 1.35)

CRIZOTINIB

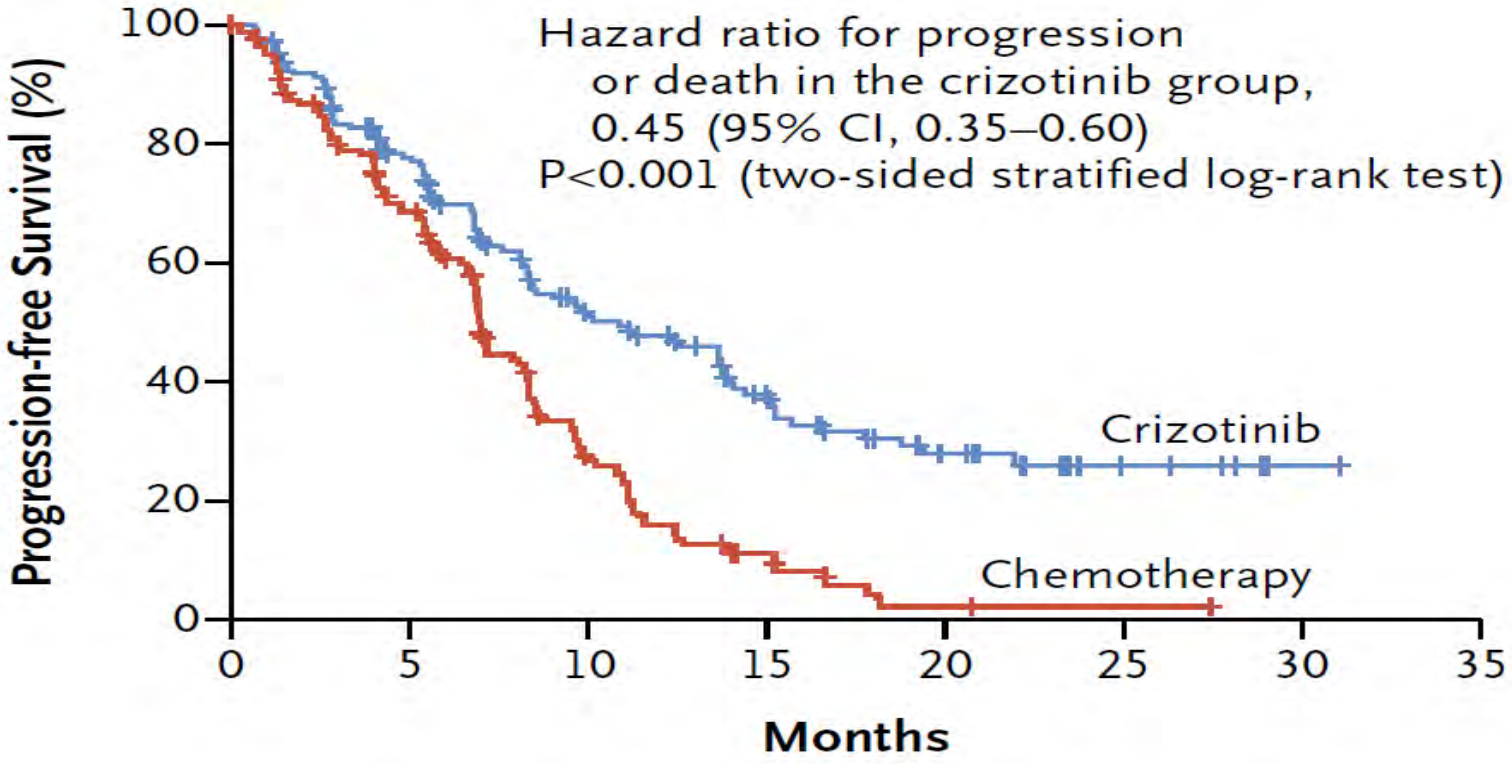
Rapid Timeline from Compound Identification, Target Discovery and Clinical Results



1. Soda et al. Nature 2007, 448: 561.
2. Bang JY et al. Oral presentation at ASCO, 2010
3. Kwak et al. New Engl J Med. 2010;363:1693–03

First line

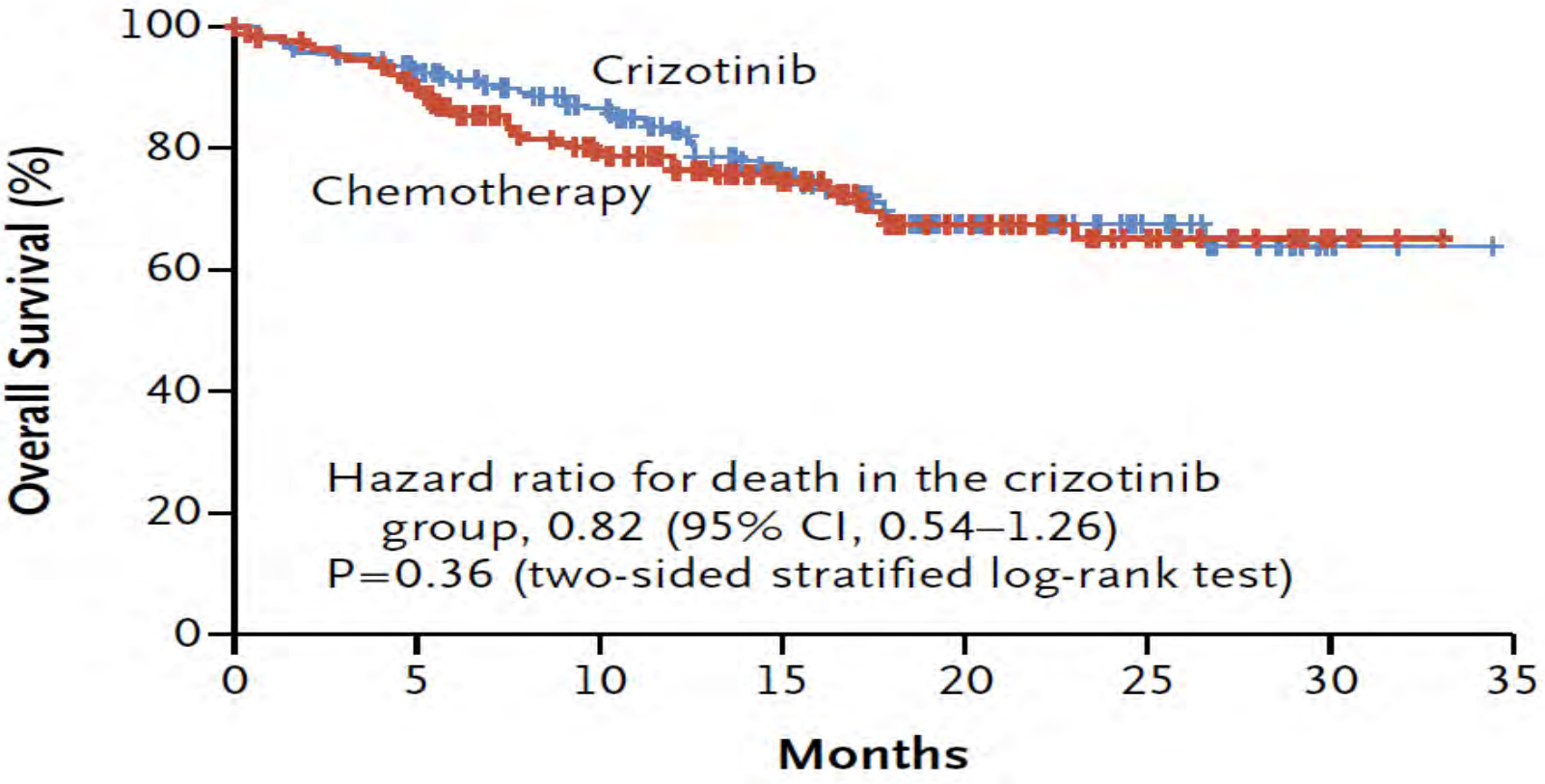
Progression-free-Survival (PROFILE 1014)



10.9 (95% CI, 8.3 to 13.9) vs 7.0 months (95% CI, 6.8 to 8.2)

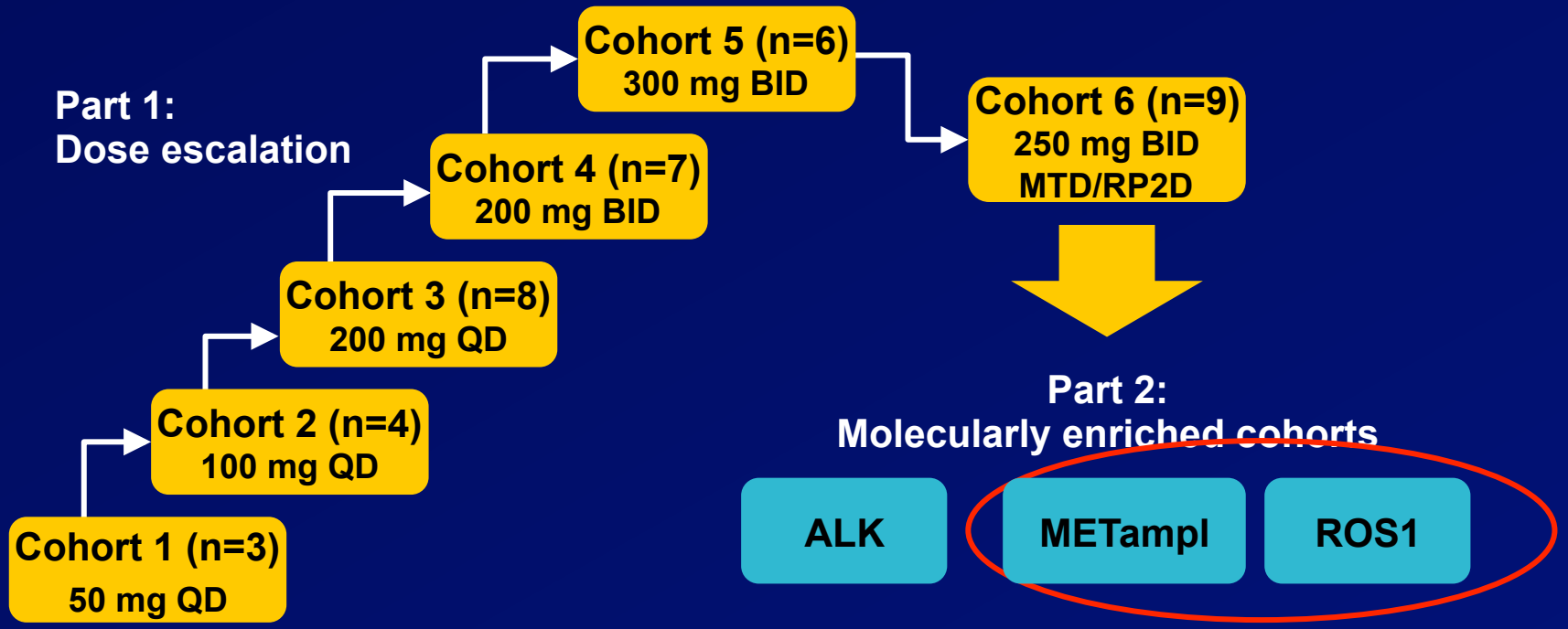
Benjamin J. Solomon et al, NEJM 2014

Overall Survival



Benjamin J. Solomon et al, NEJM 2014

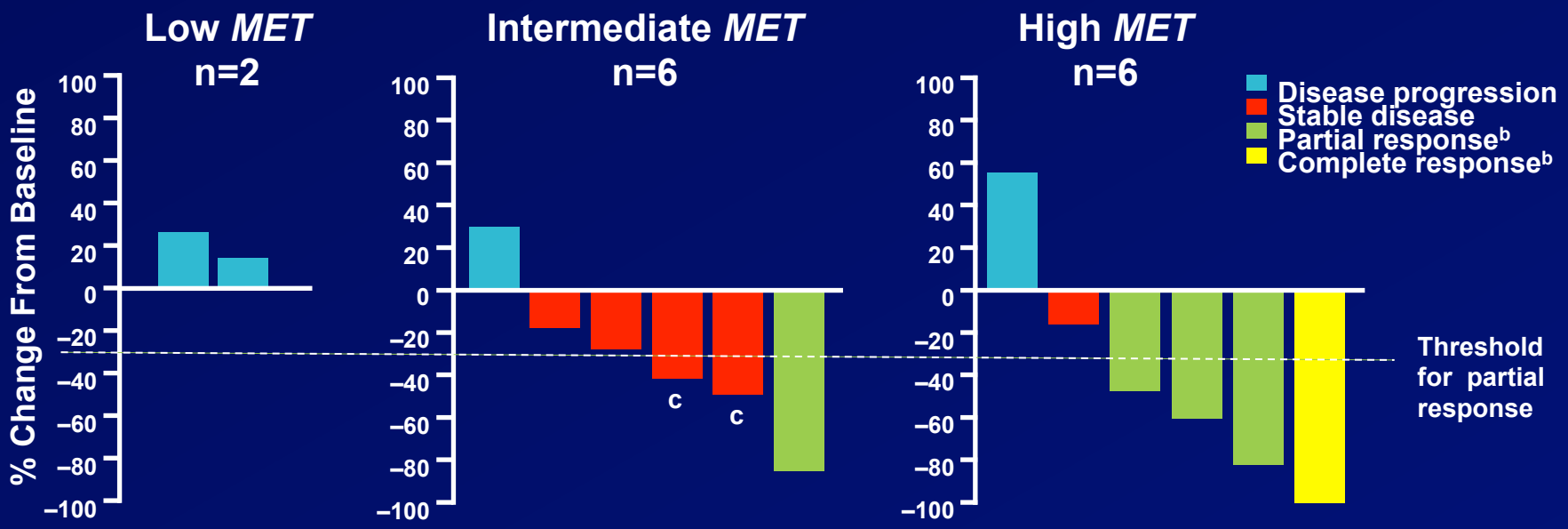
Crizotinib: First-in-human/patient trial (Study A8081001)



NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose

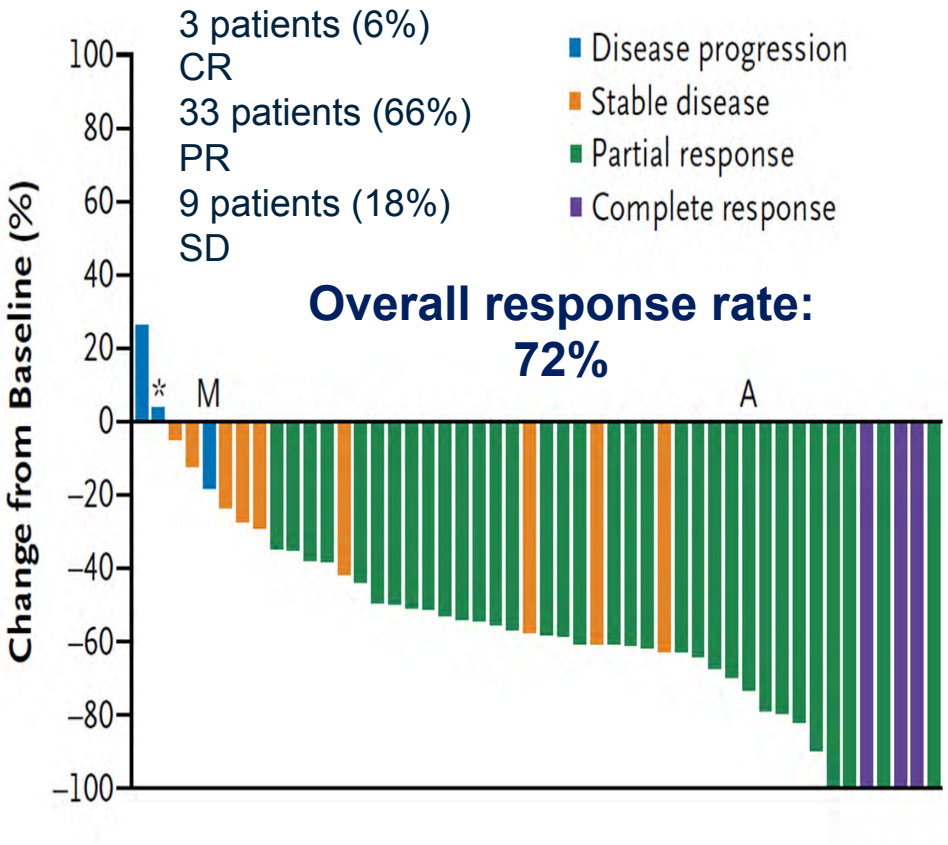
Tumor Shrinkage Seen in Intermediate and High *MET* Cohorts

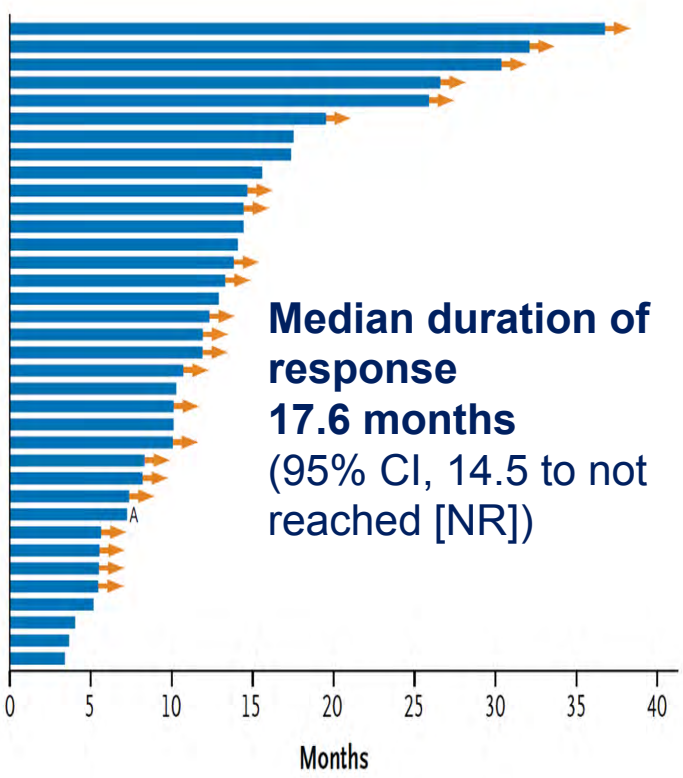
Best percent change from baseline in target tumor lesions[a] by patient



[a]Confirmed objective responses.
[b]Based on investigator assessment.
[c]Two patients in the intermediate *MET* group had an unconfirmed PR that was not confirmed in a second assessment.

Crizotinib and ROS1 pts

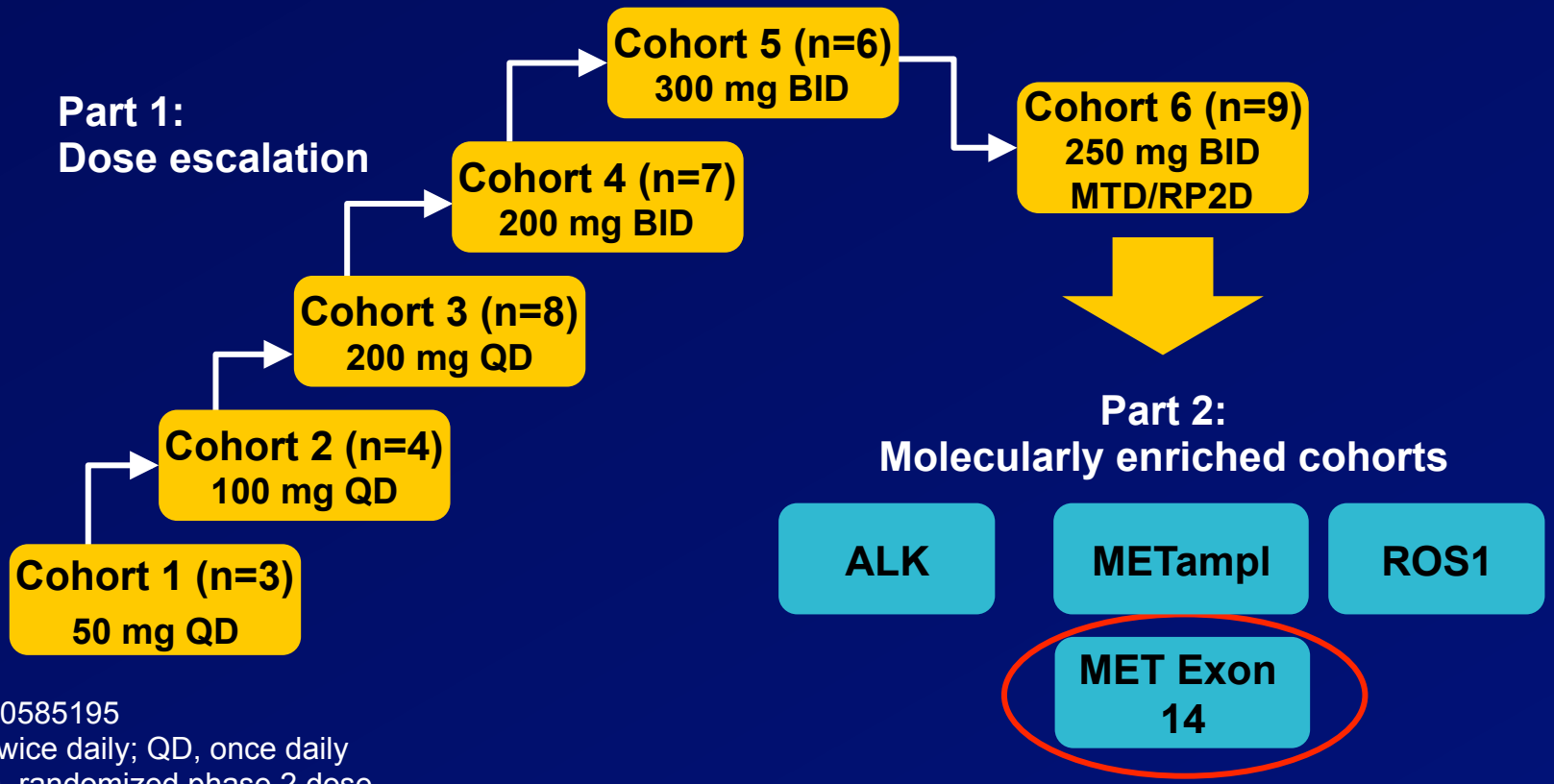




Median duration of response
17.6 months
(95% CI, 14.5 to not reached [NR])

Alice T. Shaw *et al.,* NEJM 2014

Crizotinib: First-in-human/patient trial (Study A8081001)



NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose

Antitumor Activity of Crizotinib in Patients with Advanced MET Exon 14-Altered NSCLC (PROFILE 1001 Study)

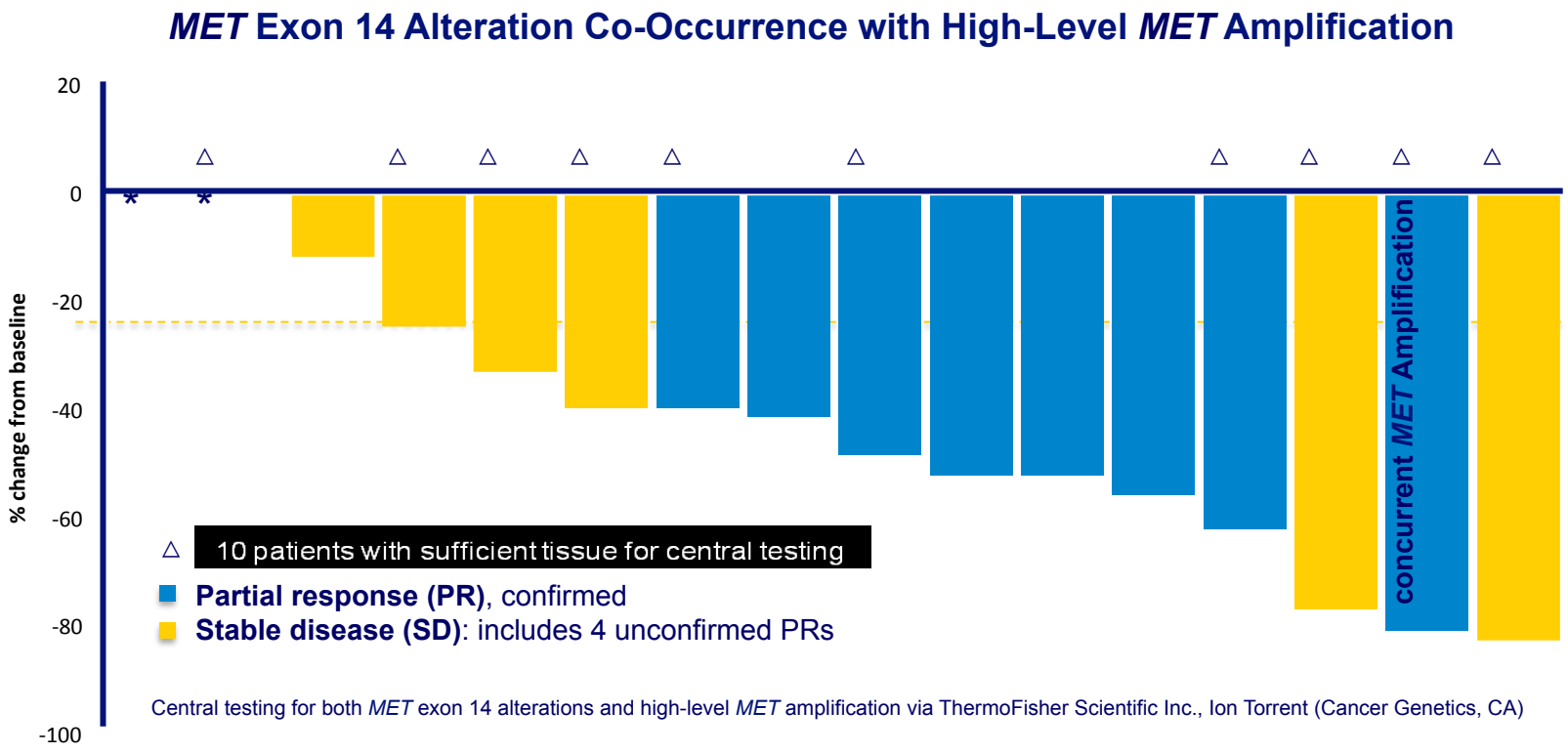
Response-Evaluable Population (n=18)		
Best overall response n (%)	Complete response (CR)	0
	Partial response (PR)	8 (44%)
	Stable disease (SD)	9 (50%)
	Unconfirmed CR/PR †	5 (28%)
	Progression of Disease (PD)	0
	Indeterminate ‡	1 (6%)
Overall response rate (ORR)		**44% (95% CI: 22–69), n=8/18**

† of the 5 patients: 2 awaiting confirmation, 3 cannot be confirmed

‡ this patient discontinued therapy in cycle 1, response imaging could not be performed but response-evaluable per protocol

Alexander Drilon MD et al, ASCO 2016

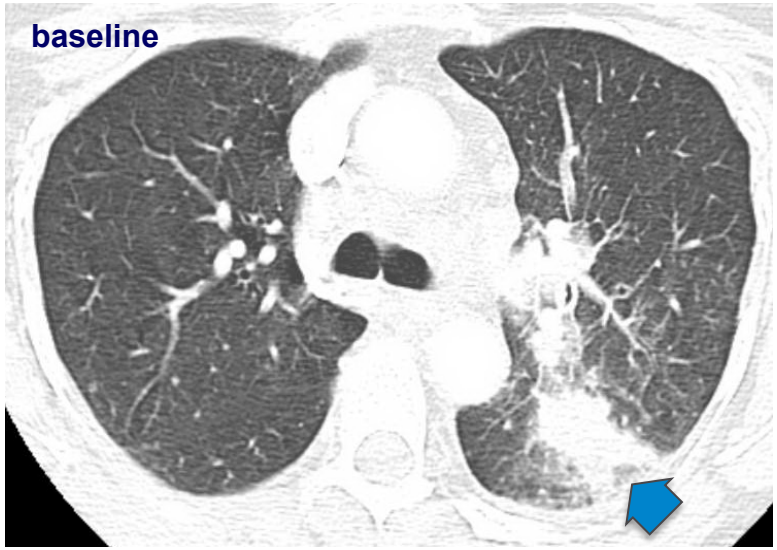
Antitumor Activity

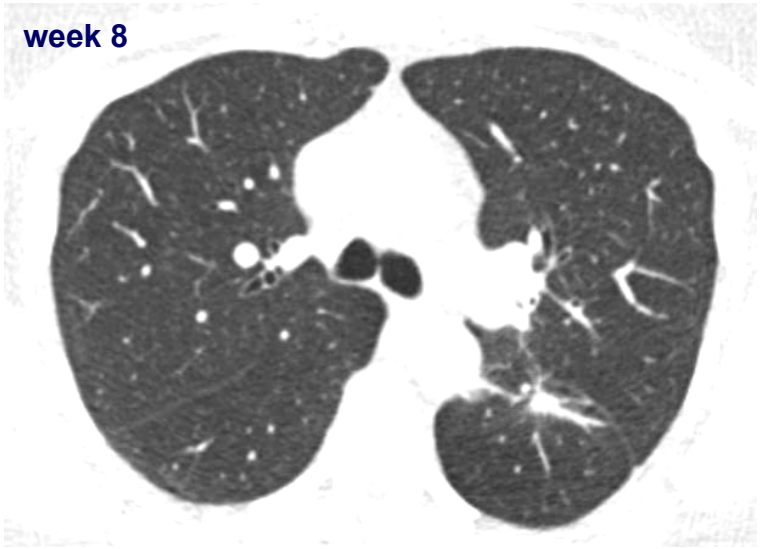


Alexander Drilon MD et al, ASCO 2016

Antitumor Activity

- 54 year-old female with *MET* exon 14-altered lung adenocarcinoma
  - metastatic disease involving lung and lymph nodes, treatment-naive
  - confirmed partial response with crizotinib (-48%), ongoing at 5+ months*



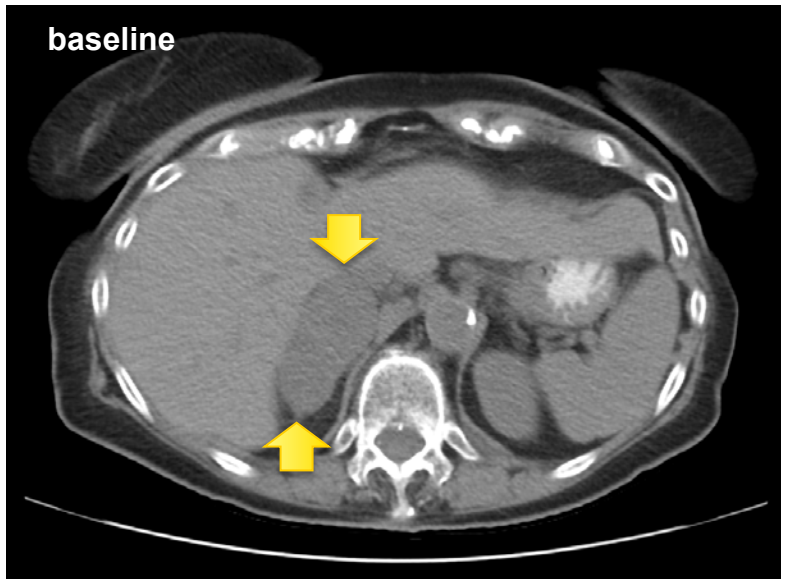


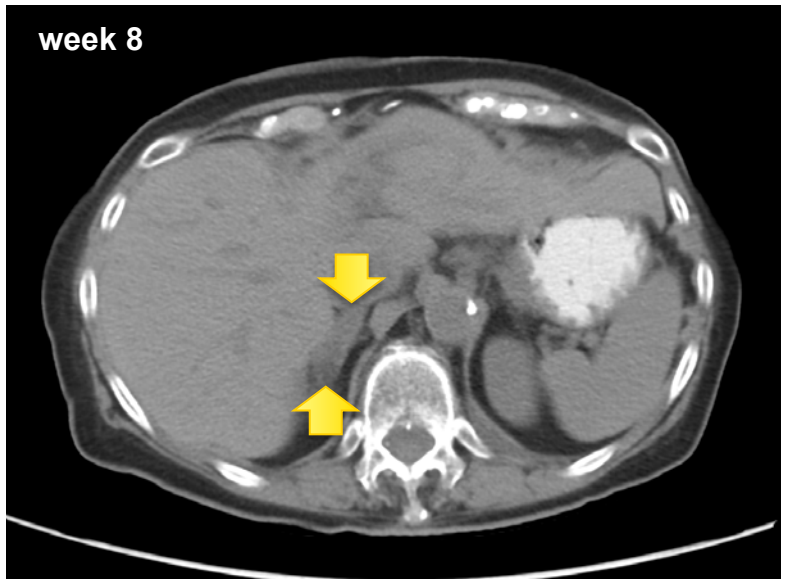
*response duration as of May 2016, Images courtesy of Ross Camidge, University of Colorado Cancer Center

Alexander Drilon MD et al, ASCO 2016

Antitumor Activity

- 87 year-old female with *MET* exon 14-altered sarcomatoid lung cancer
  - history of stage IIB disease, recurrent metastatic disease involving the adrenal
  - durable partial response (-60%) with crizotinib, ongoing at 8+ months*



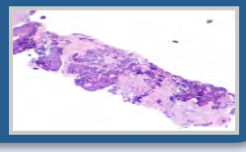


*response duration as of May 2016, Images courtesy of Alexander Drilon, Memorial Sloan Kettering Cancer Center

Alexander Drilon MD et al, ASCO 2016

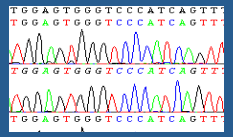
Standard precision medicine approach

Tumor sample

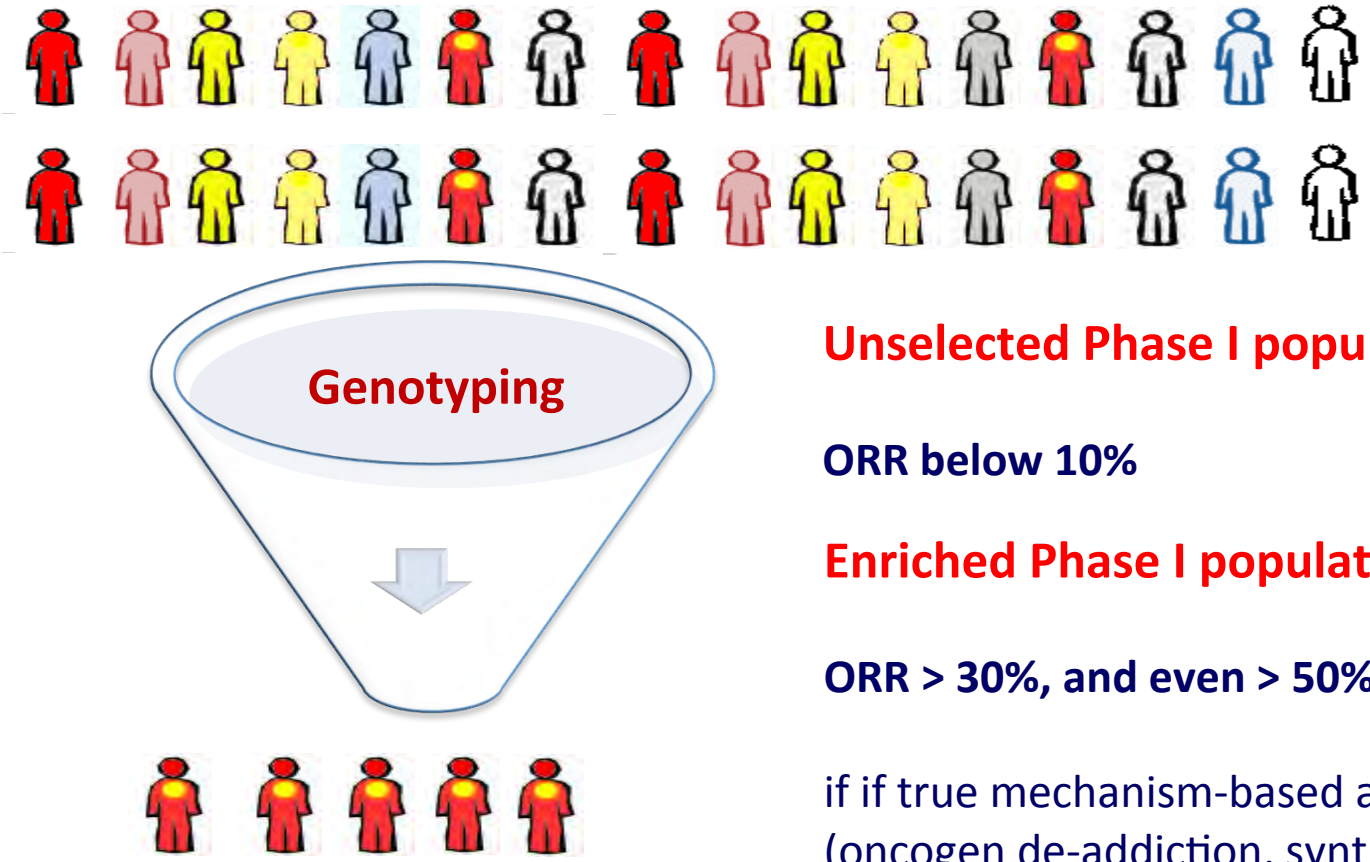


Structural DNA analysis

Mutational profile



Matched targeted therapy



Unselected Phase I population

ORR below 10%

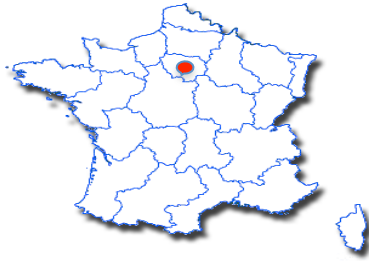
Enriched Phase I population

ORR > 30%, and even > 50%

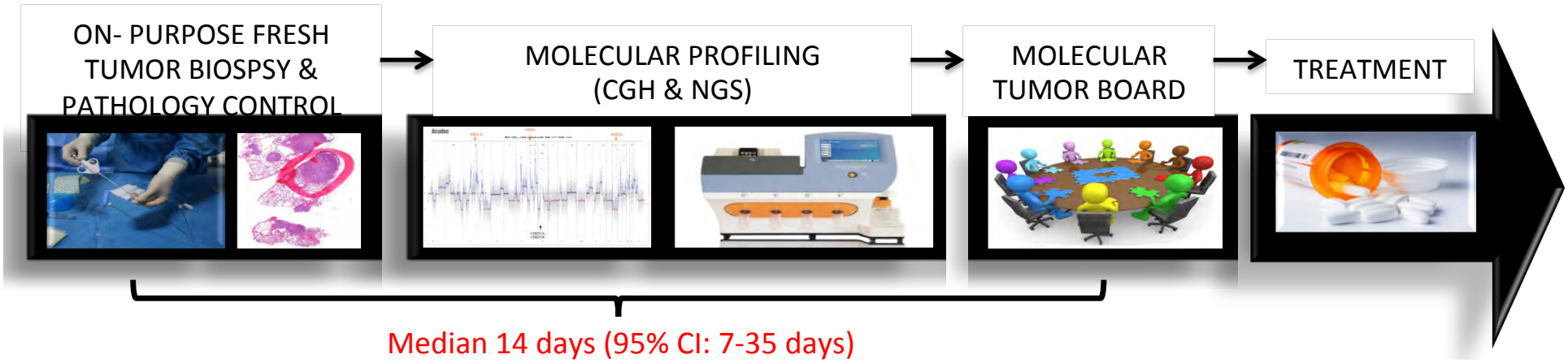
if if true mechanism-based approach
(oncogen de-addiction, synthetic lethality)

MOSCATO-01 prospective molecular screening program

- Monocentric (Gustave Roussy)

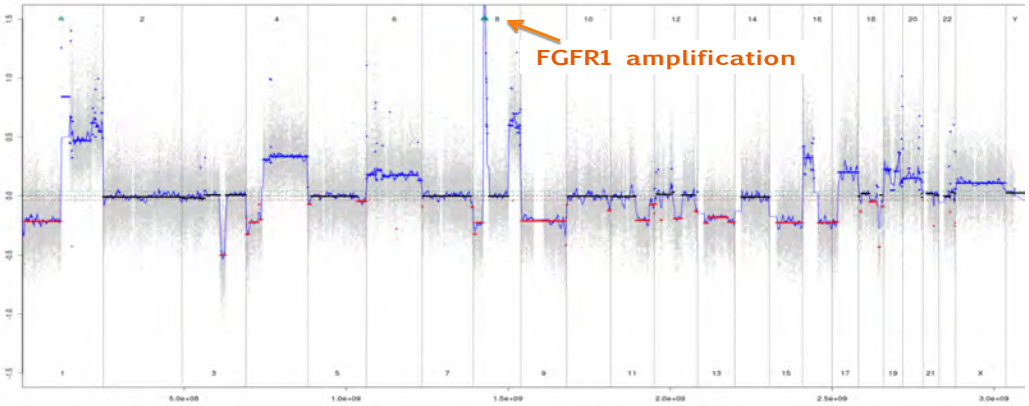


- Target Accrual = 900 patients



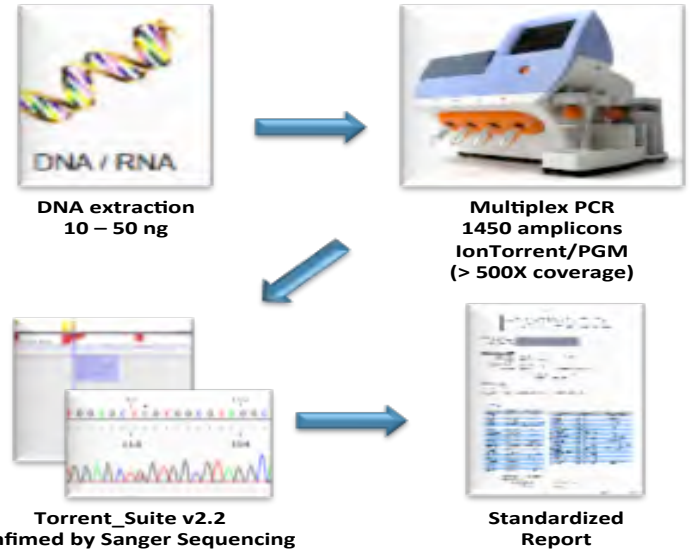
High-throughput molecular profiling using ‘on-purpose’ biopsies

CGH array Agilent
(180K, Whole genome coverage)

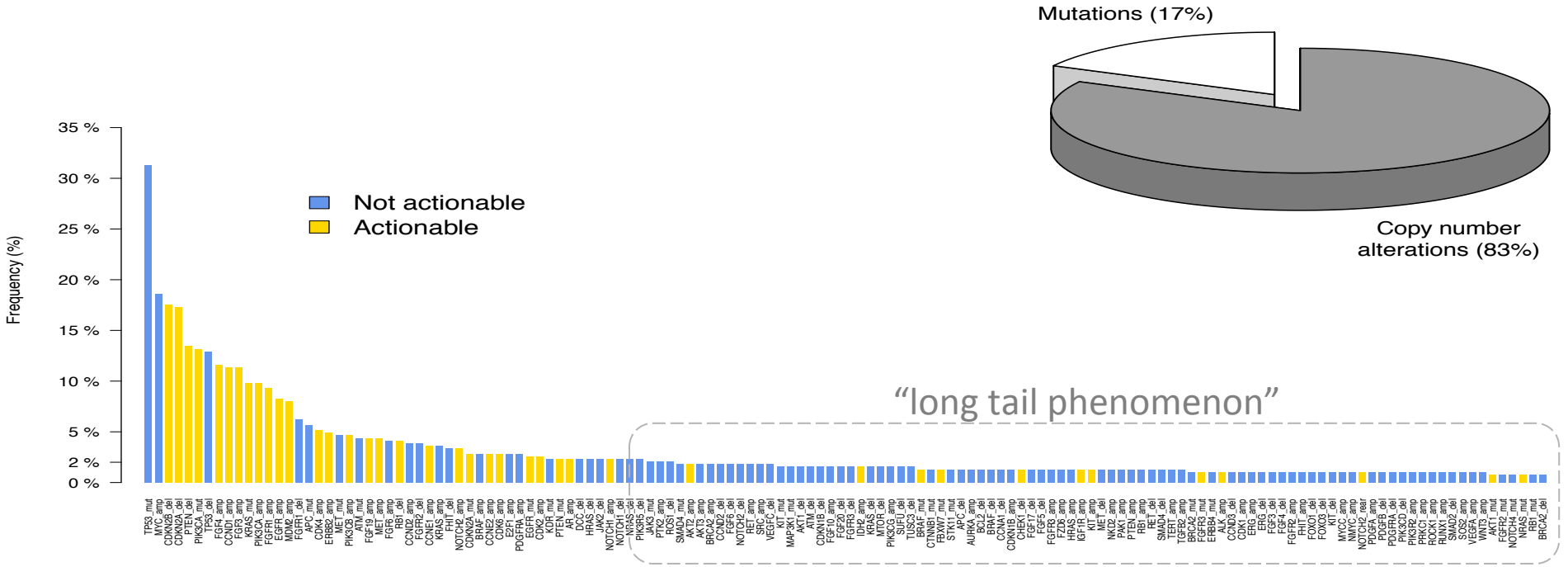


+

Ion Torrent PGM – Life Technologies
(Ampliseq CHP2 + custom
n=74 genes, Dec 2013)



Main molecular aberrations



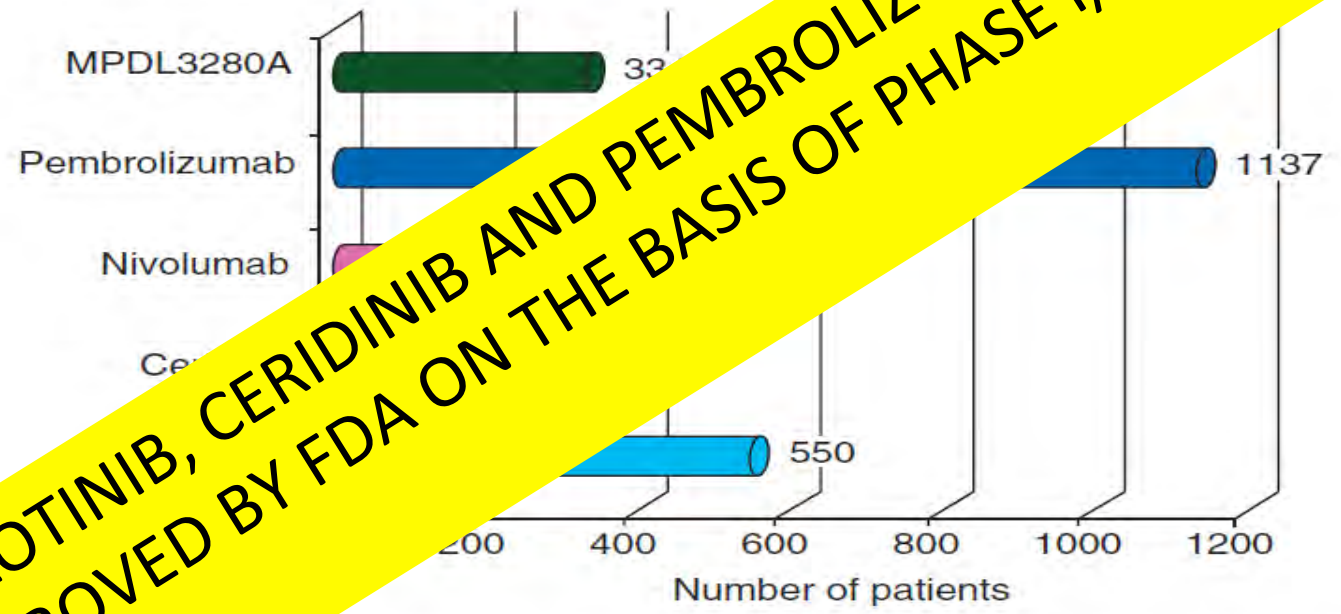
The successive phases in oncology drug development

	Type of trial		
	Phase I	**Phase II**	**Phase III**
Purpose	❖Find maximum tolerated dose ❖ screen for activity	Confirm clinical activity	Compare with standard therapy
EMPHASIS (End-point)	SAFETY/activity (Toxicity/response)	ACTIVITY (Response)	EFFICACY (PFS, Survival)
Typical number of patients	30-60	25-50+	50-1000+
Typical duration	12-24 Months	2-3 years	3-5Years
Randomized ?	Never	Sometimes	Always
Multicentre ?	Sometimes	Often	Always
Tumor-specific?	Sometimes	Always	Always

The new trend of drug development in oncology

	Phase I/II	Phase III
Purpose	Find MTD & confirm activity	Compare with standard therapy
EMPHASIS (End-point)	SAFETY/(toxicity) ACTIVITY / (response)	EFFICACY (PFS, Survival)
Typical number of patients	50-200+	50-1000+
Typical duration	12 to 36 months	Years
Randomized ?	Rarely	Always
Multicentre ?	Always	Always
Tumor-specific?	At expansion	Always

The new trend in oncology drug d nt



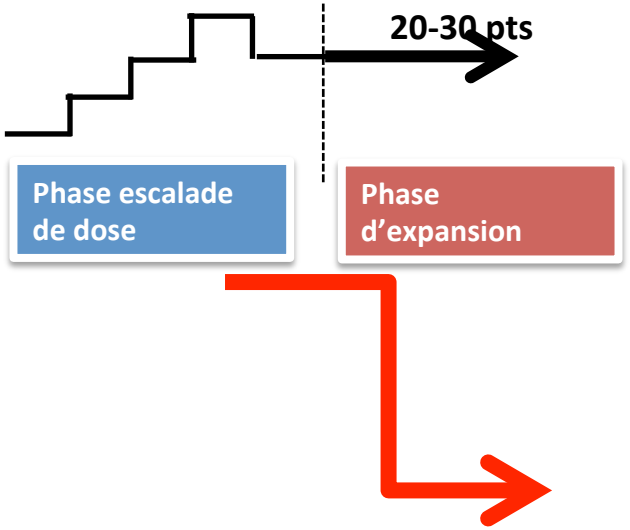
CRIZOTINIB, CERIDINIB AND PEMBROLIZUMAB APPROVED BY FDA ON THE BASIS OF PHASE I/II TRIALS

nber of patients enrolled in recent phase 1 trials having led to approval or breakthrough designations (based on www.

Postel-Vinay S Annals of Oncology 2014

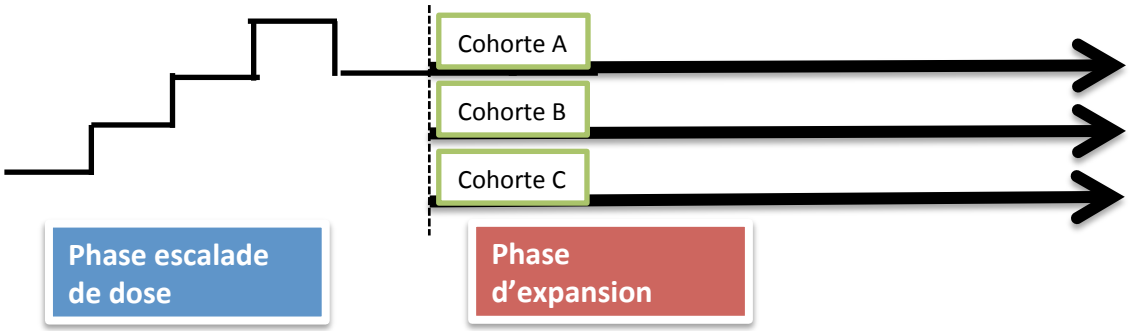
Phase I design modifications

Etude de phase I "classique"



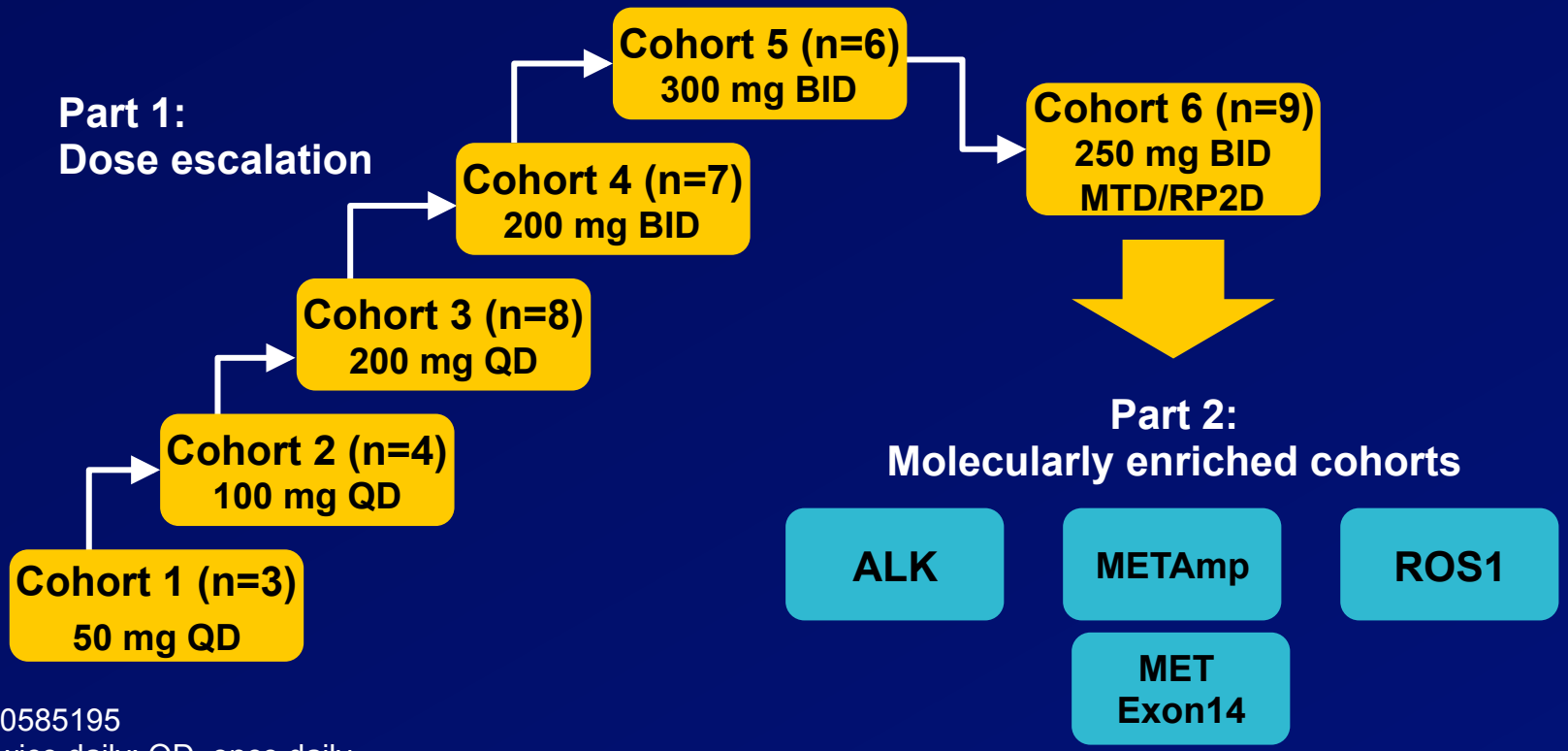
100-1000 patients

+/- enrichissement selon biomarqueurs



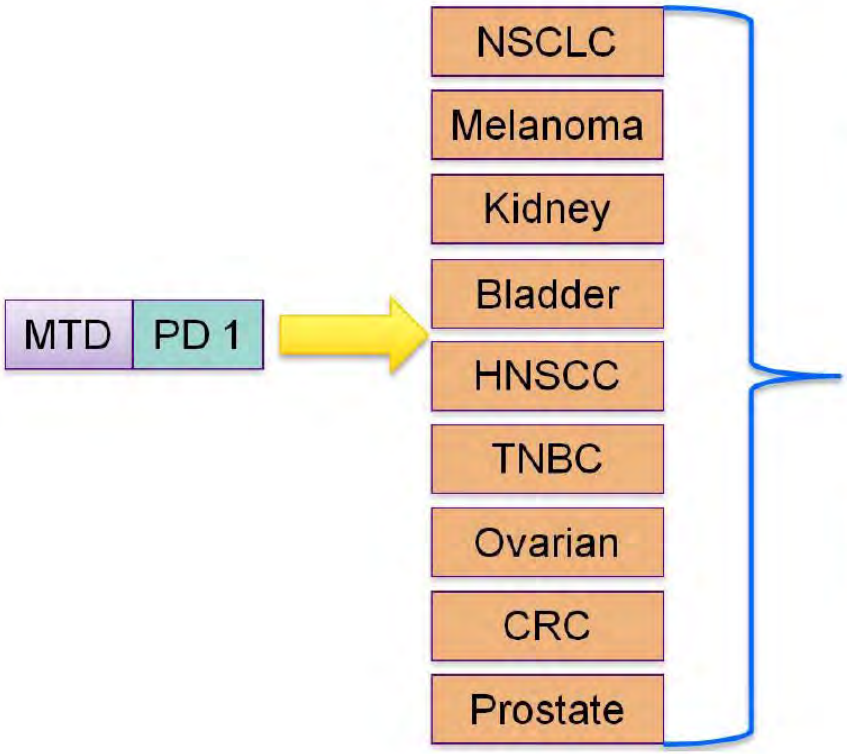
Etude de phase I avec multiples cohortes d'expansion

Crizotinib: First-in-human/patient trial (Study A8081001)



NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose

Is this the end of single-arm Phase 2 studies ?

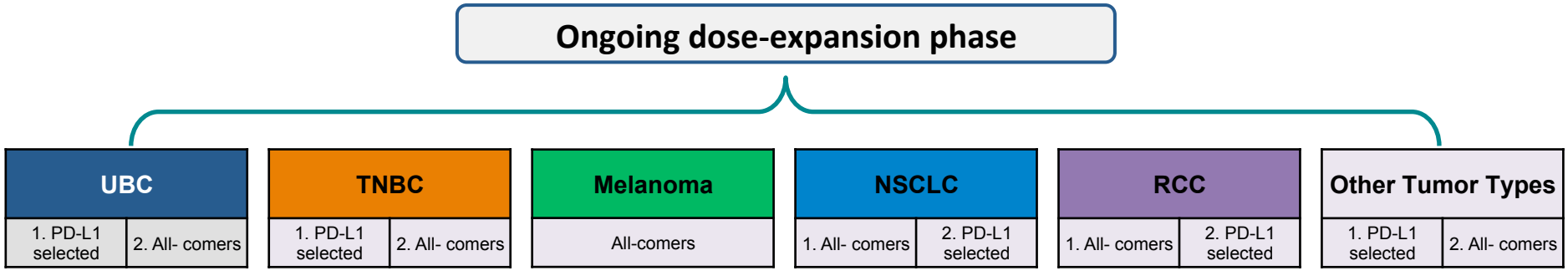


Will single arm expansions be good enough to make a "**No Go**" decision?

Will single arm expansions be good enough to make a "**Go**" decision?

Will the future provide us with only two types of studies: Non-randomized Early (Ph1/2) Studies and Randomized Late (Ph2/3) Studies?

Atezolizumab (MPDL3280A): Phase Ia Study

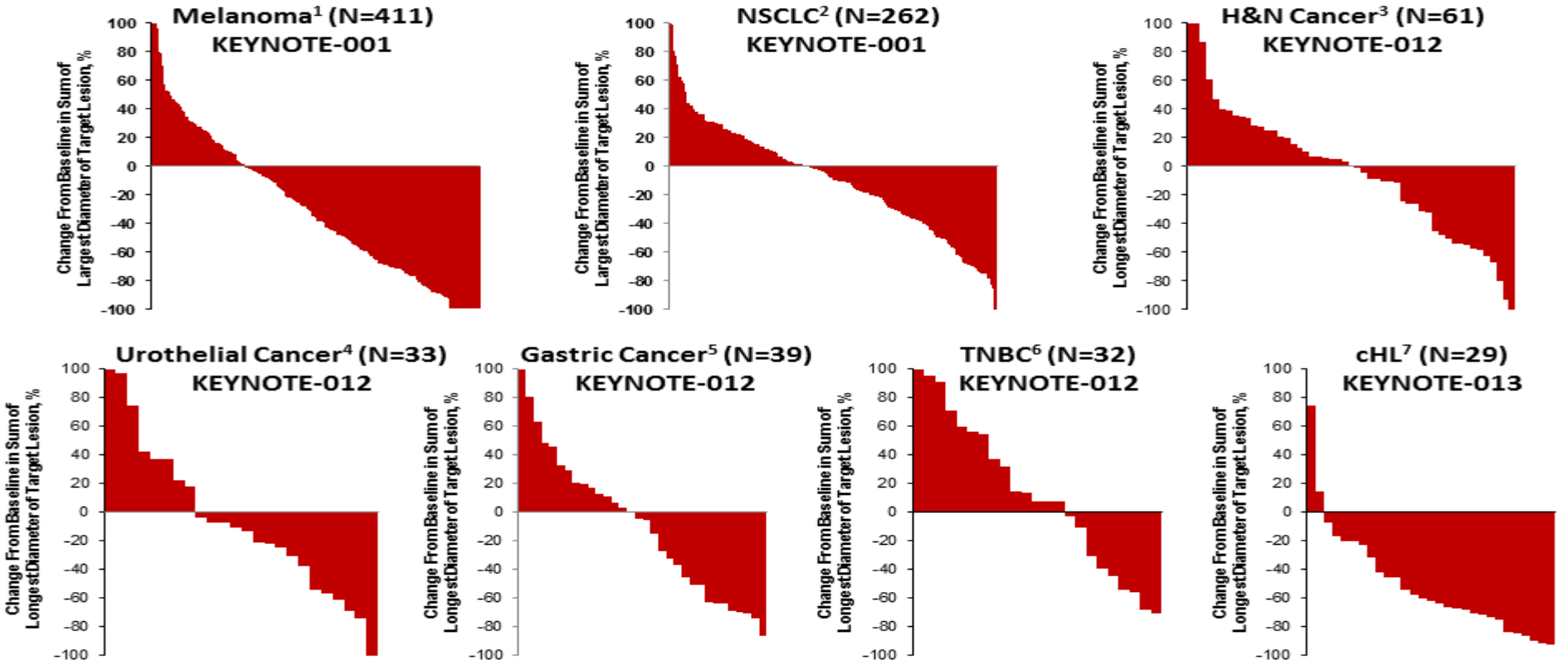


ORR ranging from 10% to 80% according to PDL1 status and tumor type

N > 350 patients

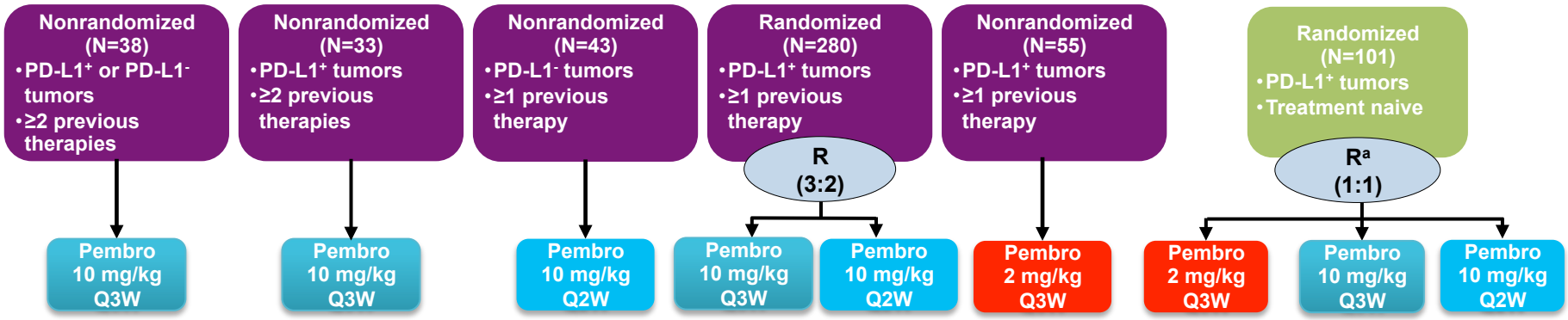
NCT 01375842

Pembrolizumab antitumor activity



1. Daud A et al. Presented at SMR Annual Meeting 2014; Nov 13-16, 2014; Zurich, Switzerland; 2. Garon EB et al. Presented at ESMO 2014 Congress; Sep 26-30, 2014; Madrid, Spain; 3. Chow LQ et al. Presented at ESMO 2014 Congress; Sep 26-30, 2014; Madrid, Spain; 4. O'Donnell P et al. Presented at 2015 Genitourinary Cancers Symposium; Feb 26-28, 2015; Orlando, FL; 5. Muro K et al. Presented at 2015 Gastrointestinal Cancers Symposium; Jan 15-17, 2015; San Francisco, CA; 6. Nanda R et al. Presented at SABCS 2014; Dec 9-13, 2014; San Antonio, TX; 7. Moskowitz C et al. Presented at 56th ASH Annual Meeting and Exposition; Dec 5-9, 2014; San Francisco, CA.

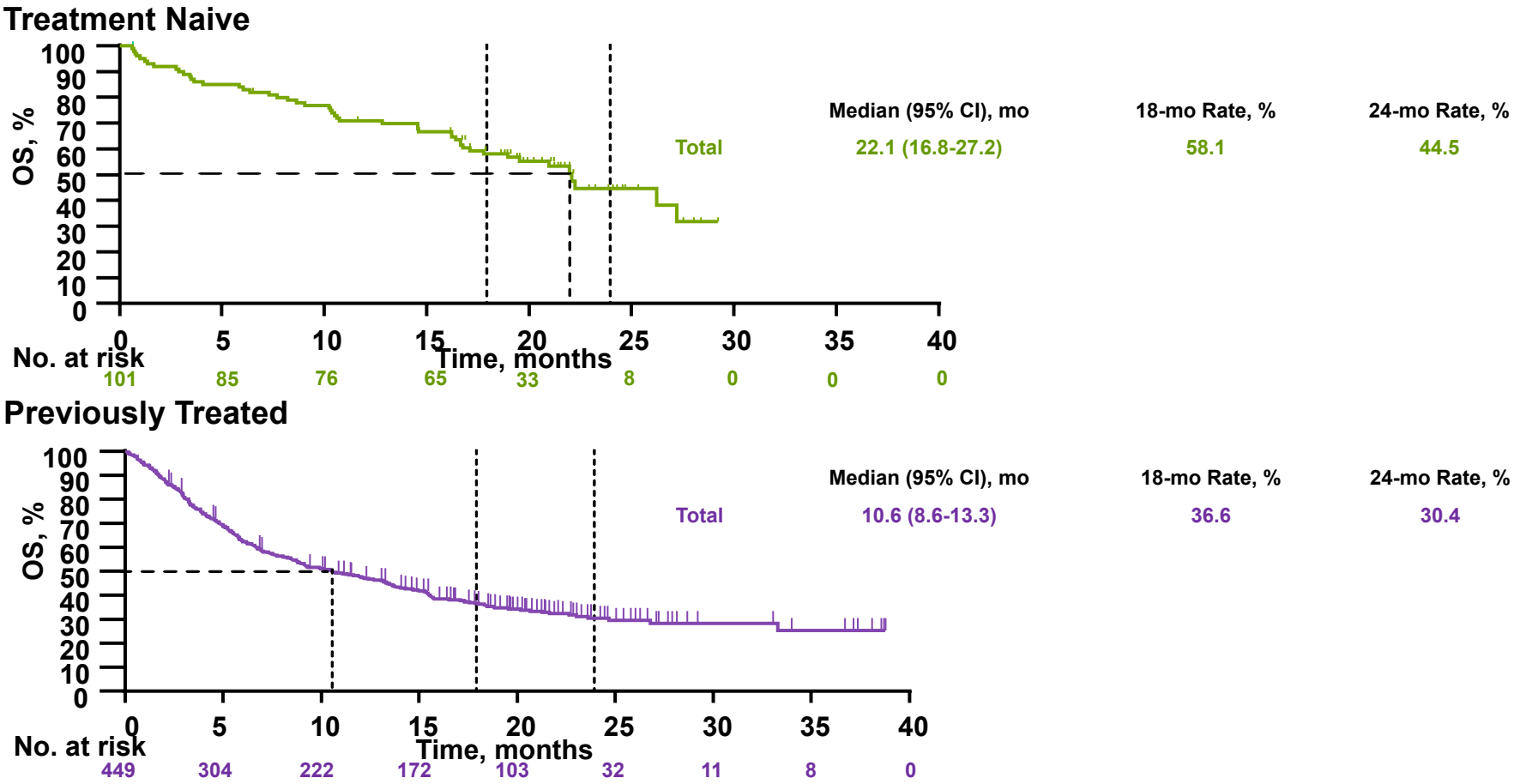
KEYNOTE-001 NSCLC Cohorts (N = 550)



- Pembrolizumab IV over 30 minutes until intolerable toxicity, disease progression, investigator decision, or patient withdrawal
- Primary endpoint: ORR per RECIST v1.1 by independent central review
- Secondary endpoints: PFS, OS, and duration of response
- Data cutoff: September 18, 2015
- Median follow-up: 22.2 months (range, 17.8-30.5) for treatment naive; 23.3 months (range, 14.2-40.1) for previously-treated patients

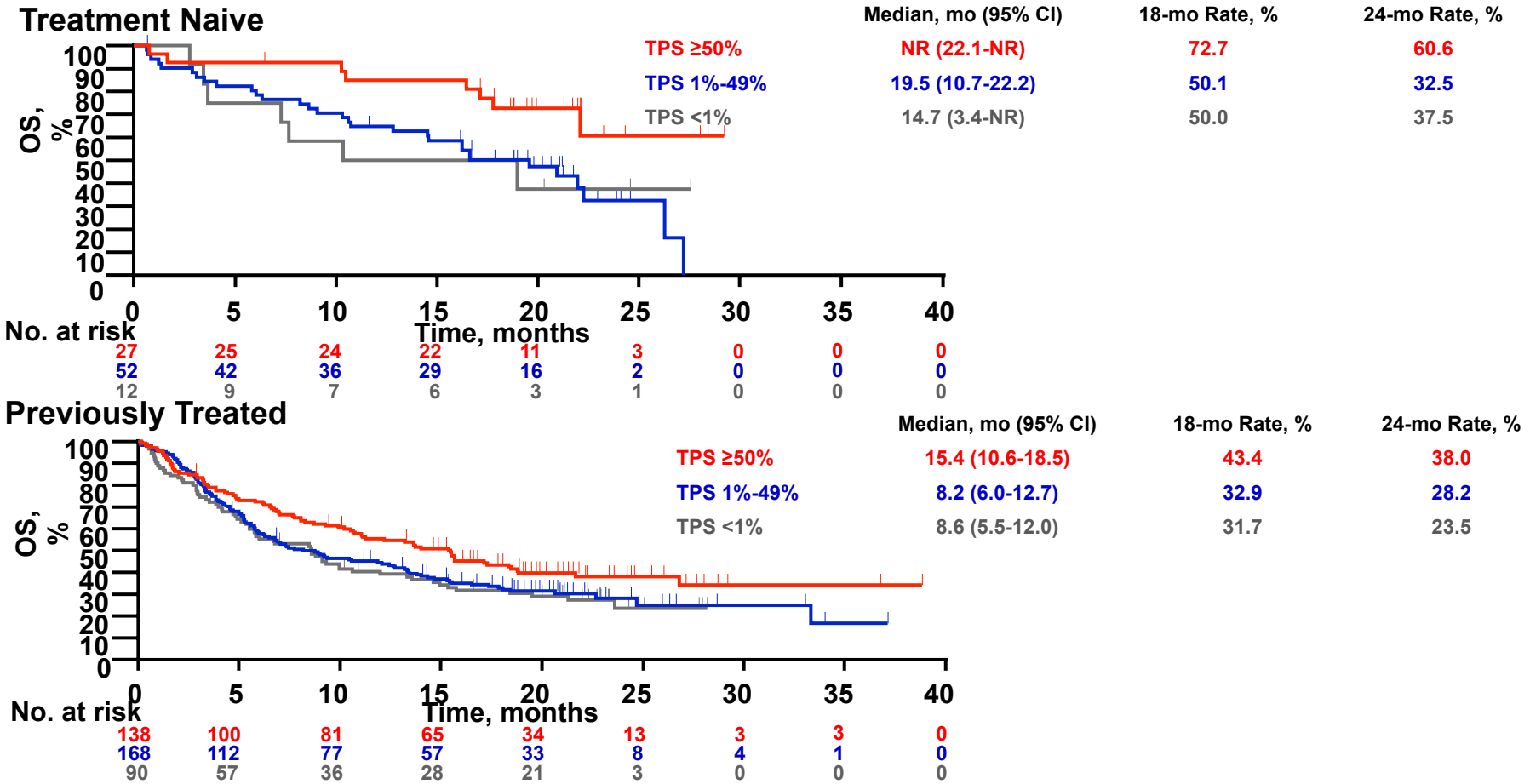
[a]First 11 pts randomized to 2 mg/kg Q3W vs 10 mg/kg Q3W; 90 randomized to 10 mg/kg Q3W vs 10 mg/kg Q2W.

Overall Survival



Vertical dotted lines represent 18 months and 24 months; the horizontal line at 50% drops vertically to the x-axis at the time of the median OS. Data cutoff: September 18, 2015.

OS by PD-L1 TPS ≥50%, 1%-49%, <1%



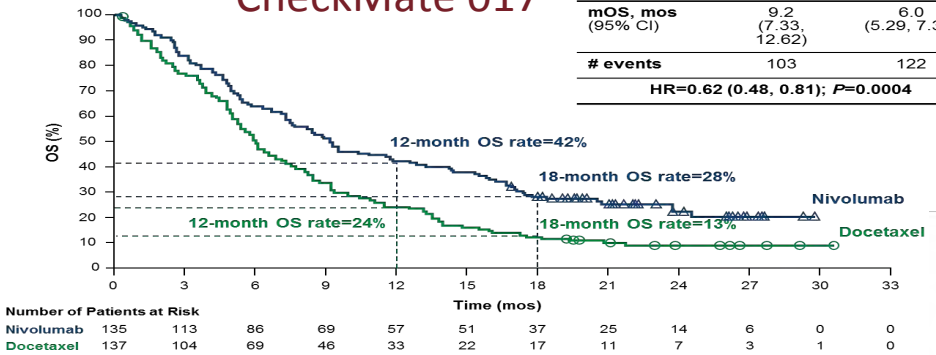
Patients with unknown PD-L1 TPS were excluded. Data cutoff: September 18, 2015.

Phase III trials

Nivolumab (SQCC)

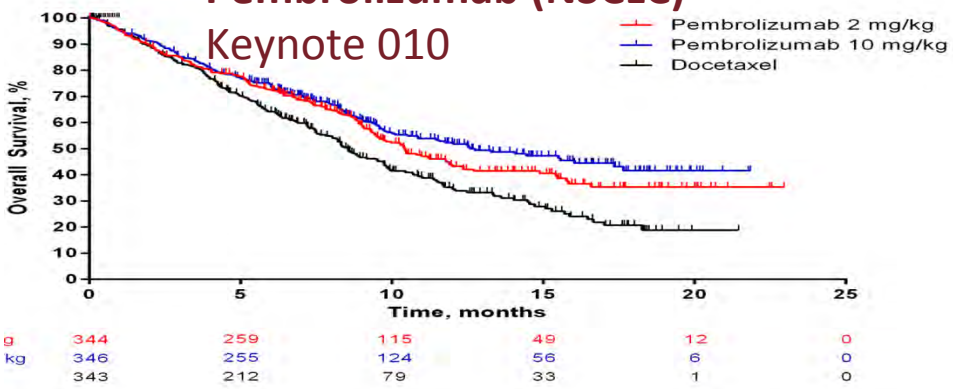
CheckMate 017

	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		



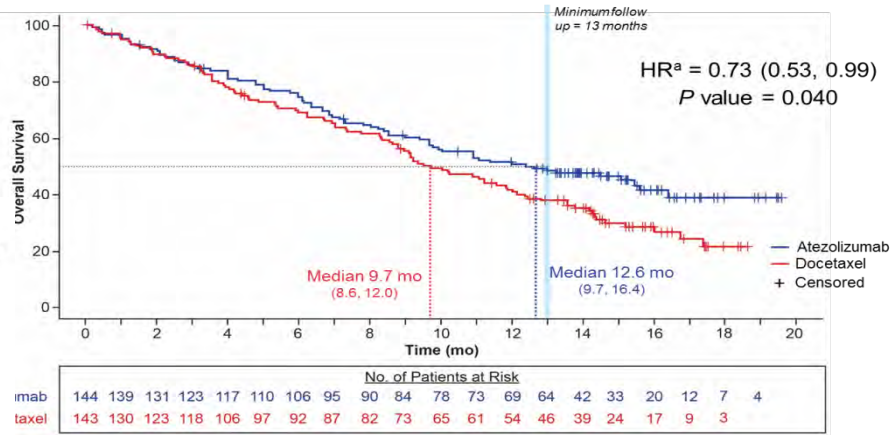
Pembrolizumab (NSCLC)

Keynote 010



Atezolizumab (NSCLC)

POPLAR



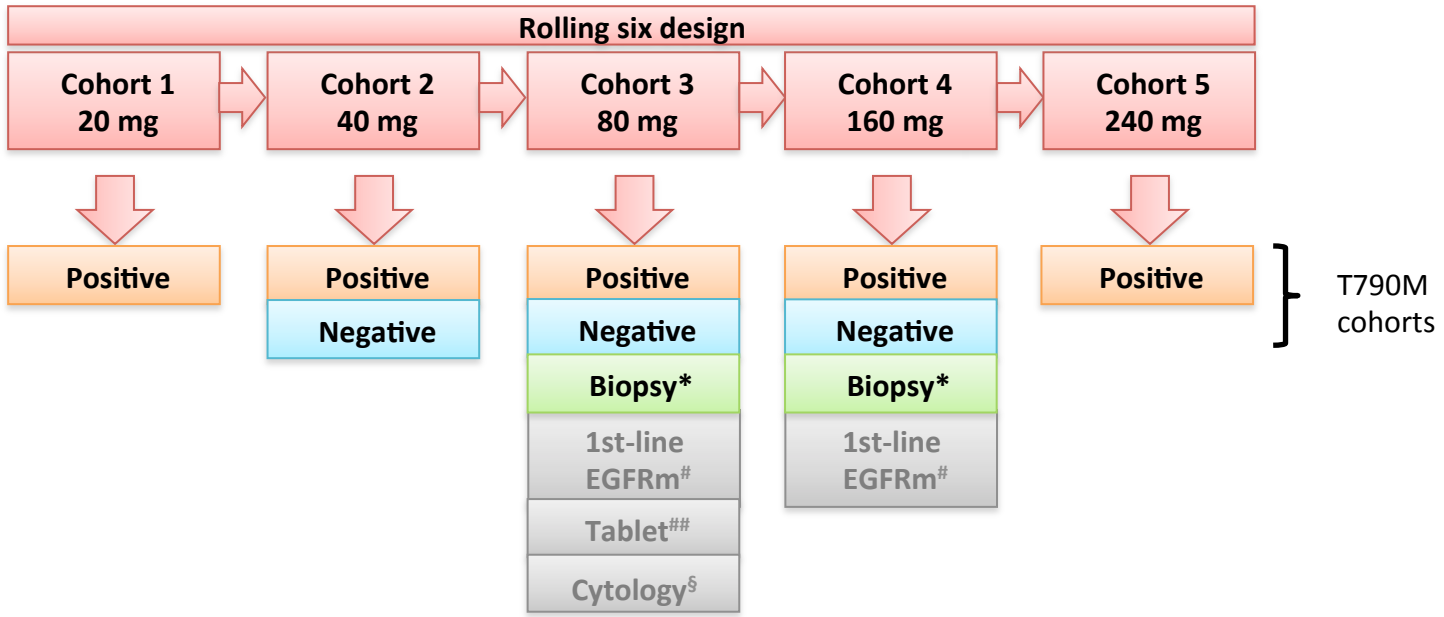
Brahmer J et al, NEJM 2015; Roy S. Herbst et al, ESMO Asia 2015, lancet 2015; L Fehrenbacher et al, lancet 2016

Phase I/II dose escalation-expansion Osimertinib

Primary objective – assessment of the safety, tolerability and efficacy (ORR) of Osimertinib in patients with acquired resistance to EGFR-TKIs

Phase 1 Escalation
Not preselected by T790M status

Phase 1 Expansion
Enrolment by local testing followed by central laboratory confirmation (cobas™ EGFR Mutation Test) of T790M status or by central laboratory testing alone



Pasi A Jänne at al; ELCC 2015- Ann Oncol 2015; 26(Suppl1) LBA3, NEJM 2015

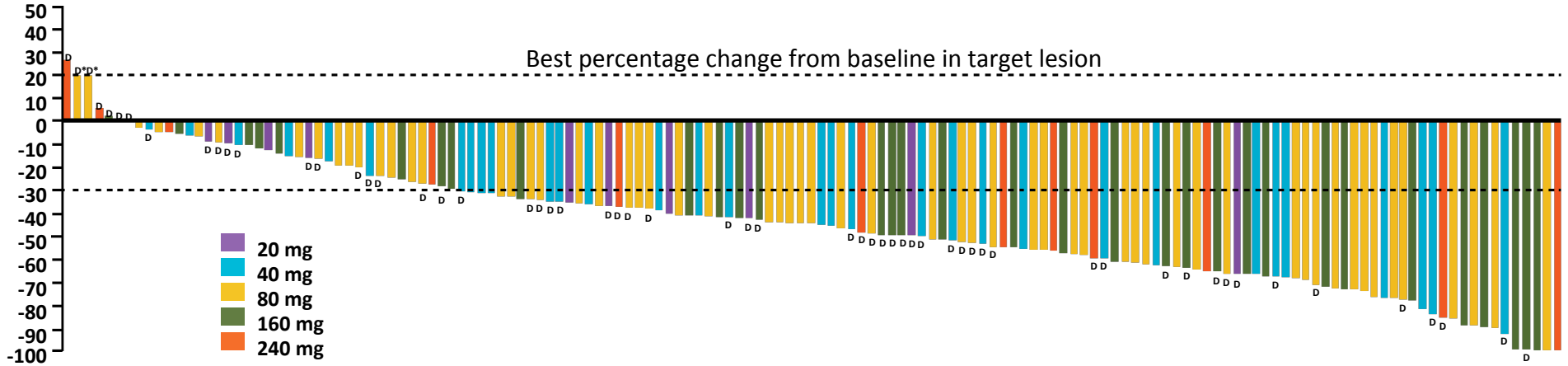
Baseline demographics and disease characteristics

Characteristic	Escalation N=31	Expansion N=252
Gender, n (%) Male / Female	11 / 20 (35 / 65)	97 / 155 (38 / 62)
Age, median (range); years	61 (39–81)	60 (28–88)
Race, n (%) Caucasian / Asian / Other / Not reported	5 / 21 / 1 / 4 (16 / 68 / 3 / 13)	84 / 152 / 5 / 11 (33 / 60 / 2 / 4)
Histology, n (%) Adeno / Squamous / Other / Missing	29 / 1 / 1 / 0 (94 / 3 / 3 / 0)	TBC
Prior lines of systemic therapy, median (range)	3 (1–12)	3 (1–12)
Prior EGFR-TKIs, median (range)	1 (1–4)	2 (1–5)
Regimen, n (%)		
Gefitinib	22 (71)	150 (60)
Erlotinib	15 (48)	146 (58)
Afatinib	1 (3)	59 (24)
EGFR mutation type by central test Exon 19 / L858R / Other / None / Unknown, n Exon 19 / L858R / Other / None / Unknown, %	Central testing not performed for escalation	136 / 73 / 10 / 13 / 20 54 / 29 / 4 / 5 / 8

Population: pre-treated, capsule-dosed patients (excluding Japanese cytology cohort). Data cut-off 2 Dec 2014

Pasi A Jänne at al; ELCC 2015- Ann Oncol 2015; 26(Suppl1) LBA3, NEJM 2015

Response rate in T790M positive cohorts (central test) - Osimertinib



DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

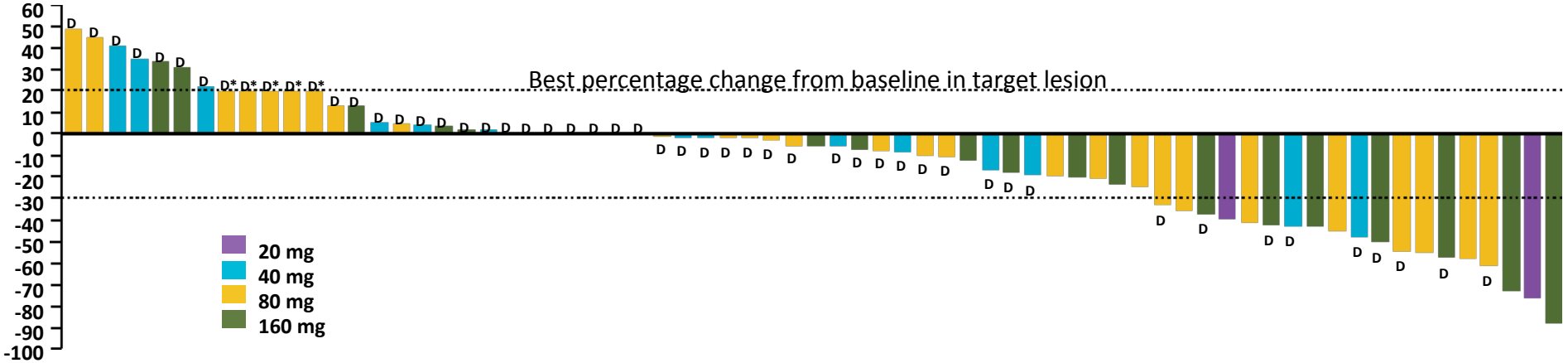
	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

La dose 80 mg d'Osimertinib est la dose de l'AMM

Pasi A Jänne at al; ELCC 2015- Ann Oncol 2015; 26(Suppl1) LBA3, NEJM 2015

Response rate in T790M negative cohorts (central test) - Osimertinib



DCR (CR+PR+SD) in patients with centrally tested T790M negative tumours was 64% (44 / 69; 95% CI 51, 75)

	20 mg	40 mg	80 mg	160 mg	Total
N (69)	3	17	29	20	69
ORR (95% CI)	67% (9, 99)	12% (2, 36)	21% (8, 40)	30% (12, 54)	23% (14, 35)

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014

Bras T790M négatif - données non enregistrées

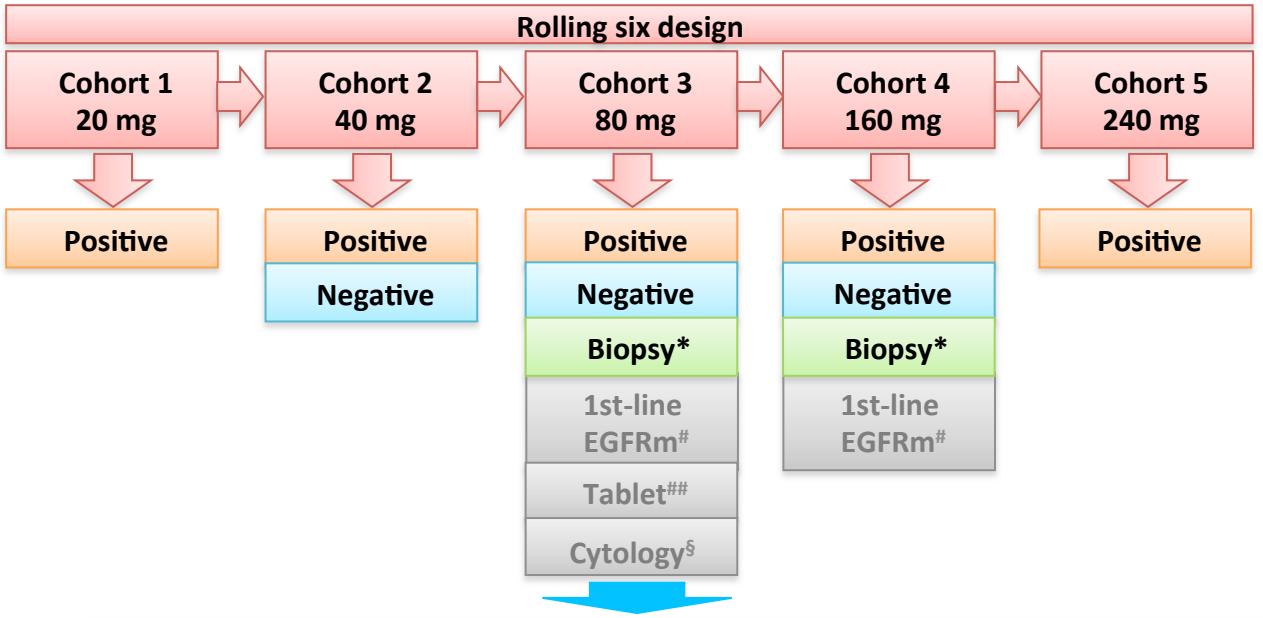
Pasi A Jänne at al; ELCC 2015- Ann Oncol 2015; 26(Suppl1) LBA3, NEJM 2015

Phase II dose extension

Primary objective – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs

Escalation
Not preselected by T790M status

Expansion
Enrolment by local testing followed by central laboratory confirmation (cobas™ EGFR Mutation Test) of T790M status or by central laboratory testing alone



Phase 2 extension
Enrollment by central Laboratory confirmtation of T790M status

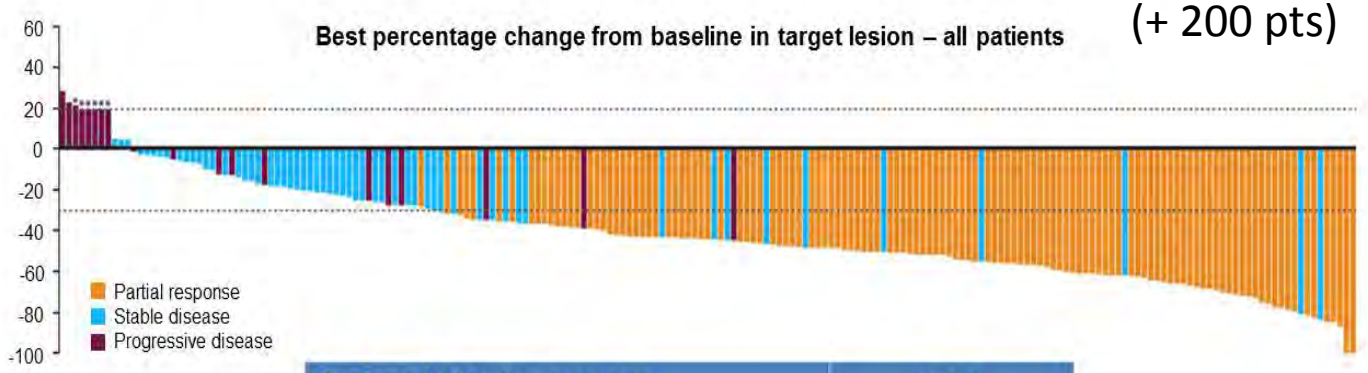
Phase II extension

Osimertinib 80 mg once daily in patients with T790M+ NSCLC who have progressed on EGFR-TKI

Phase II extension

Tumor reponse by independent central review - Osimertinib 80mg/d

(+ 200 pts)



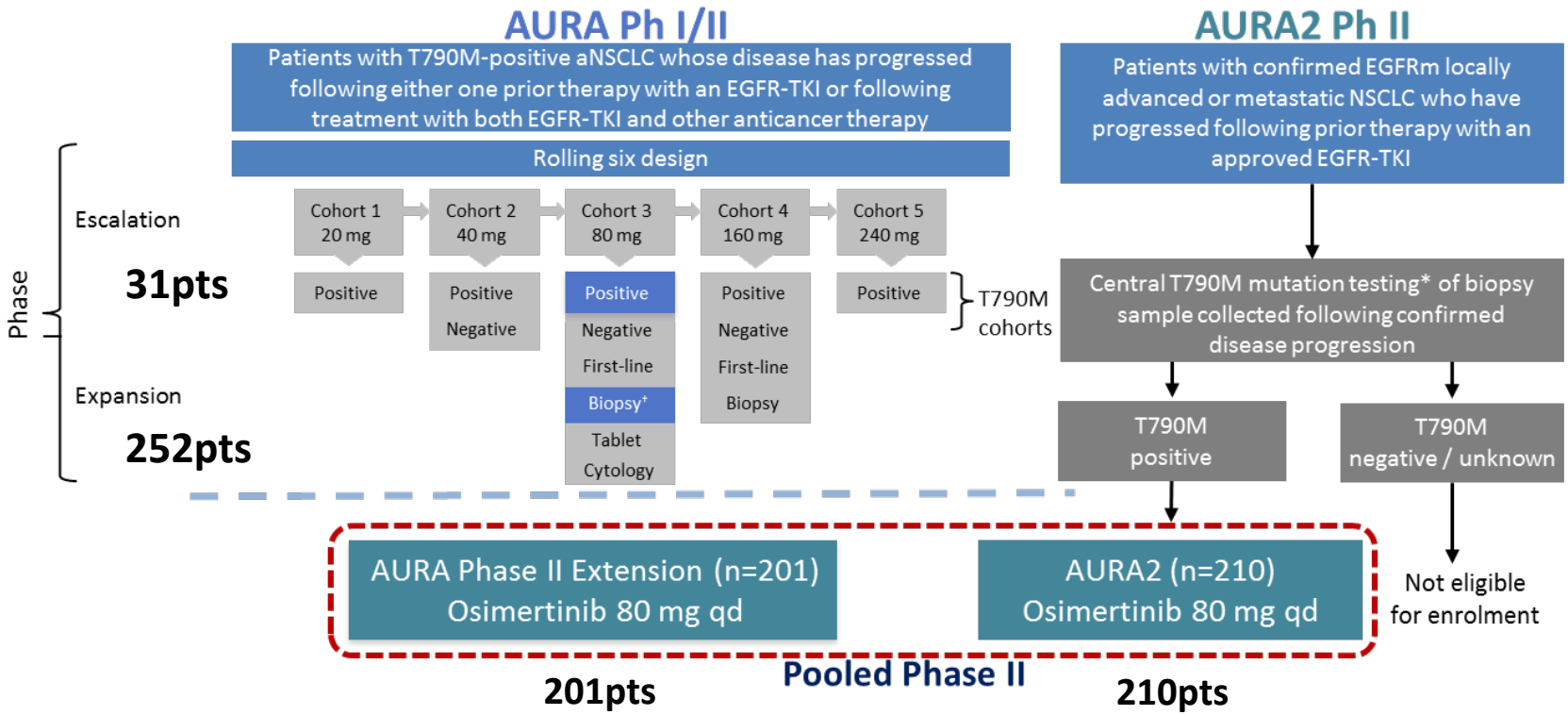
Confirmed objective response	Total
ORR,† % (95% CI)	61 (54, 68)
Complete response,‡ n (%)	0
Partial response,§ n (%)	122 (61)
Stable disease ≥6 weeks,§ n (%)	58 (29)
Progressive disease, n (%)	19 (10)
DCR, % (95% CI)	91 (85, 94)

NOTE: Investigator-assessed ORR was 71% (95% CI 64, 77)

Data cut-off: May 1, 2015. Population: evaluable for response set (n=199); *Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%; †ORR defined as the number (%) of patients with at least one visit response of complete response or partial response that was confirmed at least 4 weeks later; ‡Response required confirmation after 4 weeks; §Stable disease ≥6 weeks included the RECIST visit window (±7 days)
CI, confidence interval; DCR, disease control rate (complete response + partial response + stable disease)

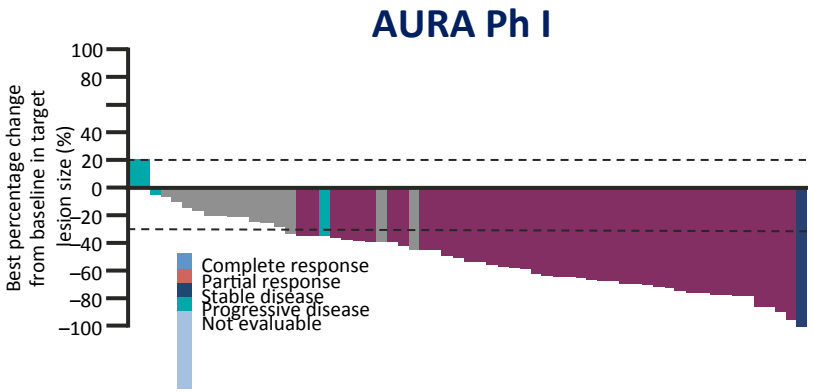
Chih-Hsin Yang et al, IASLC 2015

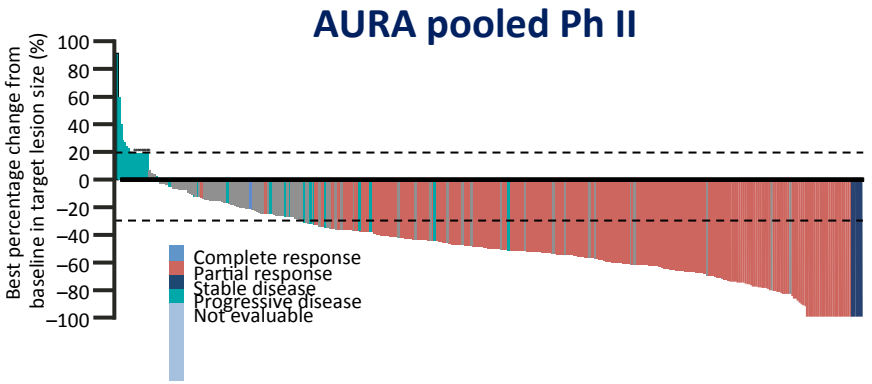
Study designs



AURA Ph I data cut-off 4 January 2016; AURA pooled Ph II data cut-off 1 November 2015
*The EGFR T790M mutation status of the patient's tumour was prospectively determined by the designated central laboratory using the Cobas® EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen; †Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here; Data from cohorts in grayed out boxes are not included in the analyses reported here. aNSCLC, advanced NSCLC; qd, once daily

Tumour response to Osimertinib treatment





	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	**71%** (95% CI 57, 82)	**66%** (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

elcc

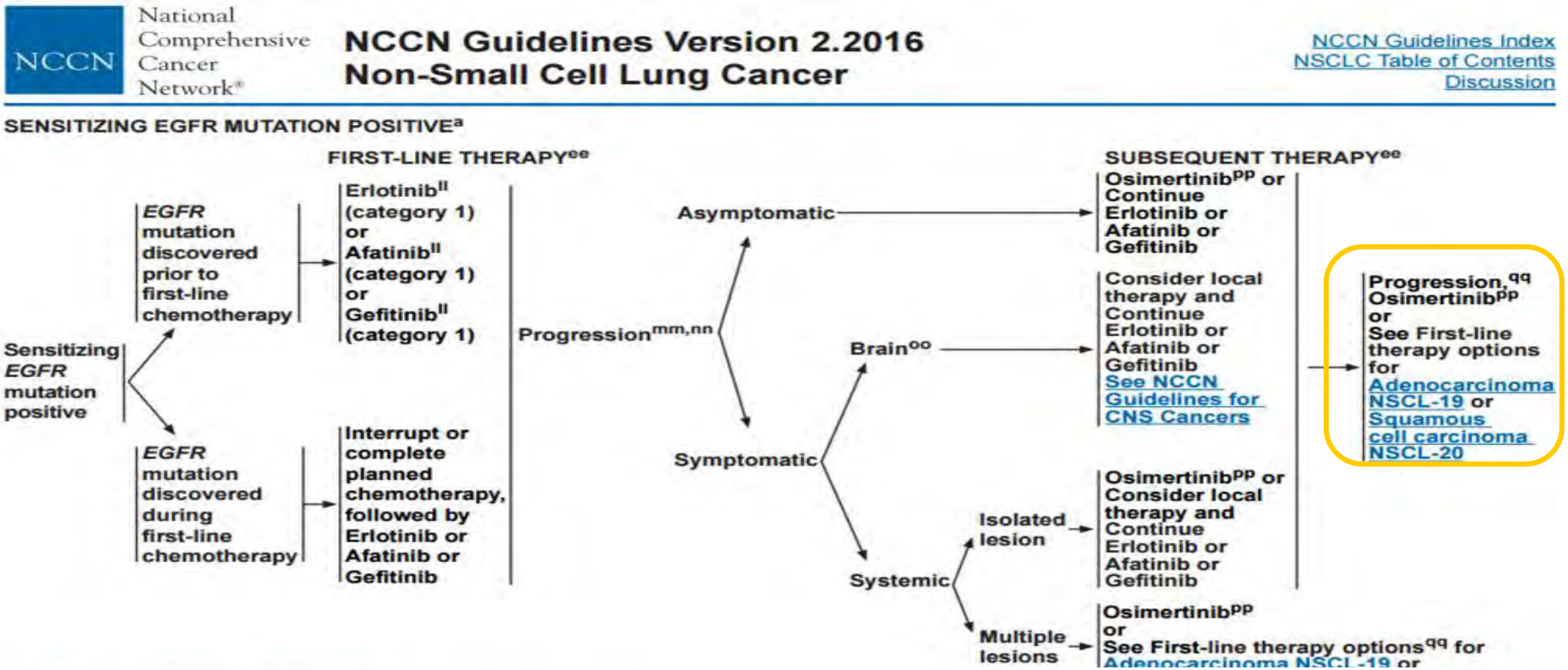
James C-H Yang et al, ELCC 2016, Geneva ; Abstract LBA2_PR.

Osimertinib….

The clinical development programme for osimertinib is the most rapid to date, taking just 2 years 8 months and 1 week from the first patient dosed to the first approved indication

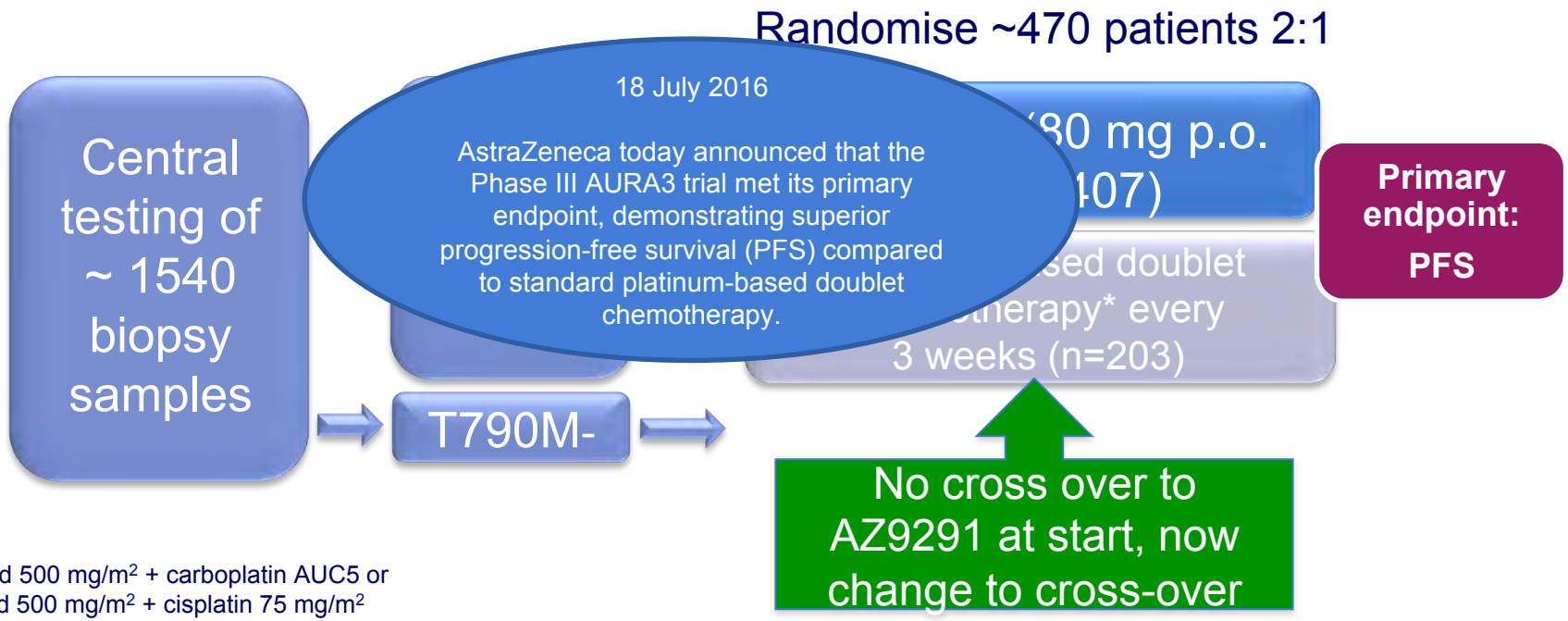
(FDA Approval Nov 2015)

Tagrisso in NCCN guidlines…



FDA's approval of Tagrisso

AURA 3 Study Design



18 July 2016

AstraZeneca today announced that the Phase III AURA3 trial met its primary endpoint, demonstrating superior progression-free survival (PFS) compared to standard platinum-based doublet chemotherapy.

*Pemetrexed 500 mg/m^2 + carboplatin AUC5 or Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

P

PI: T Mok YL Wu

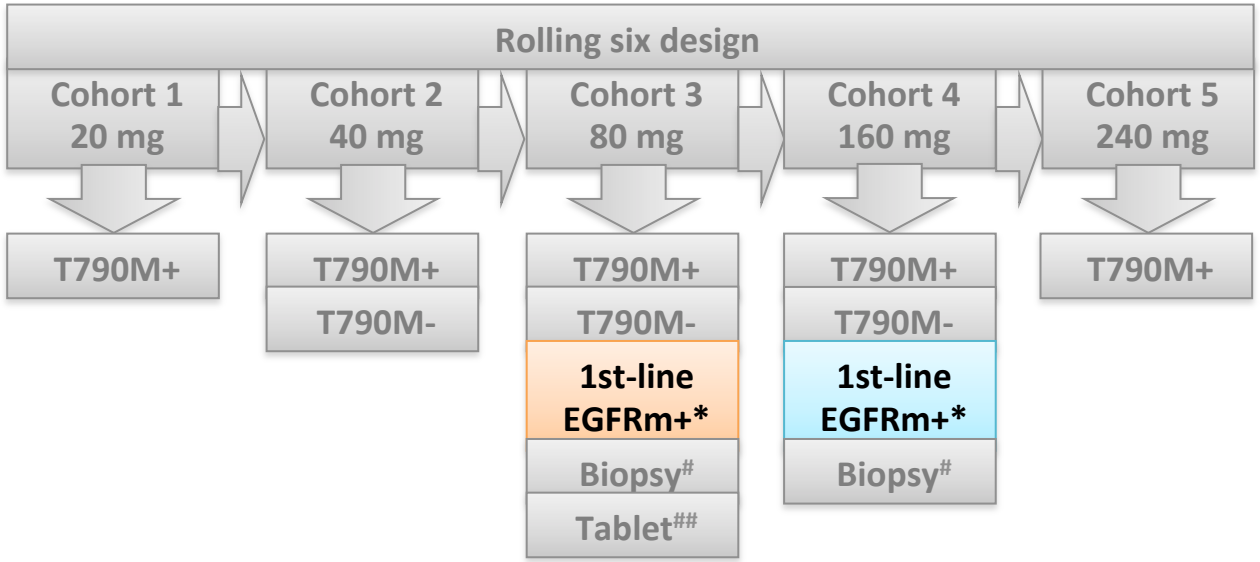
AUC5, area under the plasma concentration–time curve 5 mg/mL^{-1} per minute; *EGFR*m+, *EGFR* mutation-positive; EGFR-TKI, EGFR tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; p.o., orally; qd, once daily; T790M+, T790M mutation-positive; T790M-, T790M mutation-negative

Phase I dose escalation/expansion study design (NCT01802632)

- **For the first-line cohorts, patients with a documented EGFR-TKI-sensitising mutation and who have received no prior therapy for advanced stage NSCLC were enrolled**
- **Patients received AZD9291 once daily as an 80 mg or 160 mg capsule**

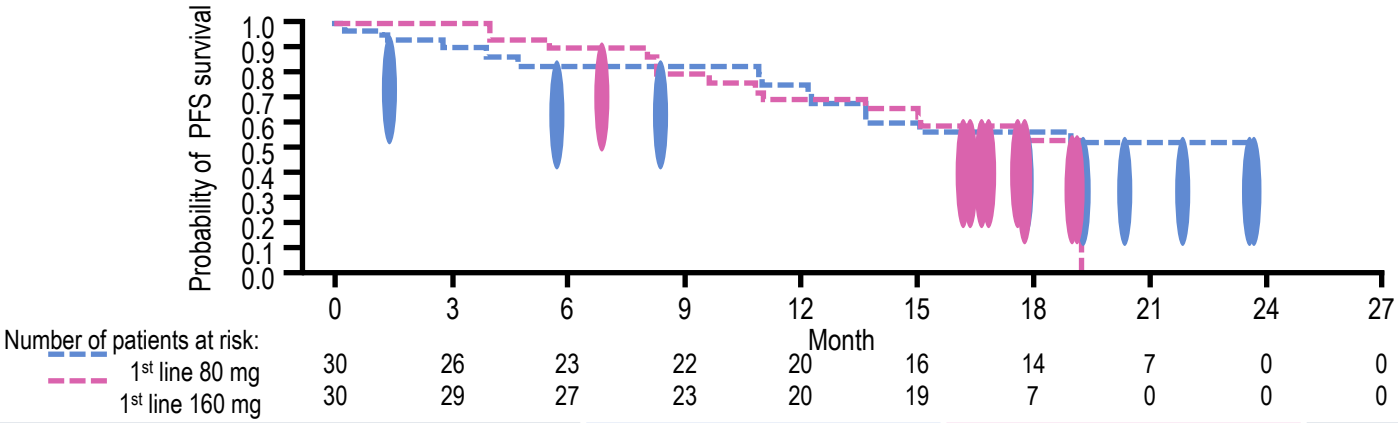
Escalation
Not preselected by T790M status

Expansion
Enrollment by local testing followed by central laboratory confirmation (cobas EGFR Mutation Test) of T790M status or by central laboratory testing alone



*Prior therapy not permissible in this cohort. #Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.

PFS in osimertinib EGFRm first-line cohorts (investigator assessed)



	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

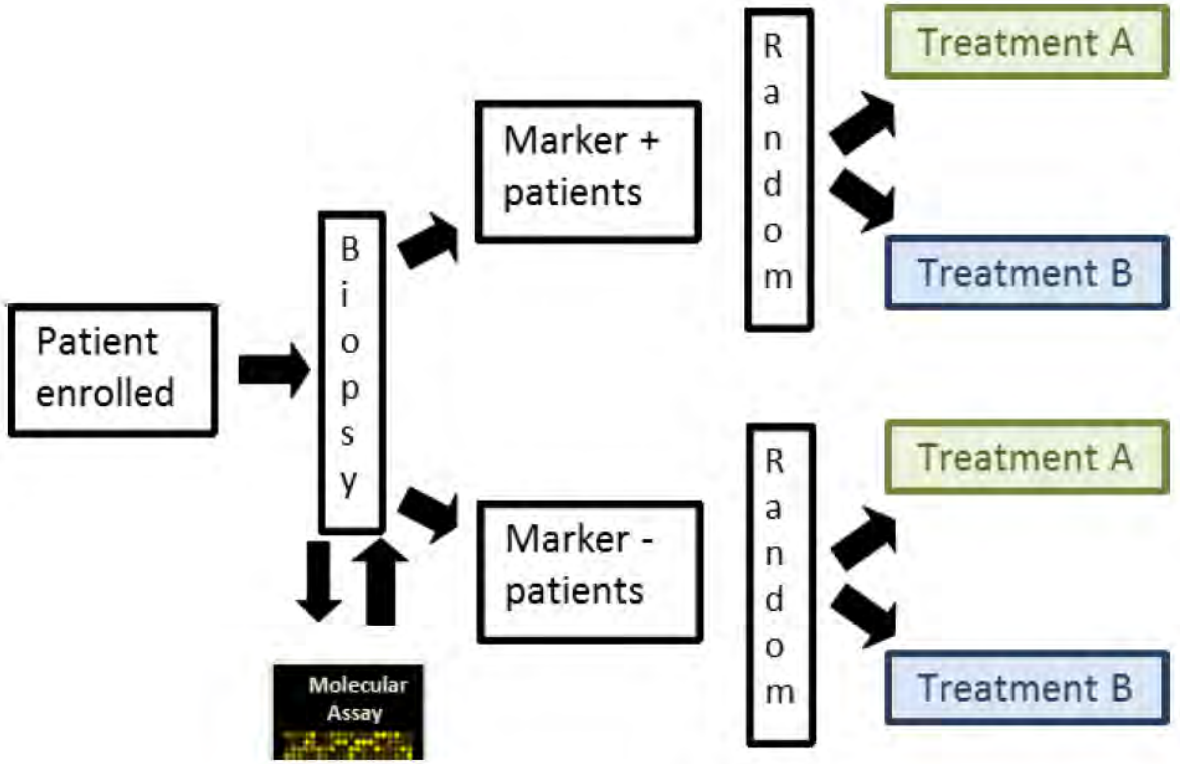
Population: safety analysis set; data cut-off: 4 January 2016
Progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Circles on the Kaplan-Meier plot denote censored observations
*Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
†Calculated using the Kaplan-Meier technique

Presented by Suresh S Ramalingam at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA1_PR.

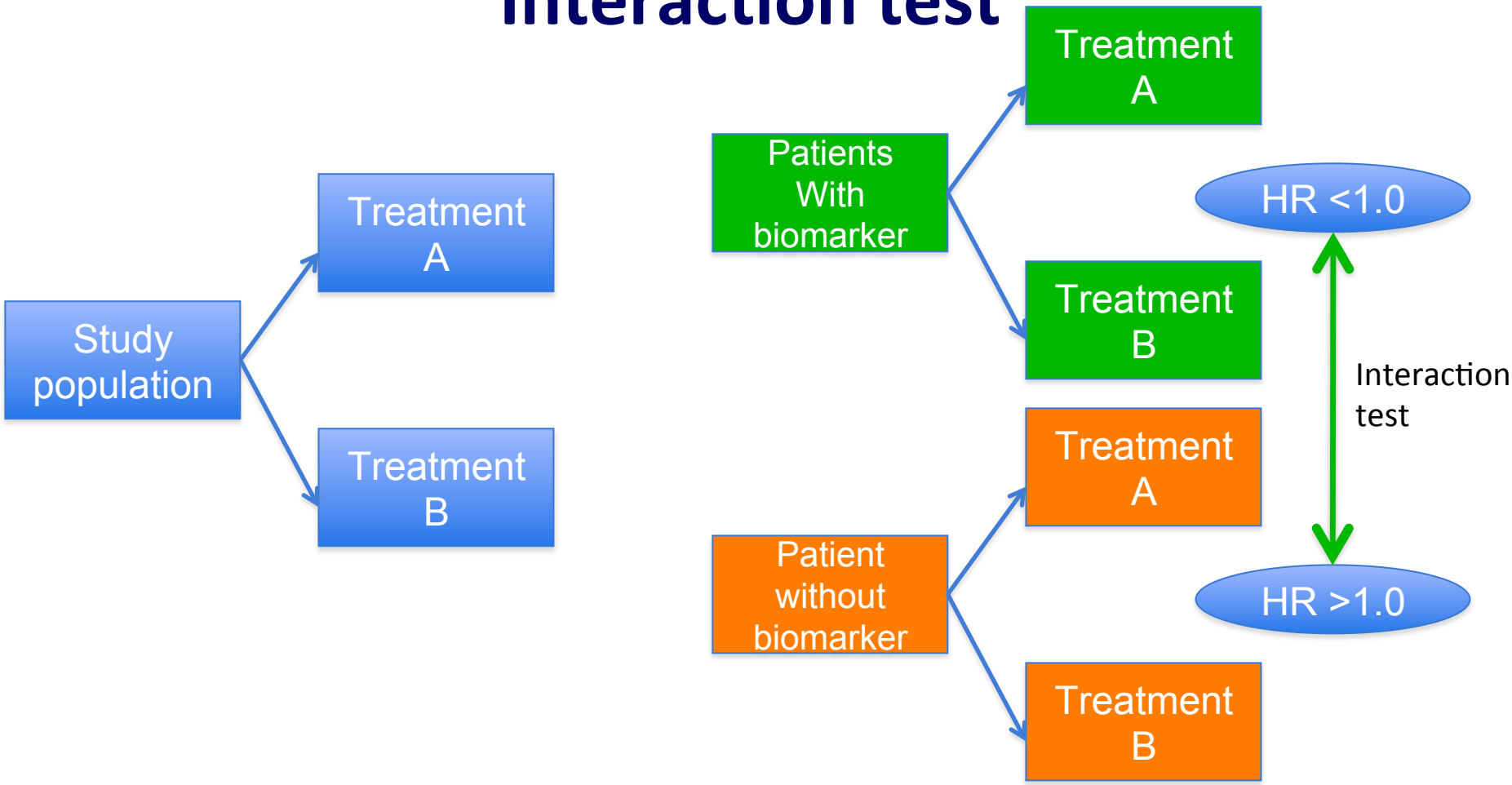
Etudes de développement Osimertinib

Phase I / II ≥ 2ème Ligne	Phase II ≥ 2ème Ligne	Phase III 2ème Ligne	Phase III 1ère Ligne
AURA **Phase I/II** Phase I : escalade / expansion de dose Phase II : extension de dose CBNPC à un stade avancé	**AURA 2** **Phase II** Etude en ouvert, monobras Traitement de seconde ligne ou plus chez des patients atteints d'un CBNPC localement avancé ou métastatique avec mutations EGFRm et T790M qui ont progressé après un traitement par TKI-EGFR	**AURA3** **Phase III** Etude randomisée, VS chimiothérapie à base de platine Traitement de seconde ligne chez les patients atteints d'un CBNPC localement avancé ou métastatique avec mutations EGFRm et T790M qui ont progressé après un traitement par TKI-EGFR	**FLAURA** **Phase III** Etude randomisée, VS gefitinib ou erlotinib CBNPC localement avancé ou métastatique avec mutation activatrice de l'EGFR

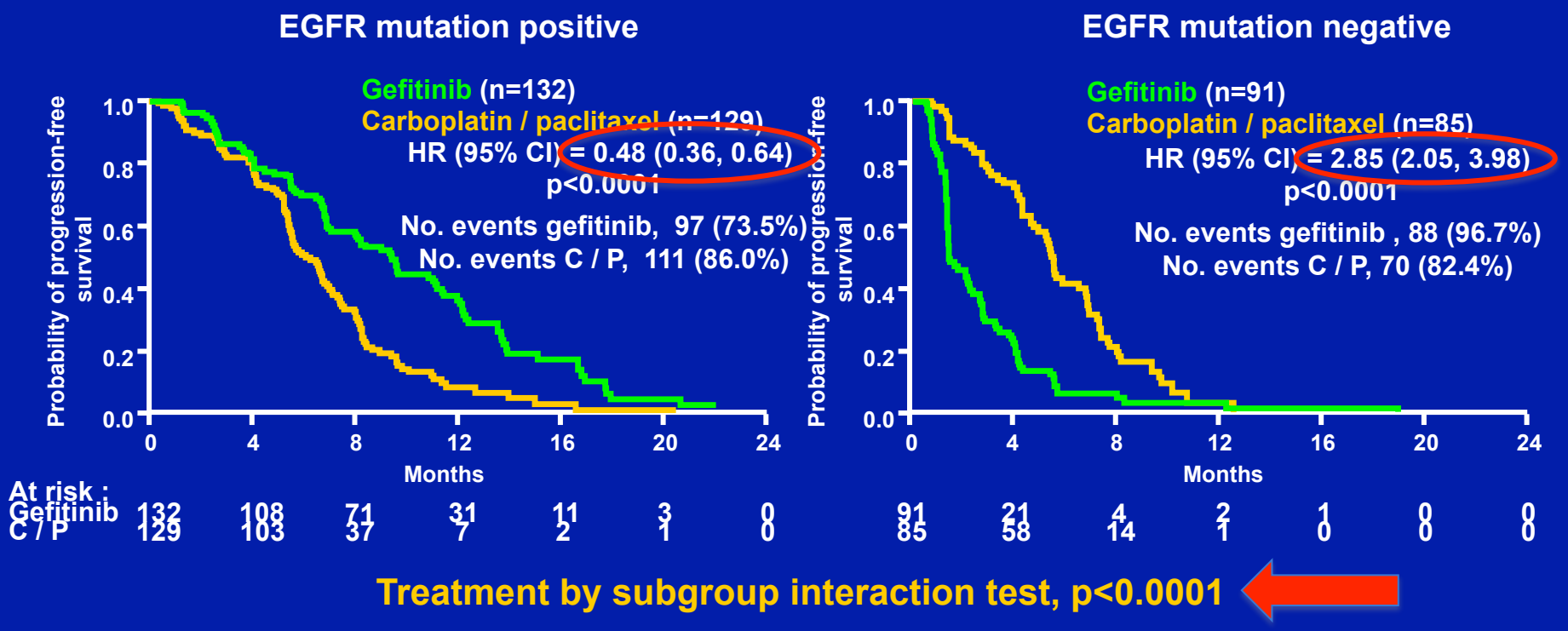
Marker-stratified



Interaction test



Progression-free survival in EGFR mutation positive and negative patients

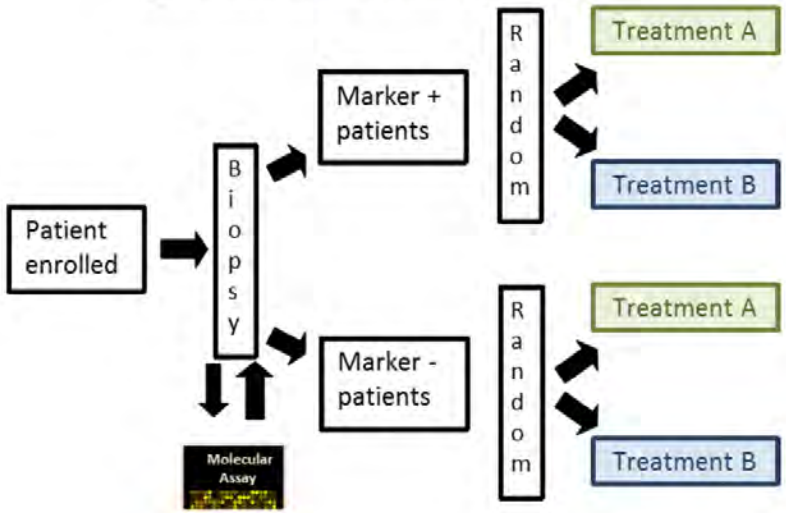


Treatment by subgroup interaction test, p<0.0001

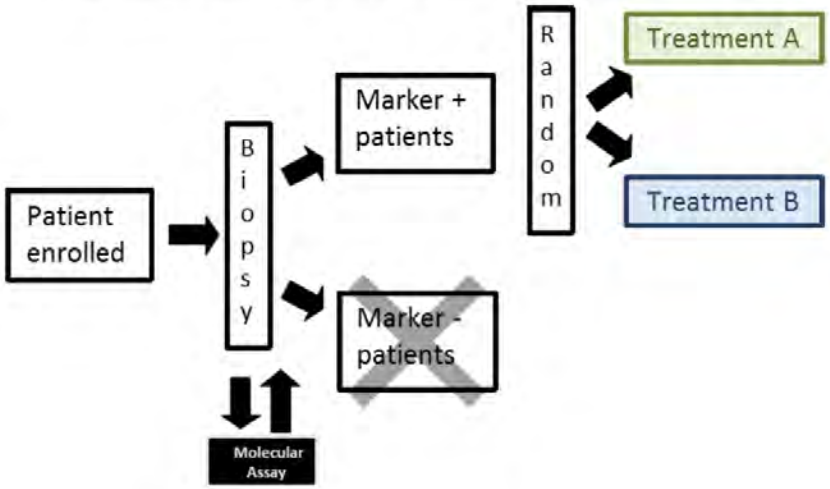
ITT population
Cox analysis with covariates

Mok *et al*. *NEJM* 361:947-957. 2009.

Marker-stratified



Marker-enriched / directed



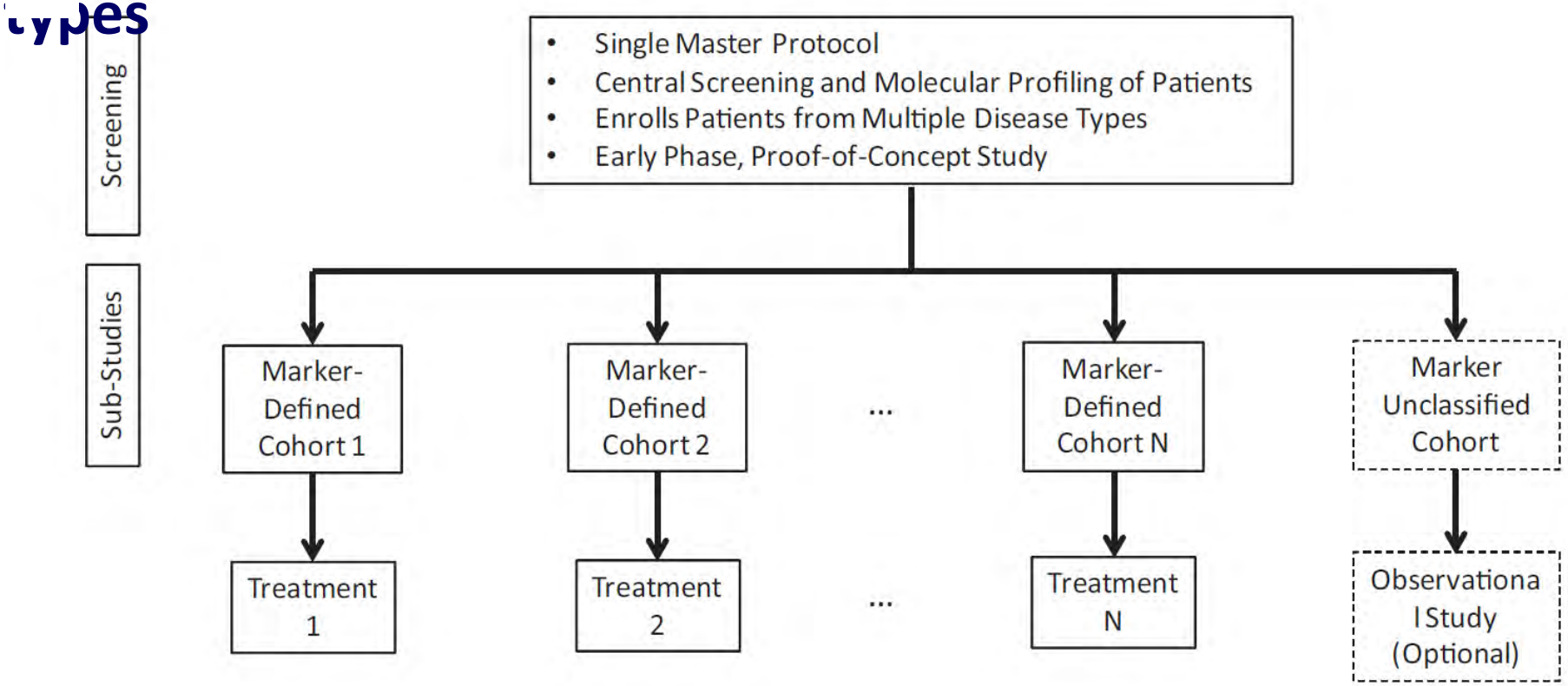
Move (staged or potentially seamlessly) from a marker-stratified to a marker-enriched design

Randomized studies on first line EGFR TKI

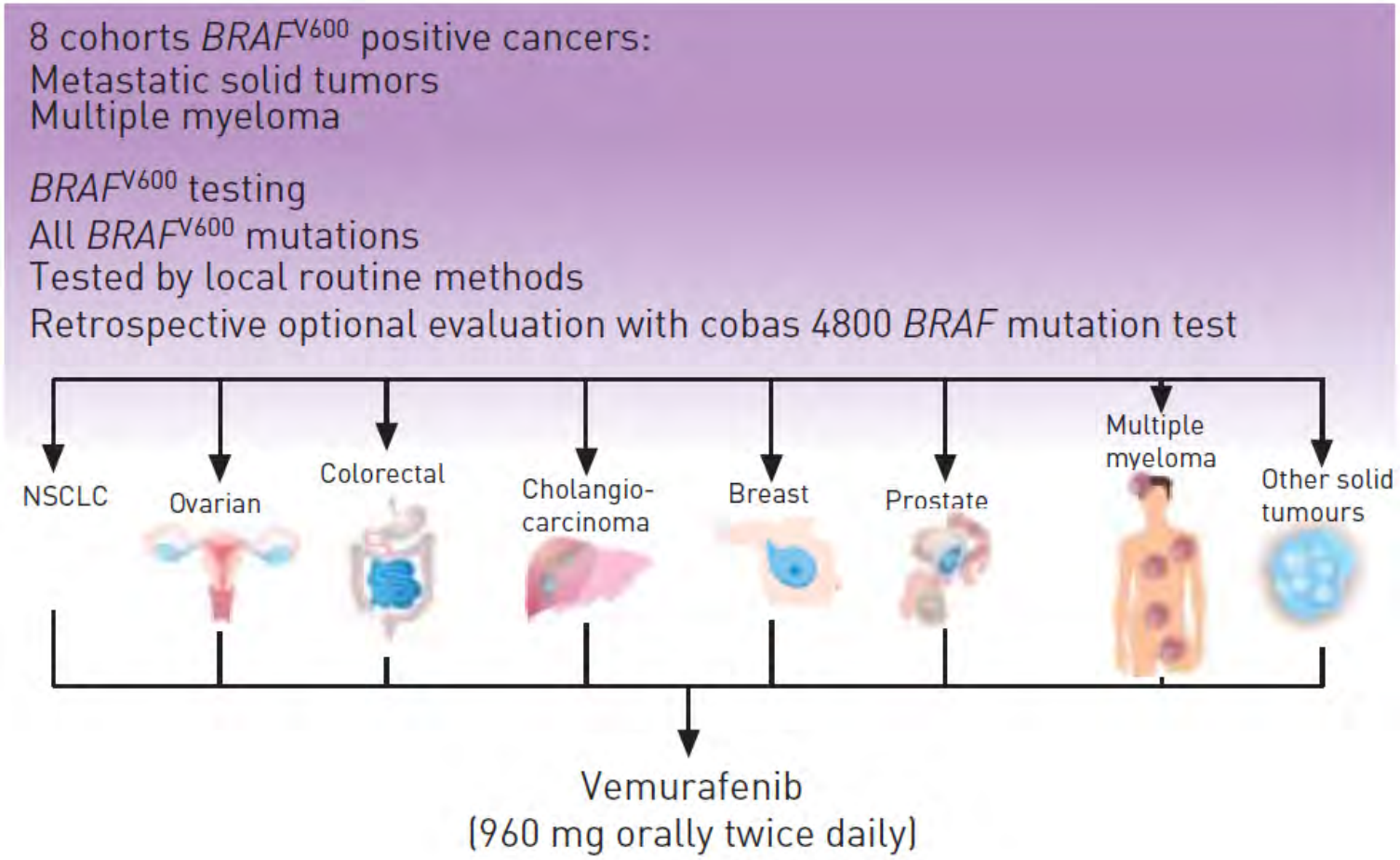
Author	Study	N (EGFR mut +)	RR	Median PFS
Mok et al	IPASS	132	71.2% vs 47.3	9.8 vs 6.4 months
Lee et al	First-SIGNAL	27	84.6% vs 37.5%	8.4 vs 6.7 months
Mitsudomi et al	WJTOG 3405	86	62.1% vs 32.2%	9.2 vs 6.3 months
Maemondo et al	NEJGSG002	114	73.7% vs 30.7%	10.8 vs 5.4 months
Zhou et al	OPTIMAL	154	83% vs 36%	13.1 vs 4.6 months
Rosell et al	EURTAC	135	56% vs 18%	9.2 vs 4.8 months
Yang et al	LUX Lung 3	345	56% vs 22%	11.1 vs 6.9 months
Wu et al	LUX Lung 6	364	67% vs 23%	11.0 vs 5.6 months

Mok *et al. NEJM.* 2009; Lee *et al.* WCLC. 2009; PRS4; Mitsudomi *et al. Lancet Oncology.* 2010; Maemondo *et al. NEJM.* 2010; Zhou *et al. Lancet Oncol.* 2011; Yang *et al. JCO.* 2013; Wu *et al. Lancet Oncol.* 2014

Schematic example of a basket trial:
One drug, one molecular alteration, several tumour types



Schematic illustration of the Vemurafenib basket trial



BASKET Trial: Vemurafenib in Multiple Non-melanoma cancers with BRAF V600 Mutations

Variable	NSCLC (N=20)	Colorectal Cancer		Cholangio-carcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)
		Vemurafenib (N=10)	Vemurafenib + Cetuximab (N= 27)			
Patients with ≥1 postbaseline assessment — no.	19	10	26	8	14	7
Complete response — no. (%)	0	0	0	0	1 (7)	1 (14)
Partial response — no. (%)	8 (42)	0	1 (4)	1 (12)	5 (36)	1 (14)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing data — no. (%)†	1 (5)	0	0	0	0	1 (14)
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]	1 (12) [<1–53]	6 (43) [18–71]	2 (29) [4–71]

ECD/LCHErdheim–Chester disease or Langerhans'-cell histiocytosis

David M. Hyman *et al.,* NEJM 2015

French national AcSé Program

INSTITUT NATIONAL DU CANCER

Programme AcSé 2013-2015

278000 tests
144000 patients
En 2010

Criblage Moléculaire

ALK, MET, RON, ROS, BRAF

10000 à 18000 patients
14000 à 25000 tests

28 plateformes
Génétique moléculaire
INCA

AcSé Crizotinib

Essai

500 patients

AcSé Vemurafenib

Essai

UNICANCER promoteur

Jusqu' à 250
Centres investigateurs

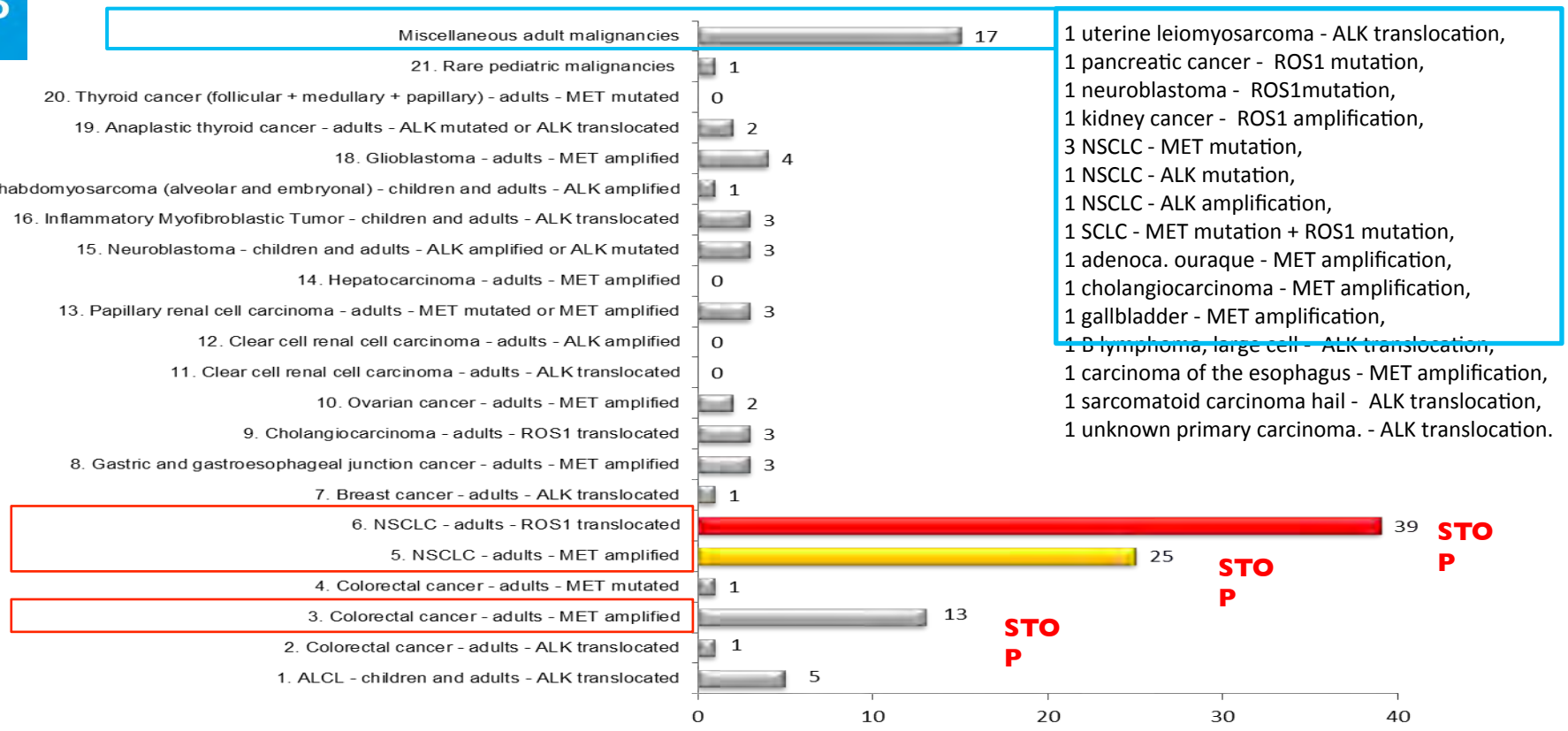
One drug, several molecular alterations, several tumour types

Biomarker-driven access to crizotinib In ALK, MET or ROS1 positive malignancies in adults and children: the French national AcSé Program

Gilles Vassal, Denis Moro Sibilot, Marie-Cécile Le Deley, Natalie Hoog-Labouret, Frédérique Nowak, Marta Jimenez, Christophe Tournigand, Roch Houot, David Malka, Thomas Aparicio, Bernard Escudier, Isabelle Ray Coquard, Yann Godbert, Luc Taillandier, Ivan Bièche, Sylvie Lantuejoul, Gilbert Ferretti, Yves Menu, Jean-Yves Blay, Agnès Buzyn.

12LBA – S 15, Vienna

Results : 24 cohorts



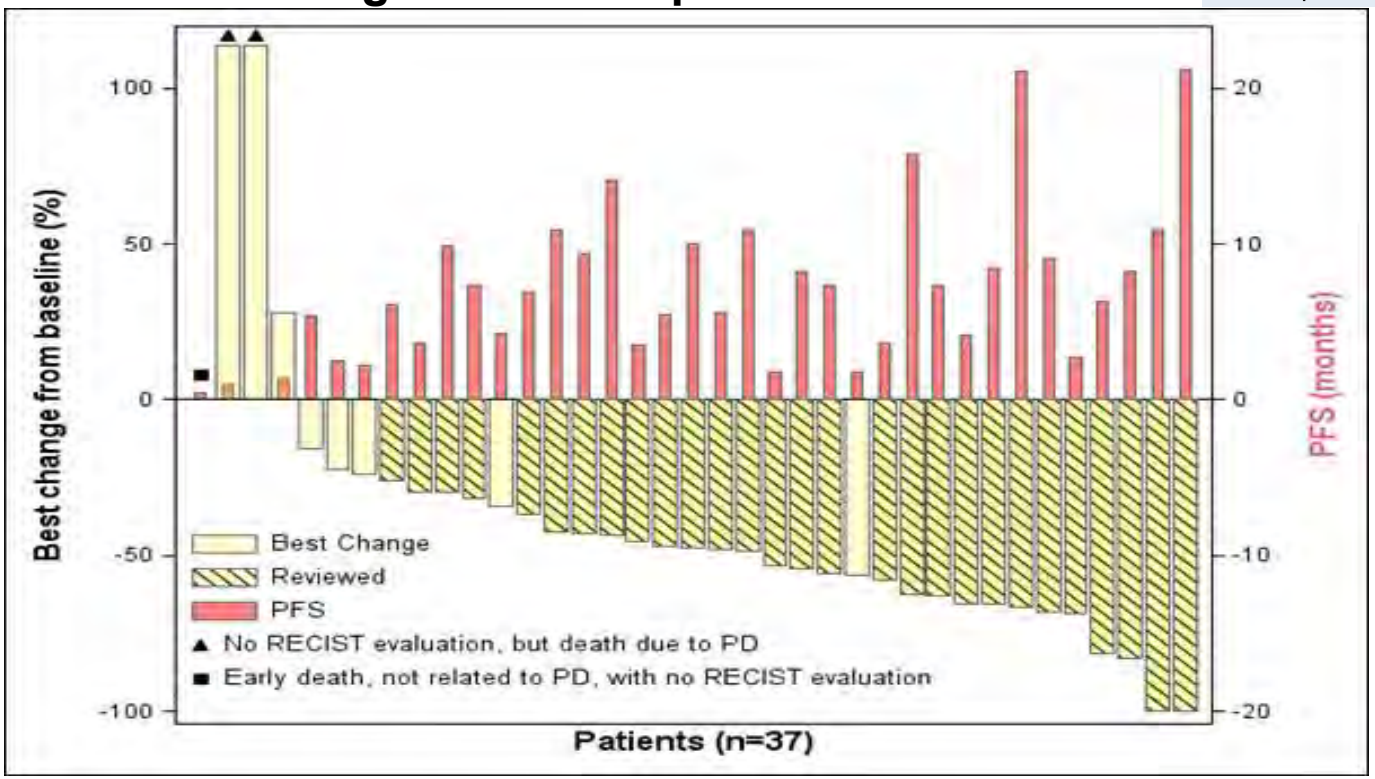
1 uterine leiomyosarcoma - ALK translocation,
1 pancreatic cancer - ROS1 mutation,
1 neuroblastoma - ROS1mutation,
1 kidney cancer - ROS1 amplification,
3 NSCLC - MET mutation,
1 NSCLC - ALK mutation,
1 NSCLC - ALK amplification,
1 SCLC - MET mutation + ROS1 mutation,
1 adenoca. ouraque - MET amplification,
1 cholangiocarcinoma - MET amplification,
1 gallbladder - MET amplification,
1 B lymphoma, large cell - ALK translocation,
1 carcinoma of the esophagus - MET amplification,
1 sarcomatoid carcinoma hail - ALK translocation,
1 unknown primary carcinoma. - ALK translocation.

Results: ROS1+ NSCLC

ROS1 or ALK translocation/amplification

- IHC signal (≥1+) ➔ **FISH (100 nuclei)**
- translocation threshold **> 15 % positive cells**
- amplificiation threshold **> 6 copies**

Tumor shrinkage at best response



Best response

ORR = 26/36

72 % [55% ; 86%]

DCR = 32/36

89 % [74% ; 97%]

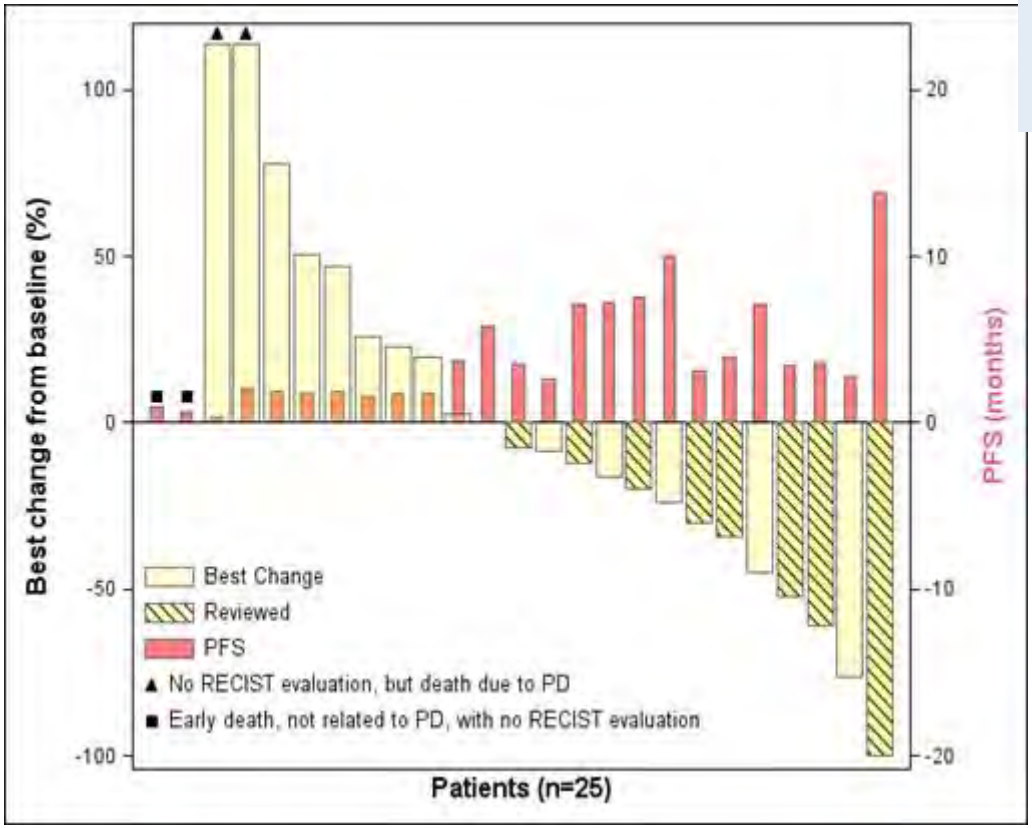
44% PFS

at 12 months

Gilles Vassal et al, 2015

MET$_{AMP}$ NSCLC

Tumor shrinkage at best response



MET amplification

- IHC signal (≥2+) ➔ **FISH (100 nuclei)**
- Amplification threshold: **> 6 copies**
- GBM two cohorts high polysomy and true amplification (MET/CEP7 ratio)

Best response

ORR = 7/25

28 % [12% ; 49%]

DCR = 15/25

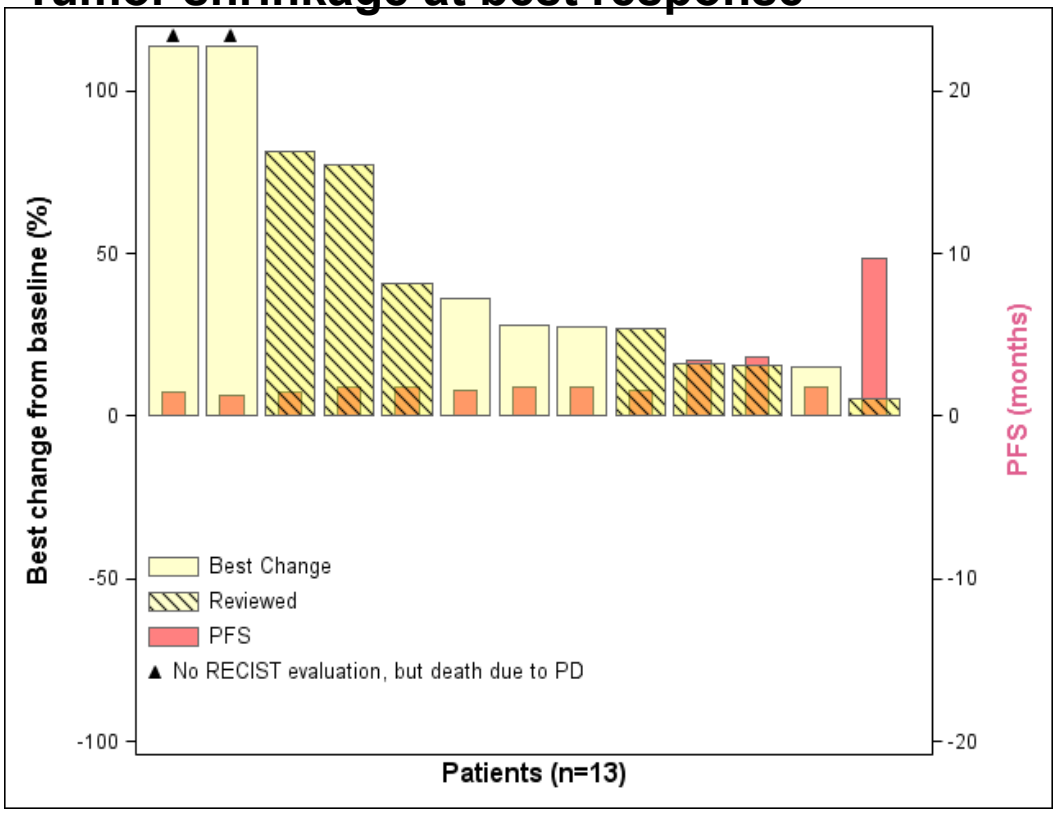
60 % [41%;79%]

No correlation observed between the number of MET copies and best response (p=0,10).

G.Vassal et al 2015

Results: METAMP Colon Cancer

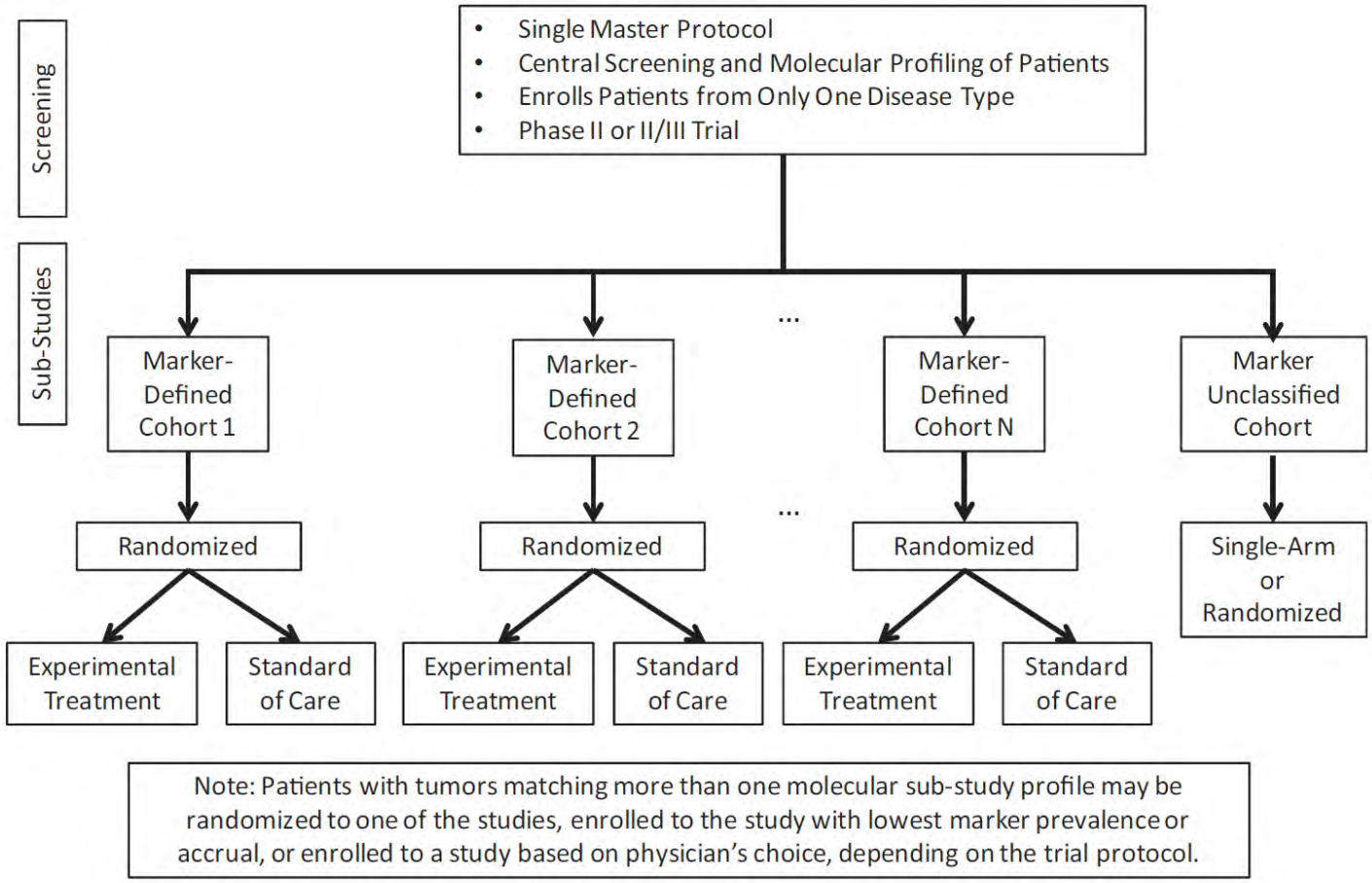
Tumor shrinkage at best response



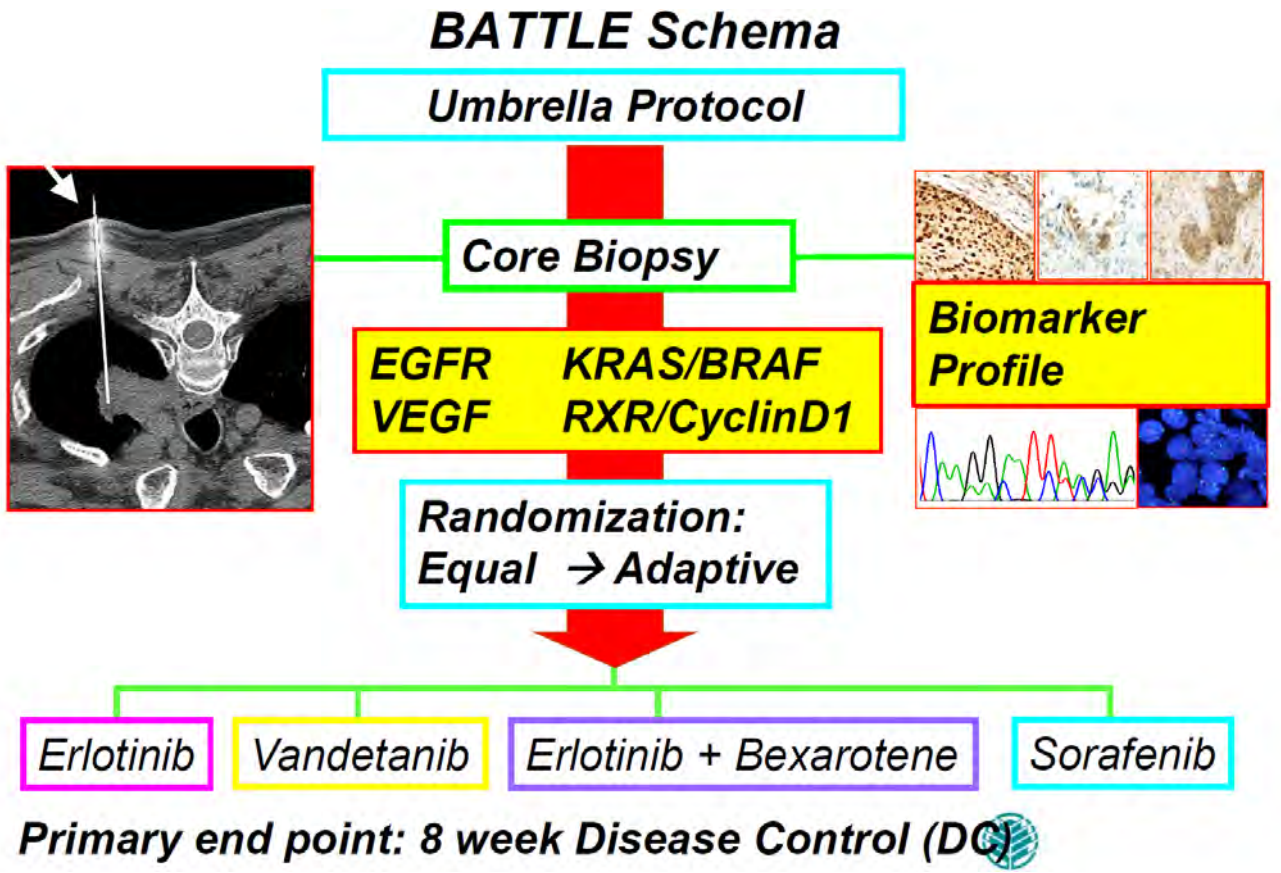
No response in 13 patients

STOP accrual at stage I

Umbrella trial (One disease type, multiple molecular alteration)

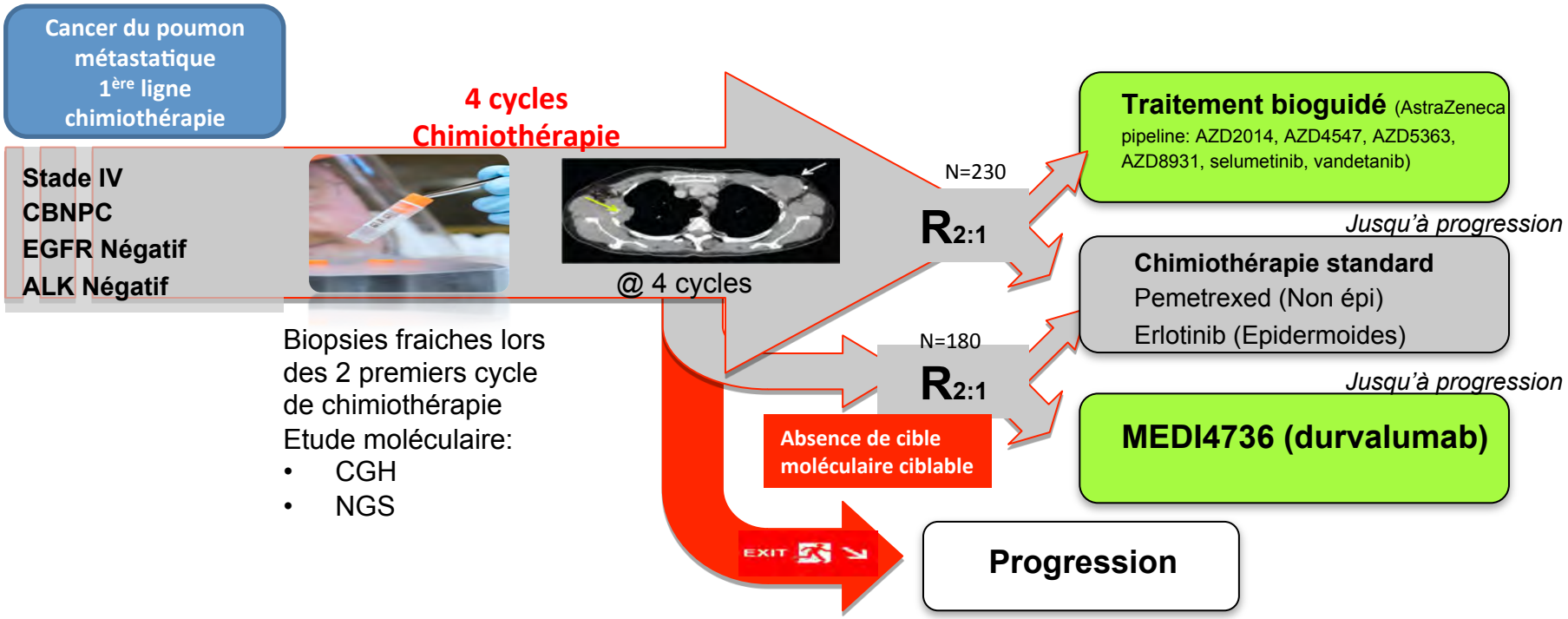


BATTLE trial in NSCLC



Kim ES et al. Cancer Discov 2011; 1: 44

SAFIR02 Lung (UNICANCER 0105-1305 / IFCT 1301)

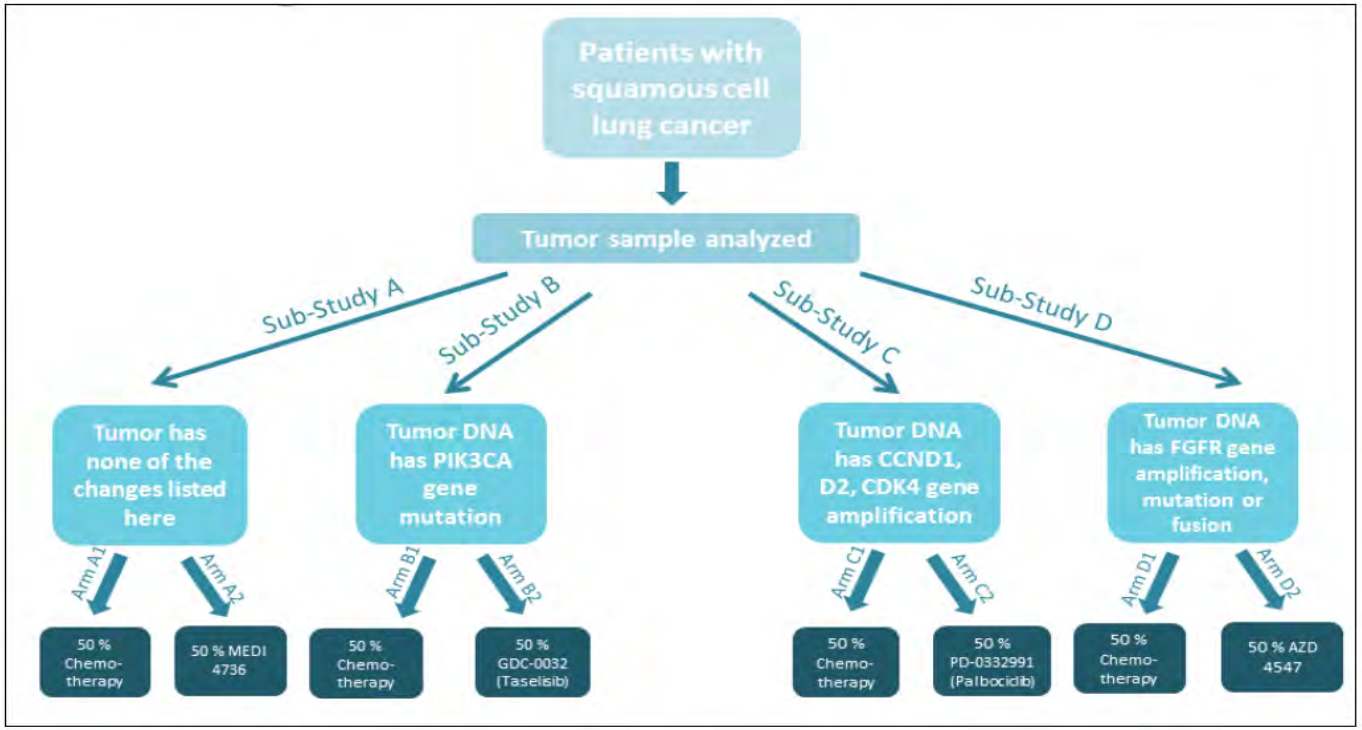


Co-principal investigateurs : Pr JC.Soria / Pr F. Barlesi

Umbrella Trials:
Moving beyond one marker/drug

LUNG-MAP

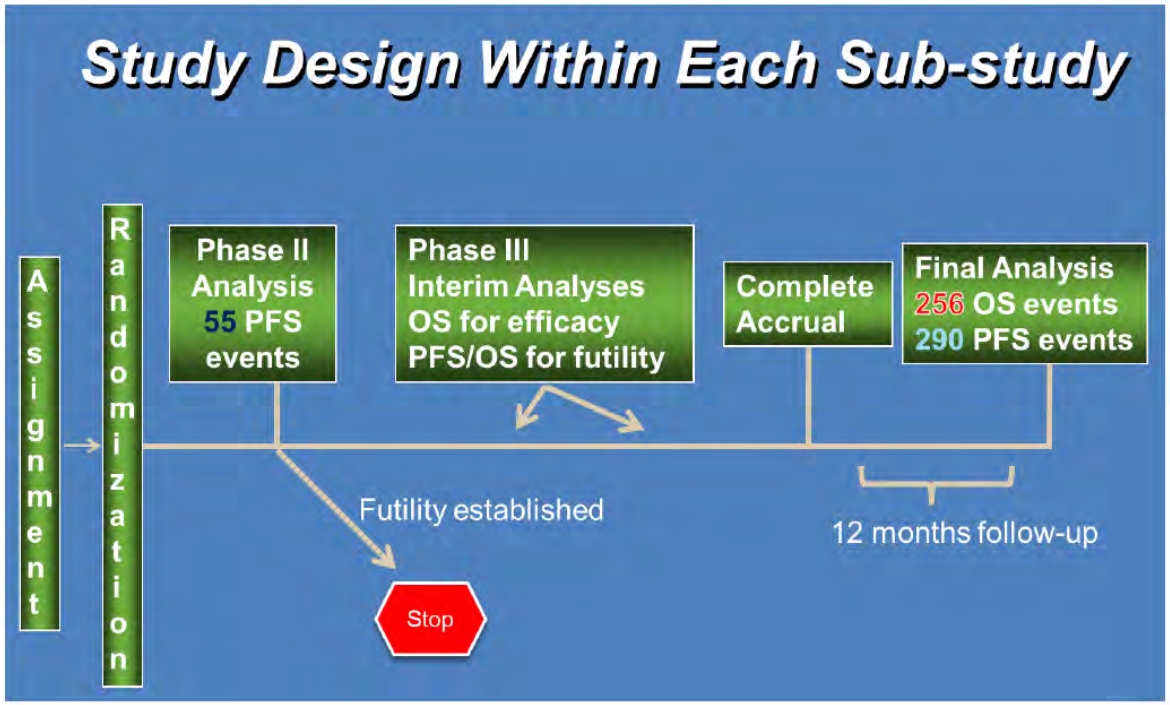
Phase II/III Biomarker-Driven Master Protocol for 2nd Line Therapy of Squamous Cell Lung Cancer



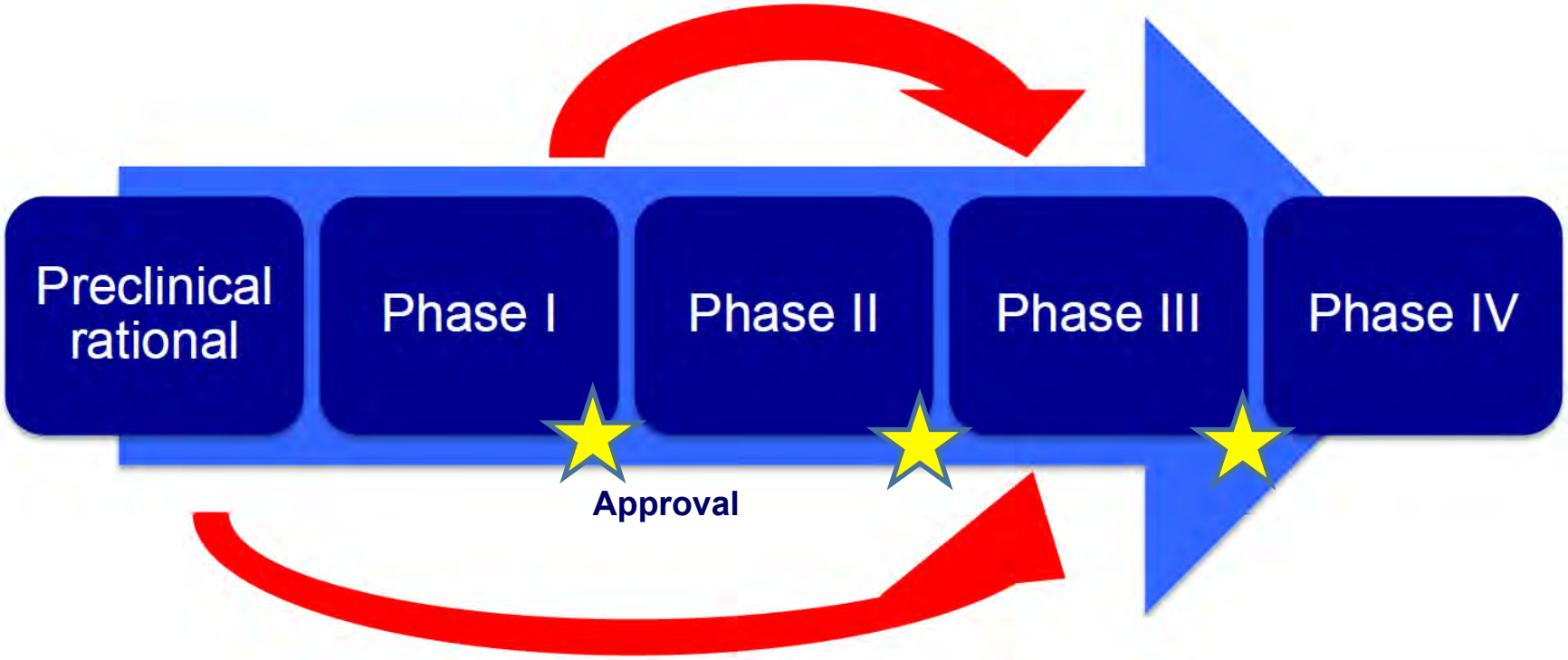
Adaptive designs

LUNG-MAP

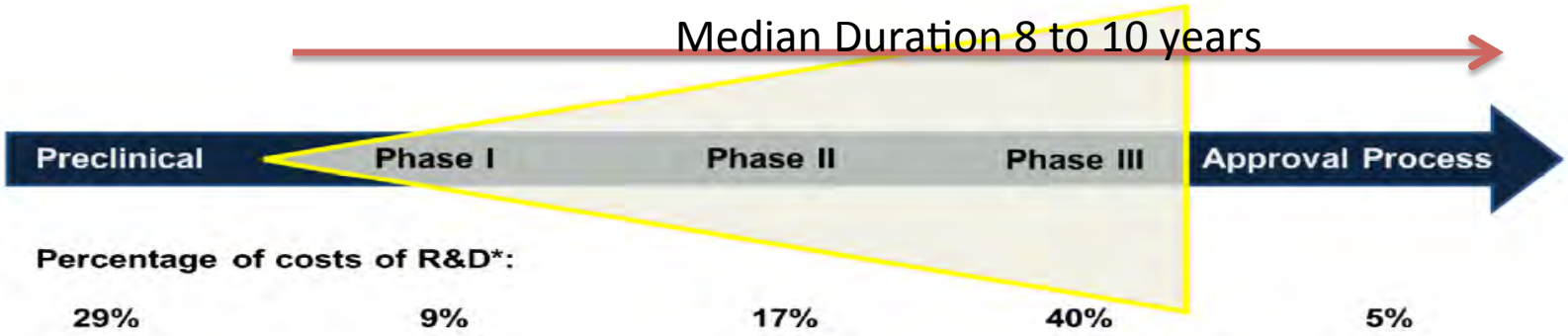
Phase II/III Biomarker-Driven Master Protocol for 2nd Line Therapy of Squamous Cell Lung Cancer



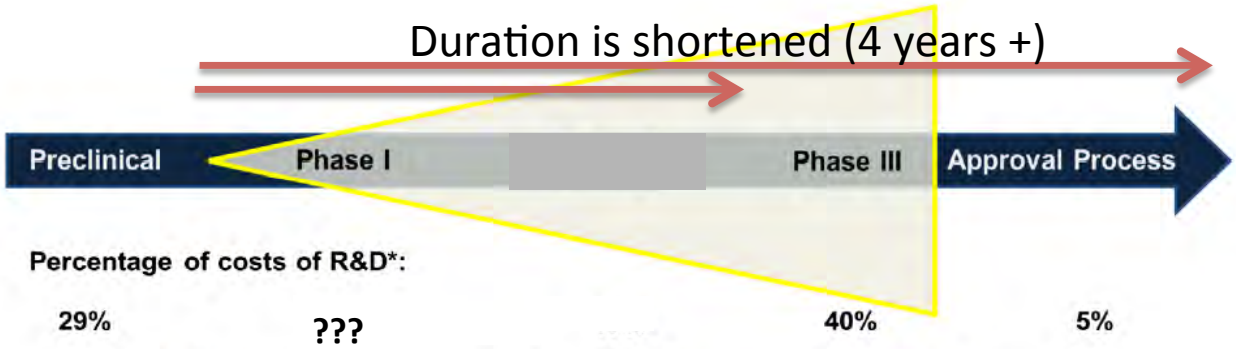
In Summary….Non-linear clinical development

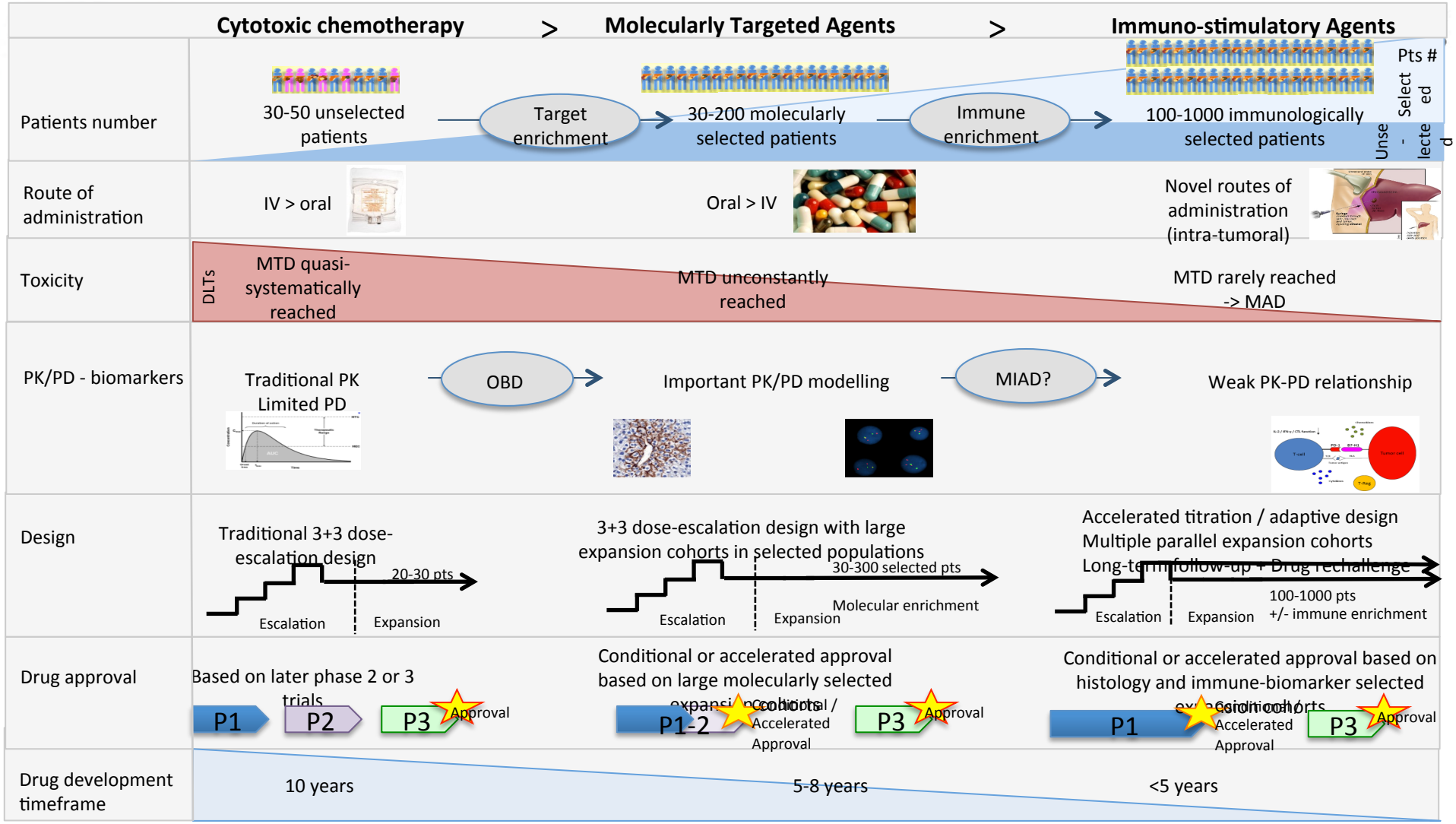


The revolution in drug development has profound implications



Burock S, EJC 2013
Paul S, Nat rev Drug Discovery 2010




Cytotoxic chemotherapy
>
Molecularly Targeted Agents
>
Immuno-stimulatory Agents
Patients number
30-50 unselected patients
Target enrichment
30-200 molecularly selected patients
Immune enrichment
100-1000 immunologically selected patients
Pts #
Select - ed
Unse - lecte d
Route of administration
IV > oral
Oral > IV
Novel routes of administration (intra-tumoral)
Toxicity
DLTs
MTD quasi-systematically reached
MTD unconstantly reached
MTD rarely reached -> MAD
PK/PD - biomarkers
Traditional PK Limited PD
OBD
Important PK/PD modelling
MIAD?
Weak PK-PD relationship
Design
Traditional 3+3 dose-escalation design
20-30 pts
Escalation
Expansion
3+3 dose-escalation design with large expansion cohorts in selected populations
30-300 selected pts
Escalation
Expansion
Molecular enrichment
Accelerated titration / adaptive design
Multiple parallel expansion cohorts
Long-term follow-up + Drug rechallenge
Escalation
Expansion
100-1000 pts
+/- immune enrichment
Drug approval
Based on later phase 2 or 3 trials
P1
P2
P3
Approval
Conditional or accelerated approval based on large molecularly selected
P1-2
Accelerated Approval
P3
Approval
Conditional or accelerated approval based on histology and immune-biomarker selected
P1
Accelerated Approval
P3
Approval
Drug development timeframe
10 years
5-8 years
<5 years

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Acknowledgments

Jean-Charles SORIA
Benjamin BESSE
Thierry LE CHEVALIER

THANK YOU

david.planchard@gustaveroussy.fr

IOT
institut-oncologie-thoracique.com