Essais cliniques: nouveaux designs

Cours du *GOLF*
Paris – 10 Octobre 2018

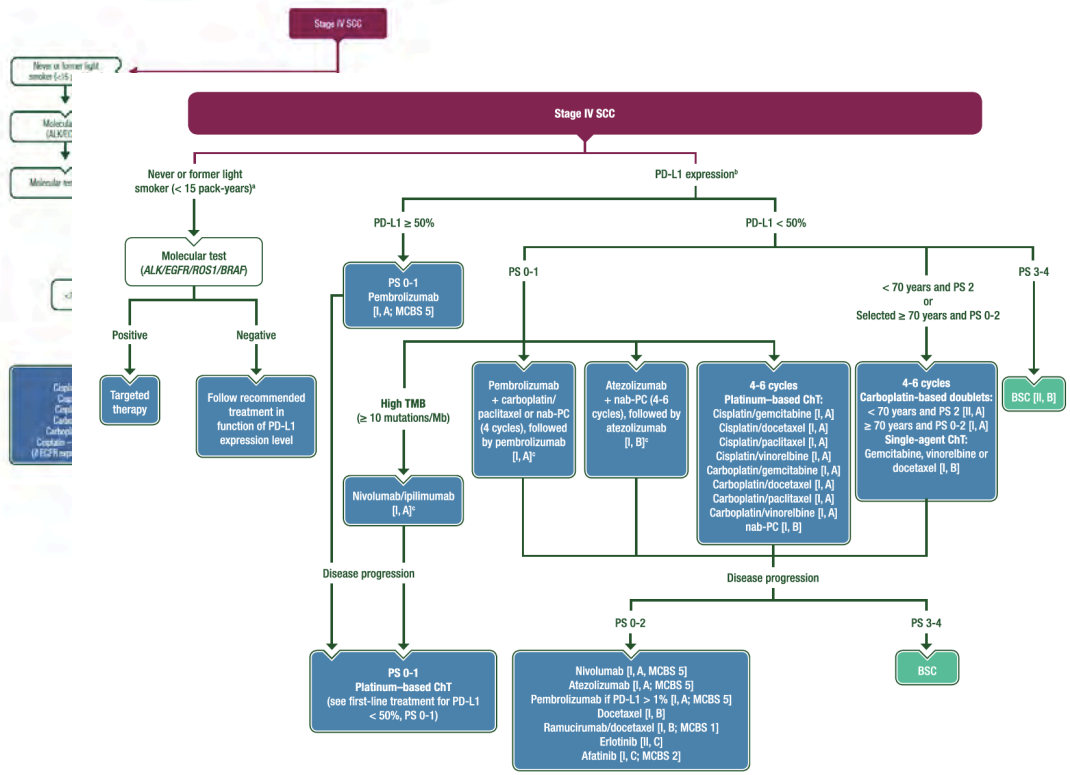
Fabrice Barlesi, MD, PhD

Disclosures

- **Personal financial interests:**
  - Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda
- **Institutional financial interests:**
  - Abbvie, ACEA, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda
- **Non-financial interests:**
  - Principal Investigator for Astra-Zeneca, BMS, Merck, Pierre Fabre and F. Hoffmann-La Roche, Ltd, sponsored trials (or ISR)
- **No other conflicts of interest**

Pourquoi de nouveaux designs ?

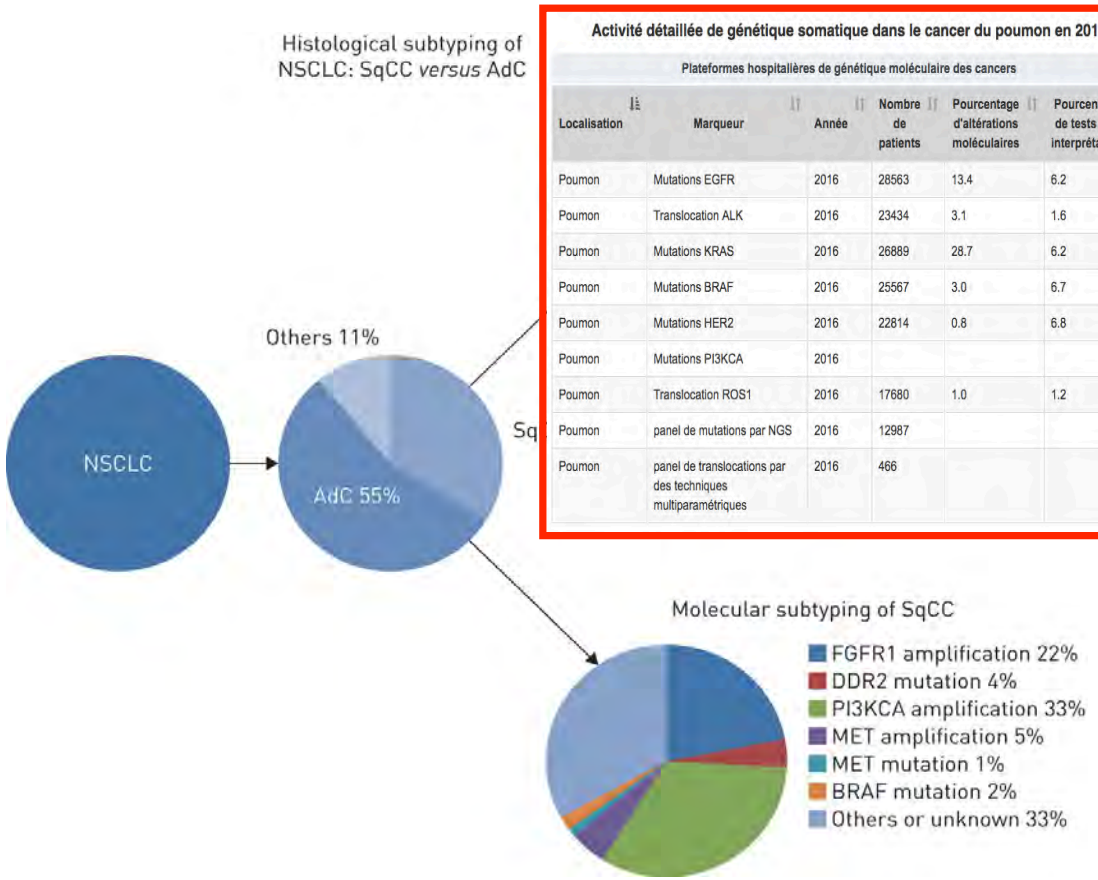
- **Accélération des connaissances**
  - Flexibilité
  - Rapidité de recrutement



Novello S, et al. Ann Oncol 2016; Planchard D, et al. Ann Oncol 2018

Pourquoi de nouveaux designs ?

- **Segmentation des pathologies**
  - Démembrement moléculaire
  - Inégalité de screening



Activité détaillée de génétique somatique dans le cancer du poumon en 2016

Plateformes hospitalières de génétique moléculaire des cancers

Localisation	Marqueur	Année	Nombre de patients	Pourcentage d'altérations moléculaires	Pourcentage de tests non interprétables
Poumon	Mutations EGFR	2016	28563	13.4	6.2
Poumon	Translocation ALK	2016	23434	3.1	1.6
Poumon	Mutations KRAS	2016	26889	28.7	6.2
Poumon	Mutations BRAF	2016	25567	3.0	6.7
Poumon	Mutations HER2	2016	22814	0.8	6.8
Poumon	Mutations PI3KCA	2016			
Poumon	Translocation ROS1	2016	17680	1.0	1.2
Poumon	panel de mutations par NGS	2016	12987		
Poumon	panel de translocations par des techniques multiparamétriques	2016	466		

Bubendrof L, et al. Eur Respir Rev 2017

Impact #1

- 1er défi: médecine de précision (screening moléculaire)

http://busytoddler.com/2016/08/sponge-targets/

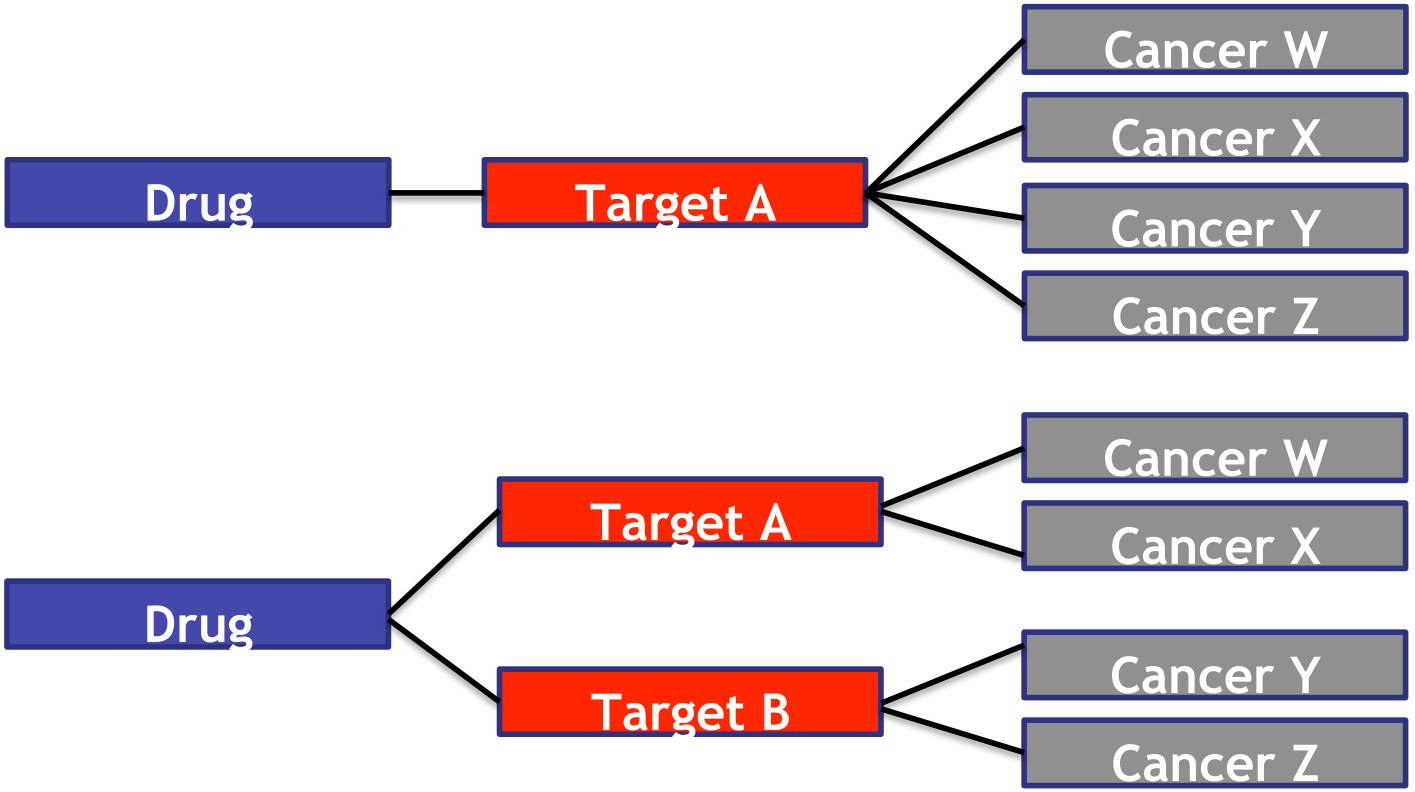
NG Essais bio-guidés

- To reach an FDA/EMEA registration: 11%
  - 5 phases I
  - 7 phases II
  - 4 phases III
- Change? Receptor targeted therapy: 31%
- Change? Bio-marker guided therapy: 62%

- Sélection (moléculaire) des patients: un défi payant

Falconi A *et al*, J Thorac Oncol 2014

NG Essais bio-guidés



- Basket trials

Courtesy Julien Mazières

NG Essais bio-guidés

Localisation tumorale	ALK transloc.	ALK amp.	MET amp.	ROS1 transloc.	ALK mut.	MET mut.	Références
ALCL	50,0%						Merkel et al., 2011
Colorectal	2,4%		3,6%			3,3%	Lin et al., 2009 Lipson et al., 2012 Zen, 2008 Fumagalli, 2010
NSCLC			4,0%	3,5%			Bergethon et al., 2012 Takeuchi et al., 2012
Breast	2,4%						Lin et al., 2009
Gastric			6,0%				Graziano, 2012
Cholangiocarcinoma				9,0%			Gu et al., 2011
Ovary			12,0%				Yamamoto, 2011
Renal cell carcinoma	2,0%	10,1%				13%*	Sukov et al., 2012 Sugarawa et al., 2012 Debelenko et al., 2011 Mariño-Enriquez et al., 2011 Schmidt et al., 1997
Hepatocarcinoma			2,3%			30%#	Kondo et al., 2012 Park et al., 1999
Neuroblastoma		3,0%			7,0%		De Brouwer et al., 2010 Caren et al., 2008
Inflammatory myofibroblastic tumor	50,0%						Mano, 2012
Rhabdomyosarcoma		28,0%					Van Gaal et al., 2012
Glioblastoma			45,0%				Pierscianek et al., 2013
Thyroid					11%**	8,0%	Murugan et al., 2011 Wasenius, 2005

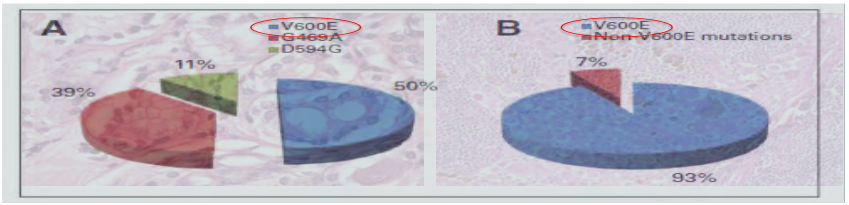
*type I papillary renal cell carcinoma. ** anaplastic thyroid cancer. #: pediatric hepatocarcinoma, very rare, not retained for a single cohort.

- Basket trials
  - Ex. Acsé

Available www.ecancer.fr

NG Essais bio-guidés

- Une altération sur le même gène mais …
  - Addiction oncogénique ou pas (*BRAF*)



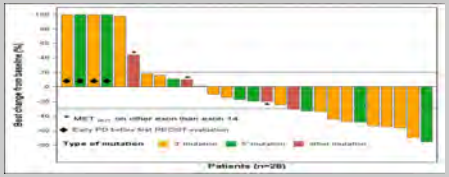
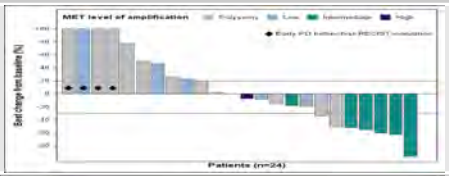
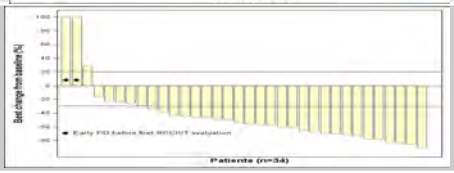
  - Diverses altérations avec des conséquences variables (*KRAS*)

- Etapes initiales du développement (essais précoces) ?

- Basket trials: difficultés ?

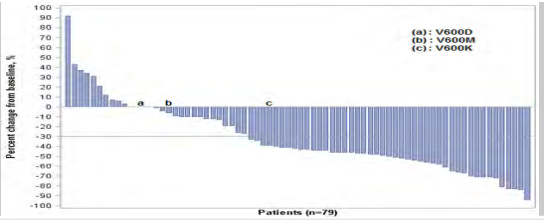
Porta M *et al*, Mut Res 2009; Paik PK *et al*, J Clin Oncol 2011

Acsé programs (ex. Crizotinib/MET, ROS1)

	screening activity	Positive cases	Patients treated in the program	Efficacy (BOR)
ROS1 translocation	4064 pts	78 pts **(1.9%)**	39 pts	
MET amplification	4191 pts	252 pts **(6.0%)**	25 pts	
MET mutation	1192 pts	86 pts **(7.2 %)**	29 pts	

Moro-Sibilot D, et al. WCLC 2018 (A12937)

Acsé programs (ex. Vemurafenib/BRAFm)

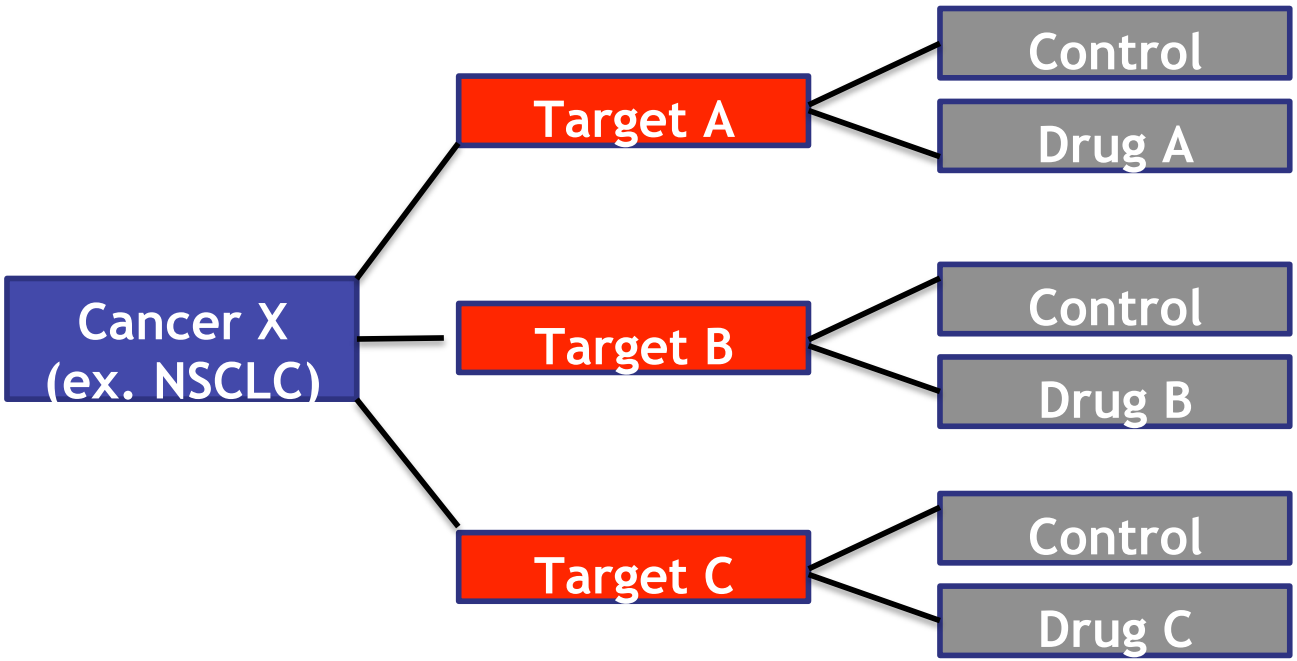
	Positive cases pts	Patients treated in the program	Efficacy (BOR)
BRAF V600	101	100	
BRAF non V600	17	15	**5% (study stopped)**

Mazières J, et al. WCLC 2018 (A)

NG Essais bio-guidés

NGS **Targeted therapy**

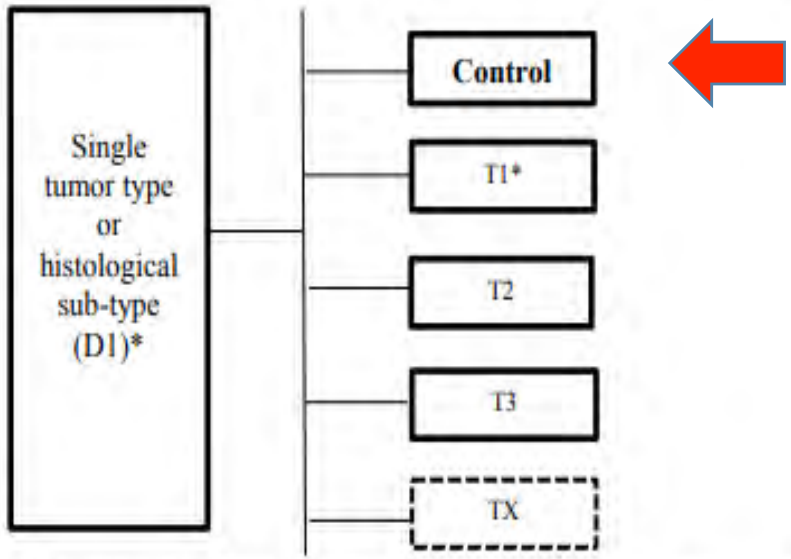
- Umbrella trials



Courtesy Julien Mazières

NG Essais bio-guidés

Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design

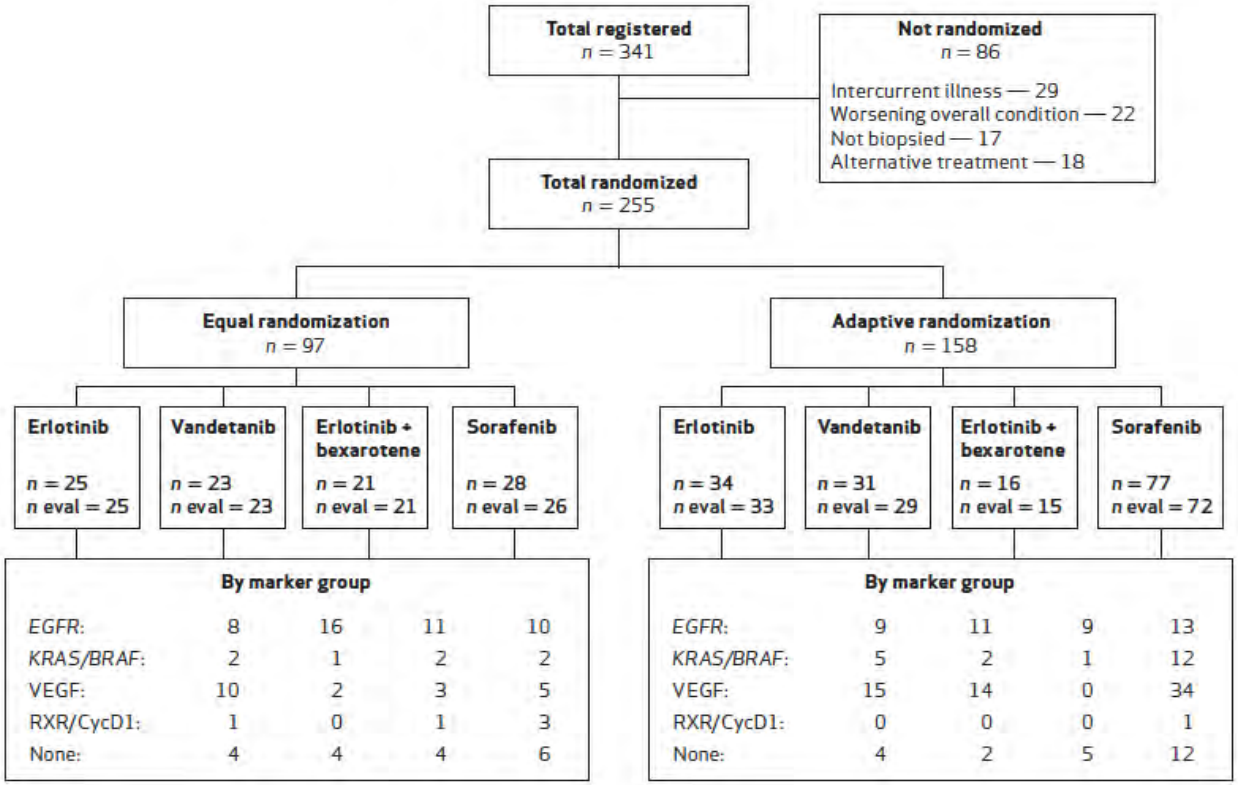


* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

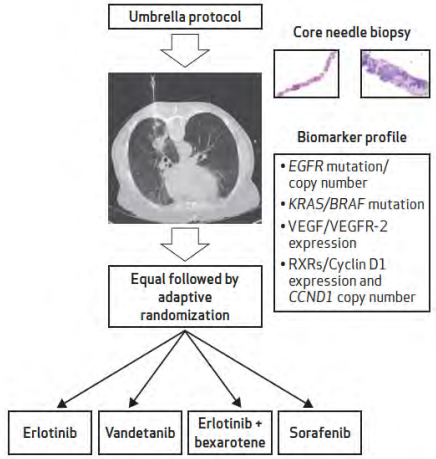
- FDA guidelines (Sep 28, 2018)

Available @ www.fda.org

NG Essais bio-guidés

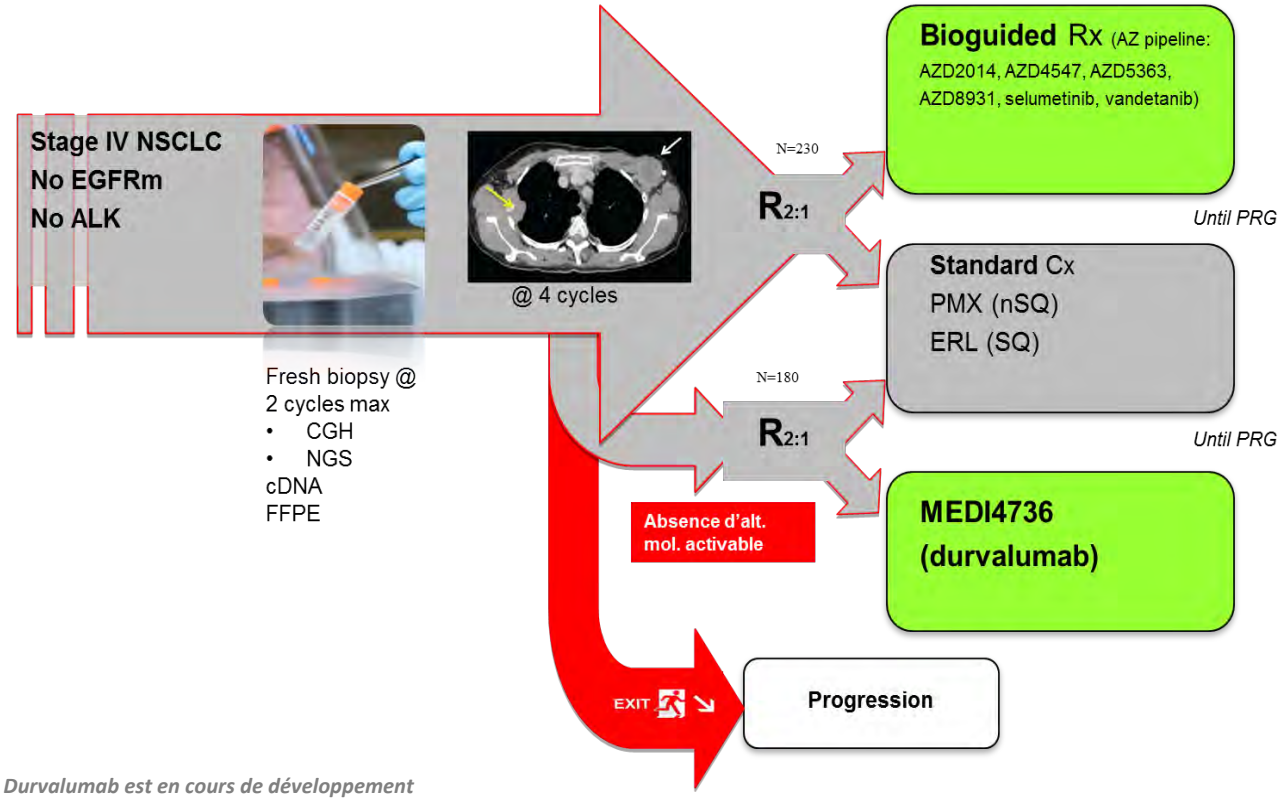


- Umbrella trials
  - Ex. Battle



Kim ES *et al*, Cancer Discov 2011

NG Essais bio-guidés



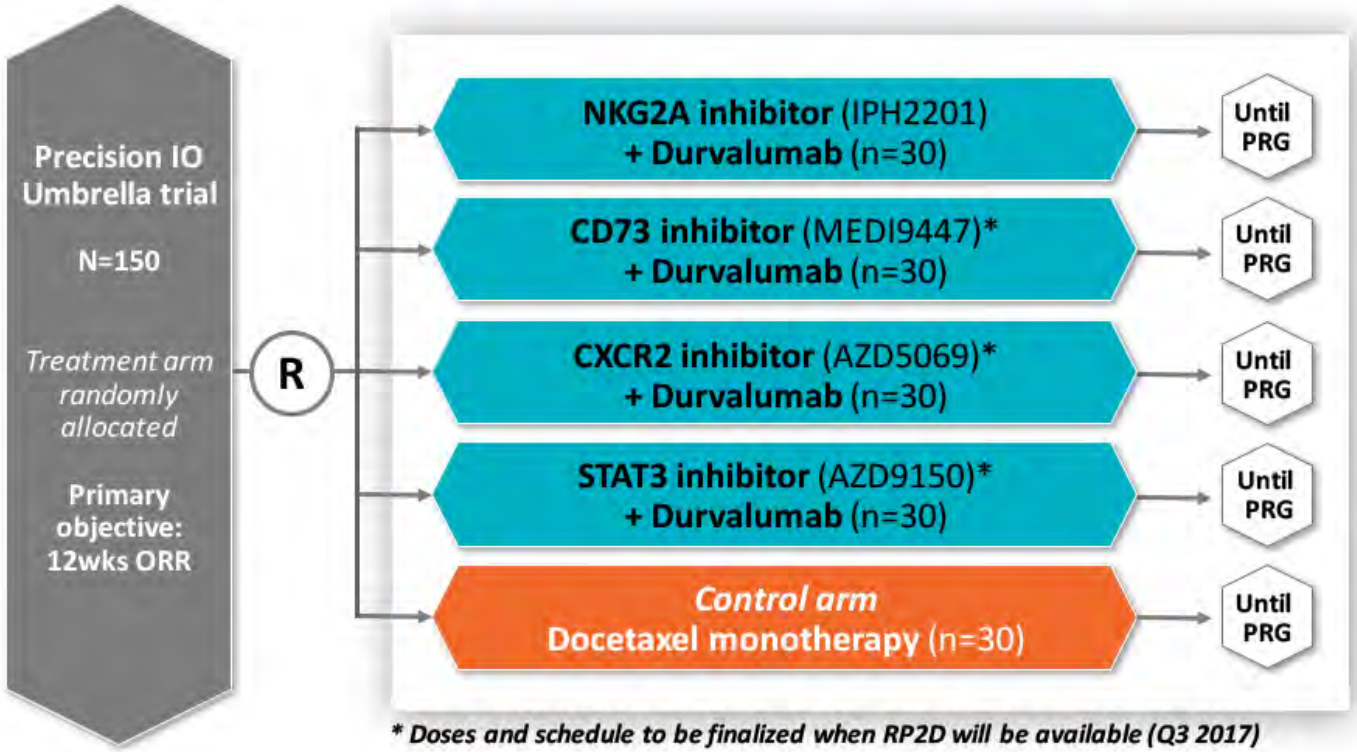
Durvalumab est en cours de développement

- Umbrella trials
  - Ex. SAFIR

IFCT Unicancer SAFIR 02 Lung trial

Pis: F Barlesi / B Besse

NG Essais bio-guidés



Durvalumab est en cours de développement

- Umbrella trials
  - Ex. PIONeeR

PIONeeR IO rescue trial

Pis: F Barlesi

NG Essais bio-guidés

	MOSCATO, n (%)	SAFIR02lung, n (%)	MATRIX trial, n (%)	PROFILER n (%)
Pts included	1036	686	3099	2676
Pts w actionable target (%)	411 **(39)**	297 **(43)**	731 **(23)**	1004 **(37)**
Pts w targeted treatment (%)	199 **(19)**	110 **(16)**	458 **(15)**	143 **(5)**

- Umbrella trials: difficultés ?

Massard C et al, Cancer Discov 2017; SAFIR trial (data as of Sep 2017);
courtesy G Middelton (data as of July 2016); Tredan O et al, ASCO 2017

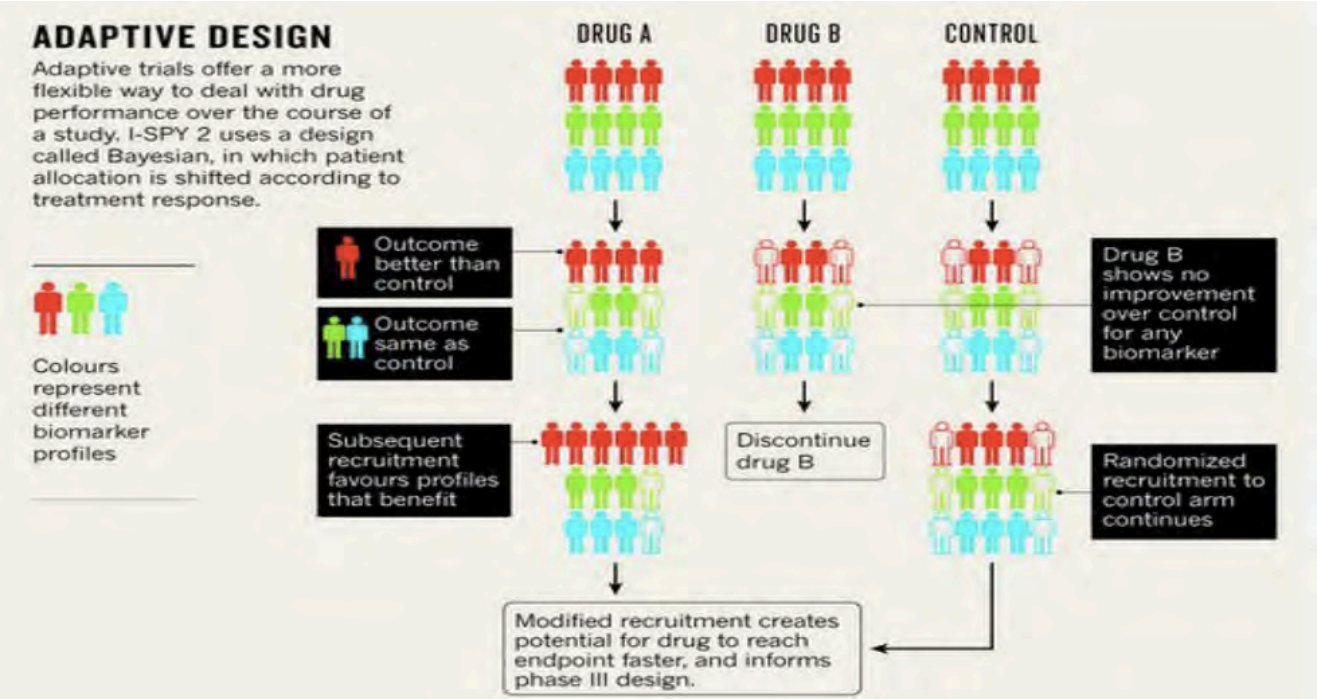
NG Essais bio-guidés

- Investigateur / clinicien
  - Gestion proche de la routine
  - Interprétation / décision collégiale
- Patient
  - Accès à des technologies biologiques de pointe
  - Accès à un panel (large) de traitements bio-guidés
- Société
  - Amélioration inclusions (**4%** aujourd'hui*)
- Promoteur / Financeur
  - Flexibilité (amendements)

- Umbrella trials: avantages ?

* Barlesi F *et al*, Lancet 2016

NG Essais bio-guidés

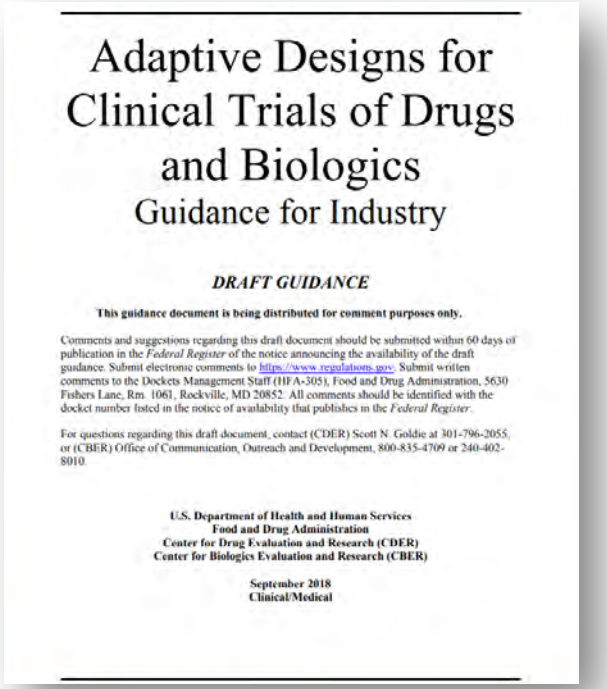


- Design adaptatif

Eisenstein M *et al*, Nature 2014

NG Essais bio-guidés

- Adaptative design (FDA guidance)



Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical

- Released on Sept. 28, 2018

www.fda.gov

NG Essais bio-guidés

- Masterprotocol (principes)
  - **Multi-arm** randomized, controlled. Each arm (min 4) able to open and close independent of other arms
  - Operations Management: **Neutral 3rd party**
  - **Independent Drug Selection Committee**
  - **Oversight Committee**: Comprised of leaders from NCI, Academia, FDA, industry, advocates


ISSUE BRIEF

Conference on Clinical Cancer Research

November 2012

Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

www.focr.org/events/design-lung-cancer-master-protocol

NG Essais bio-guidés

- Masterprotocol (avantages)
  - **Enrollment** Efficiency: reduces the screen failure rate
  - **Operational** Efficiency: amended as needed
  - **Consistency**: every drug tested in the identical manner
  - **Predictability**: If pre-specified criteria are met, the drug and accompanying companion diagnostic will be approved
  - **Patient Benefit**: bringing drugs to patients sooner than they might otherwise be available


ISSUE BRIEF

Conference on Clinical Cancer Research

November 2012

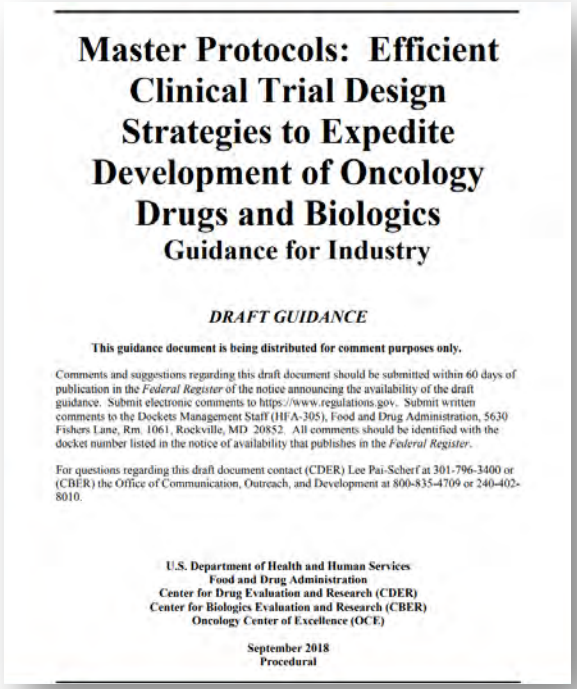
Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

www.focr.org/events/design-lung-cancer-master-protocol

NG Essais bio-guidés

- Masterprotocol (FDA guidance)



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2018
Procedural

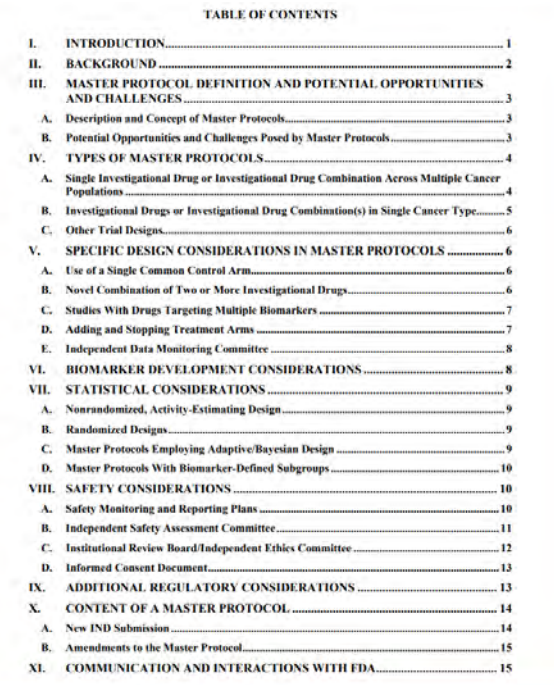
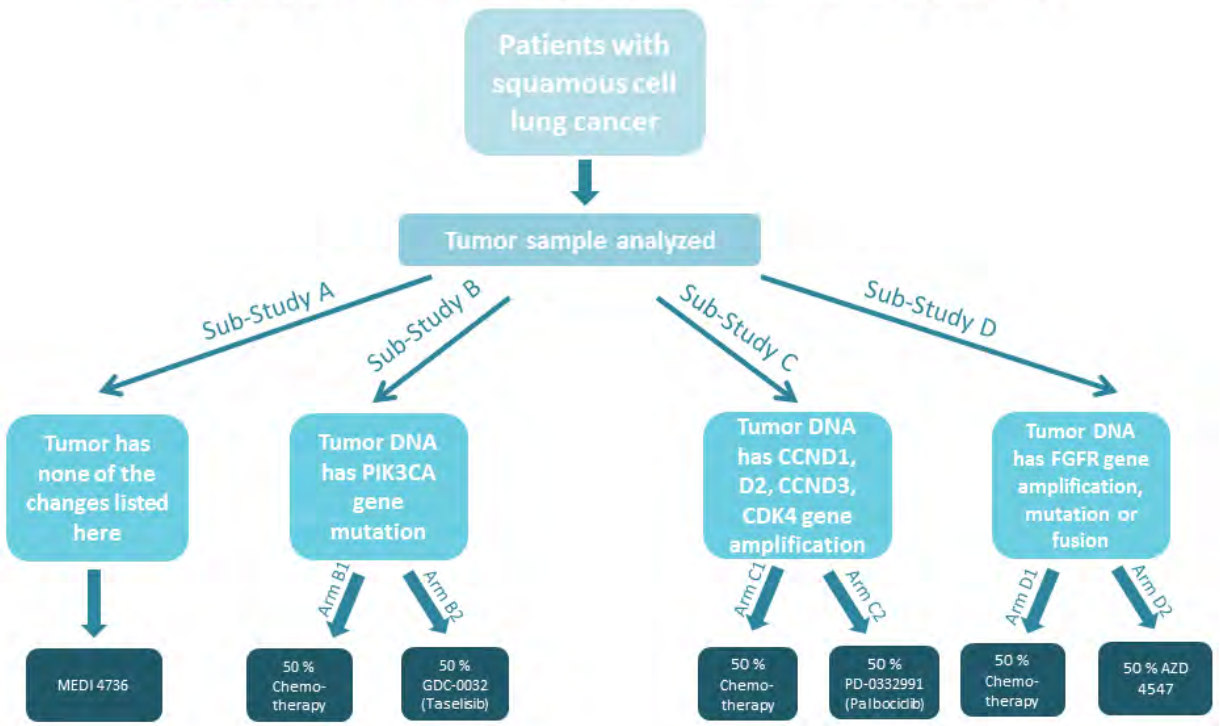


TABLE OF CONTENTS

- Released on Sept. 28, 2018

www.fda.gov

NG Essais bio-guidés



Durvalumab est en cours de développement

- NCI Lung MAP trial (SCC)

Downloaded from the NCI website

NG Essais bio-guidés

- Avantages
  - **Accès innovation**
    - Biomarqueurs
    - Traitements
  - **Efficacité supérieure**
  - **Evaluation rapide** des traitements
  - **Flexibilité** (traitement, dose, etc)

- Inconvénients
  - **Nombreux bras** de traitements
  - Nombre **élevé de patients**
  - Présence **inconstante** cible(s)
  - **Impacte nombre limité** de patients
  - **Caractérisation de la cible** à priori
    - Driver ?
    - Passenger ?
  - **Suivi dynamique** / adaptation
  - **Statistiques**

Awada A *et al*, ESMO course (available on line)

Impact #2

- 2ème défi: les premiers pas ne sont ils pas décisifs ?

https://www.babycenter.fr

Essais précoces: recherche de dose

Table 2. Prior Regimens and Patients Receiving ZD1839 by Tumor Type

	Ovarian (n = 23)	NSCLC (n = 22)	Colorectal (n = 21)	Prostate (n = 14)	Head and Neck (n = 8)	All (N = 88) No.	%
No. of previous chemotherapy regimens							
0	–	2	–	1	4	7	8.0
1	5	9	10	3	2	29	33.0
2	5	7	5	2	2	21	23.9
3	4	3	3	1	–	11	12.5
≥ 4	9	1	3	7	–	20	22.7
ZD1839 dose level							
150 mg/d	1	4	–	–	1	6	
225 mg/d	2	5	2	4	1	14	
300 mg/d	4	4	2	2	2	14	
400 mg/d	5	3	3	2	1	14	
600 mg/d	5	2	3	2	2	14	
800 mg/d	2	1	8	2	1	14	
1,000 mg/d	4	3	3	2	–	12	

150mg to 1000 mg (x #7)

Table 3. Patients With Drug-Related AEs of NCI-CTC Grade 3/4

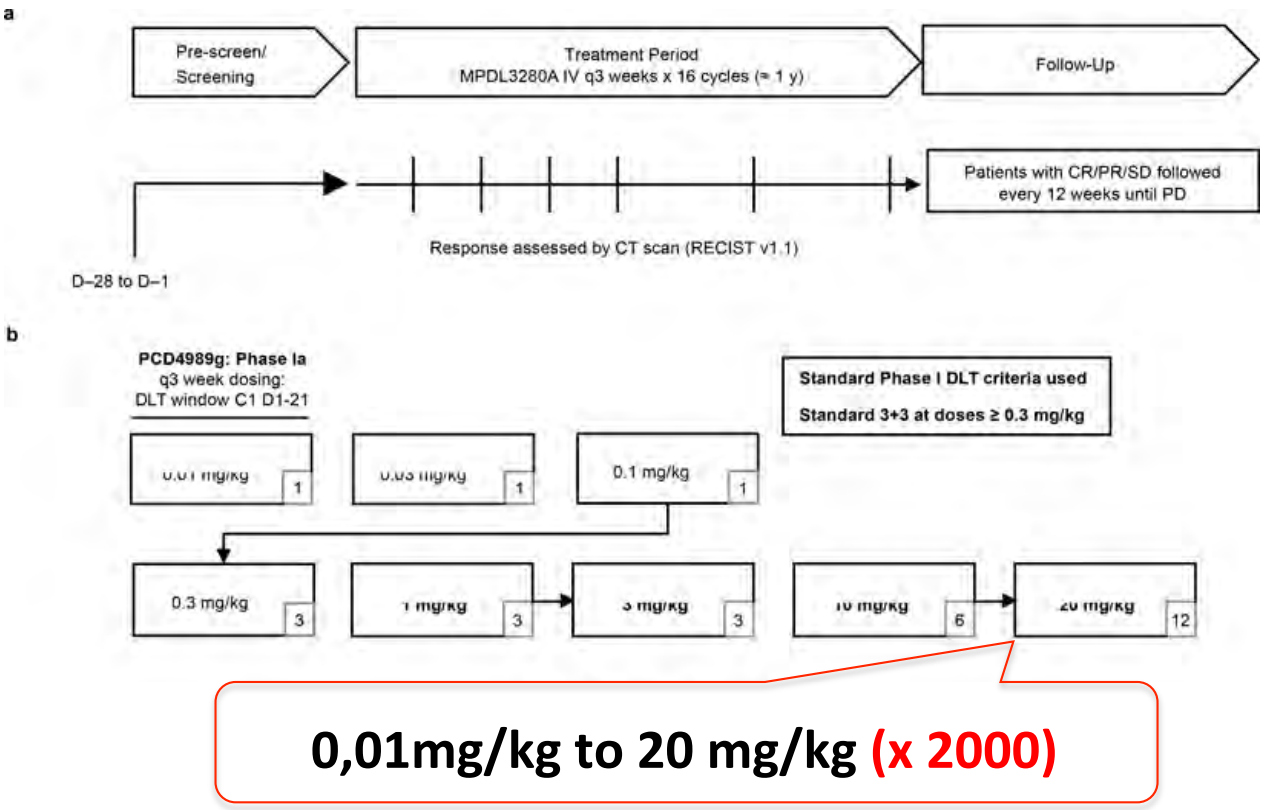
ZD1839 Dose (mg/d)	Tumor Type	AE	NCI-CTC Grade
225	Prostate	Nausea*	3
300	Prostate	Diarrhea*	3
400	Colorectal	Elevated transaminases	3
400	Colorectal	Acne-like rash*	3
400	Ovarian	Pain*†	3
		Pruritus*†	3
		Depression*†	3
600	Ovarian	Diarrhea*	3
600	Head and neck	Somnolence*	3
800	Colorectal	Asthenia (×2)*	4
800	Colorectal	Albuminuria	3
800	Colorectal	Diarrhea*	3
		Nausea	3
800	Prostate	Eye disorder	3
		Hair disorder (eyelash)	3
800	Colorectal	Elevated transaminases	3
1,000	Ovarian	Somnolence*	3
		Hematemesis*	3
		Acne-like rash*	3
		Hypokalemia*	3
		Diarrhea (×2)*	3
1,000	Prostate	Asthenia	3
		Elevated AST	3
		Diarrhea	3
1,000	Ovarian	Diarrhea*	3
1,000	Ovarian	Diarrhea*	3
		Dehydration*	3
1,000	Colorectal	Diarrhea*	3
1,000	NSCLC	Somnolence*	3

*DLT observed during first treatment period.
†Pain, pruritis, and depression all related to severe acneiform rash. Rash could not be graded as grade 3, as it involved < 50% of the body.

- Sélection de la dose (TKI) ?

Baselga J *et al*, J Clin Oncol 2002

Essais précoces: recherche de dose

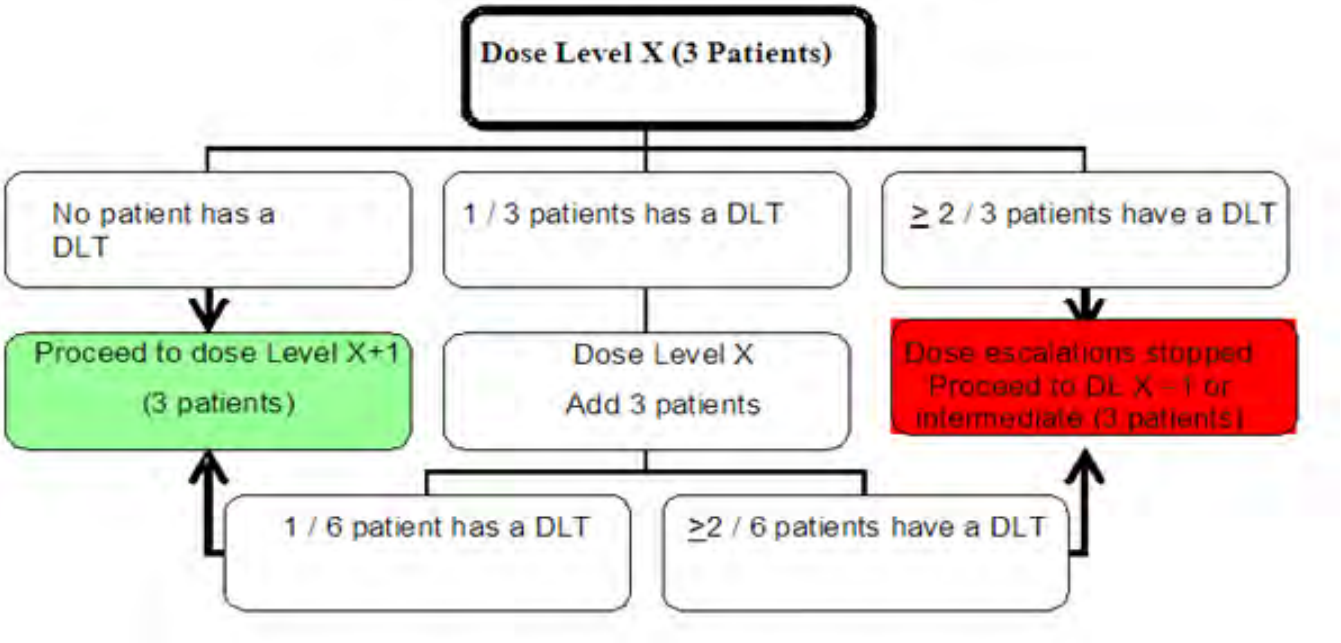


0,01mg/kg to 20 mg/kg (x 2000)

- Sélection de la dose (IO) ?

Herbst R *et al*, Nature 2014

Essais précoces: évaluation toxicités



- Classical 3+3 design
  - MTD
  - DLT – 1
  - 1er cycle

Aucune information hors DLT !

NG Essais Précoces

Table 1. Advantages and disadvantages of major Phase I trial designs.

Phase I study design	Advantages	Disadvantages
Traditional 3+3 design	■ Conservative, therefore minimization of potential patient harm ■ Safe, controlled, standardized dose increases ■ MAD is confirmed in larger cohort	■ Ethical: risk of a high proportion of patients treated at low dose levels ■ Less efficient: long periods when study on hold between dose levels
Accelerated design	■ Increases proportion of patients that will receive doses near the MAD ■ Potential to reduce the number of patients necessary to determine the MAD ■ Potential to be more efficient than 3+3 design	■ Increased risk of DLT
Continual reassessment model	■ Continual readjustment of the dose–toxicity curve based on individual patient data ■ Potentially allows for more accurate determination of MAD	■ Statistically complex ■ Potential for too rapid dose escalation
Escalation with overdose control	■ Continual readjustment of the dose–toxicity curve based on individual patient data ■ Probability of patient receiving a dose above MAD set at low level ■ Potentially allows for more accurate determination of MAD	■ Statistically complex

DLT: Dose-limiting toxicity; MAD: Maximum administered dose.

Bradbury P *et al*,

Clin Invest 2011

NG Essais précoces

- Recherche de dose
  - Pharmacocinétique ?
  - Pharmacodynamie !
- Recherche de la tolérance
  - Suivi plus prolongé ?
- Recherche d'une efficacité
  - Old G: ORR **#10%** / PRG **#50%**
  - New G: ORR up to **#80%**
- Enregistrement
  - **FDA** breakthrough therapy / **conditional approval**

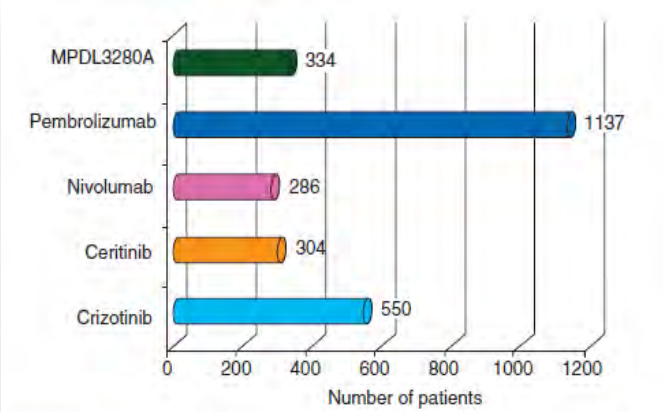
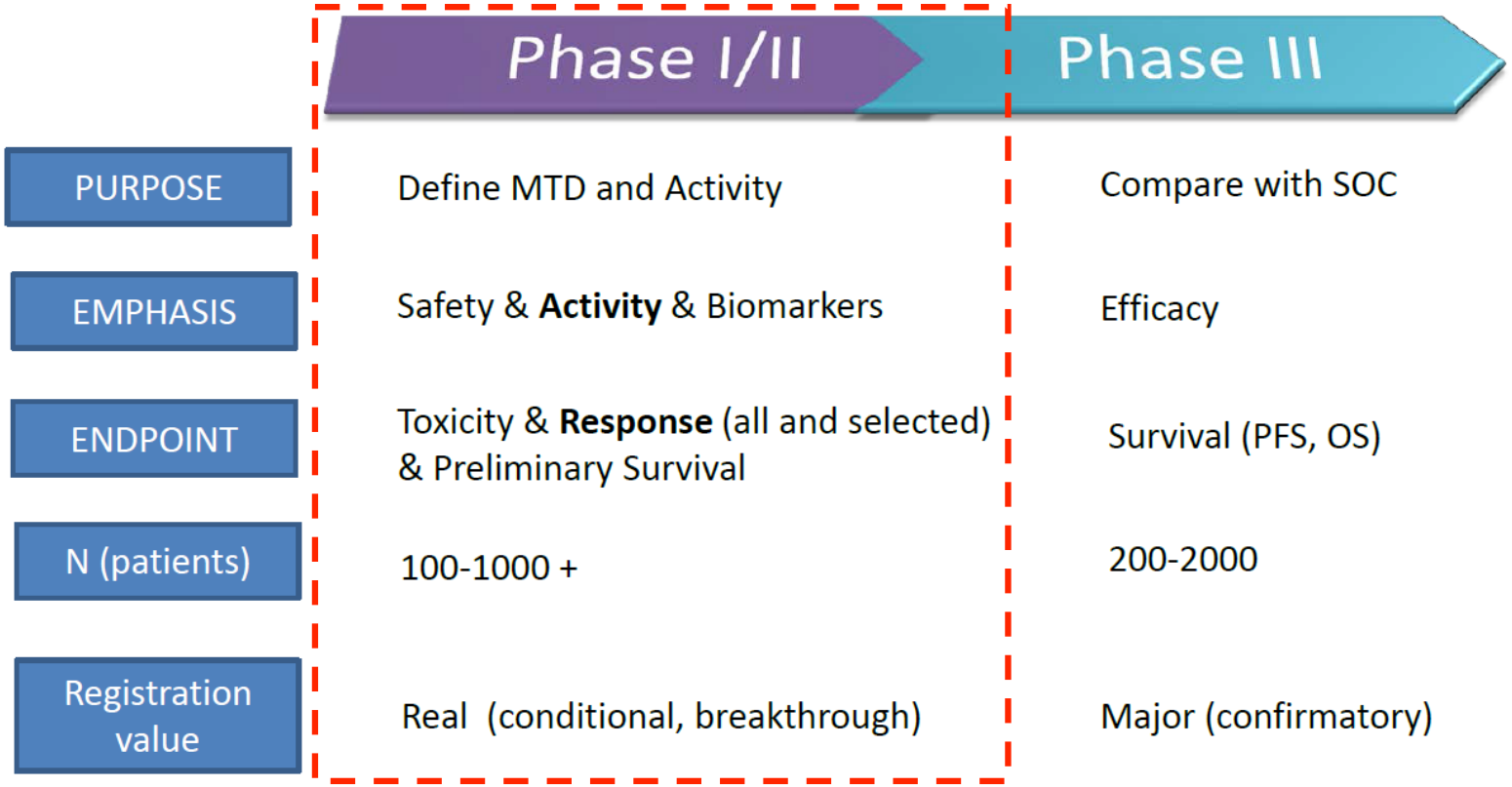


Figure 1. Number of patients enrolled in recent phase 1 trials having led to conditional approval or breakthrough designations (based on www.clinicaltrial.gov; last accessed on October 2014).

NG essais précoces



Courtesy JC Soria

Impact #3

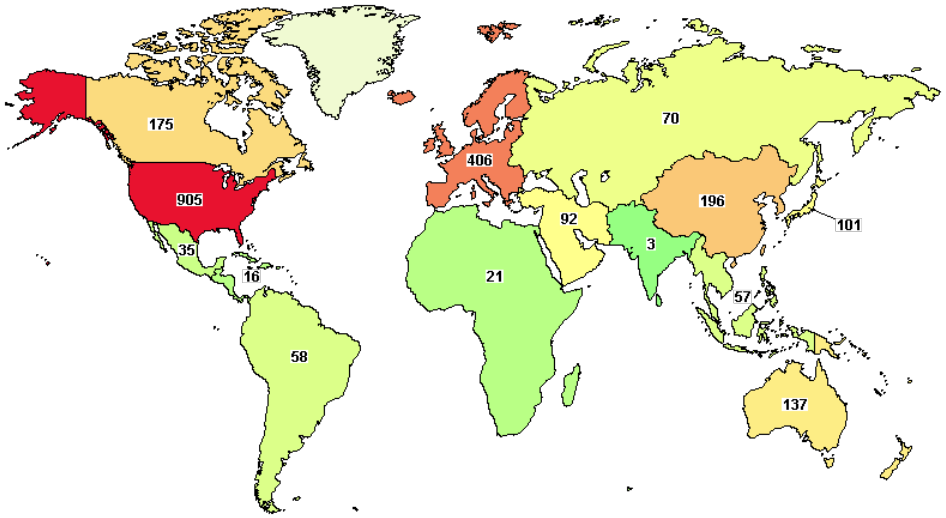
- 3ème défi: choix des combinaisons

http://photo.elsoar.com/happy-little-children-most-beautiful-gallery-19-hq-photos.html

Problématique (ex. IO)

	Options / chimiothérapie (3)		Options / chimiothérapie (3)
+	Options / radiothérapie (2)	+	Options / radiothérapie (2)
+	Agonistes (3-4)	+	Agonistes (3-4)
+	Antagonistes (3-4)	+	Antagonistes (3-4)
=	96 possibilités (min)	=	96 possibilités (min)
		x	types de tumeurs (10)
		=	960 essais

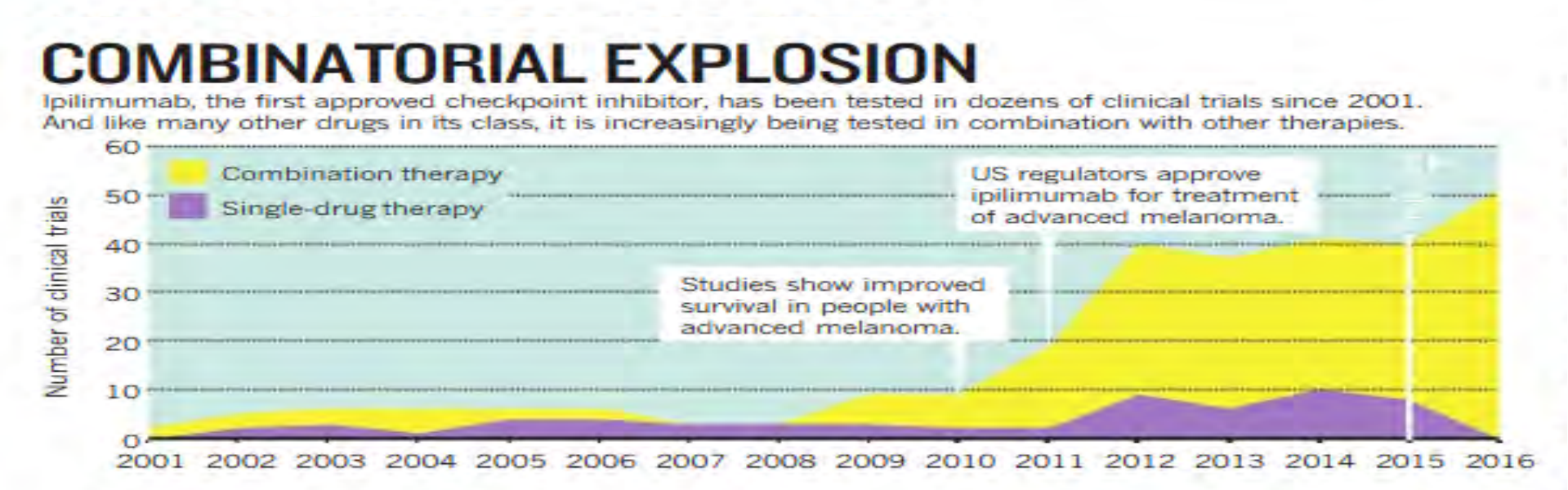
Problématique (ex. IO)



	Options / chimiothérapie (3)
+	Options / radiothérapie (2)
+	Agonistes (3-4)
+	Antagonistes (3-4)
=	96 possibilités (min)
x	types de tumeurs (10)
=	960 essais
x	#100-1000 malades min / essai
=	96,000 - #1M malades (min)

www.clinicaltrials.gov (accès au 01/02/2017)

Le coût de l'empirisme



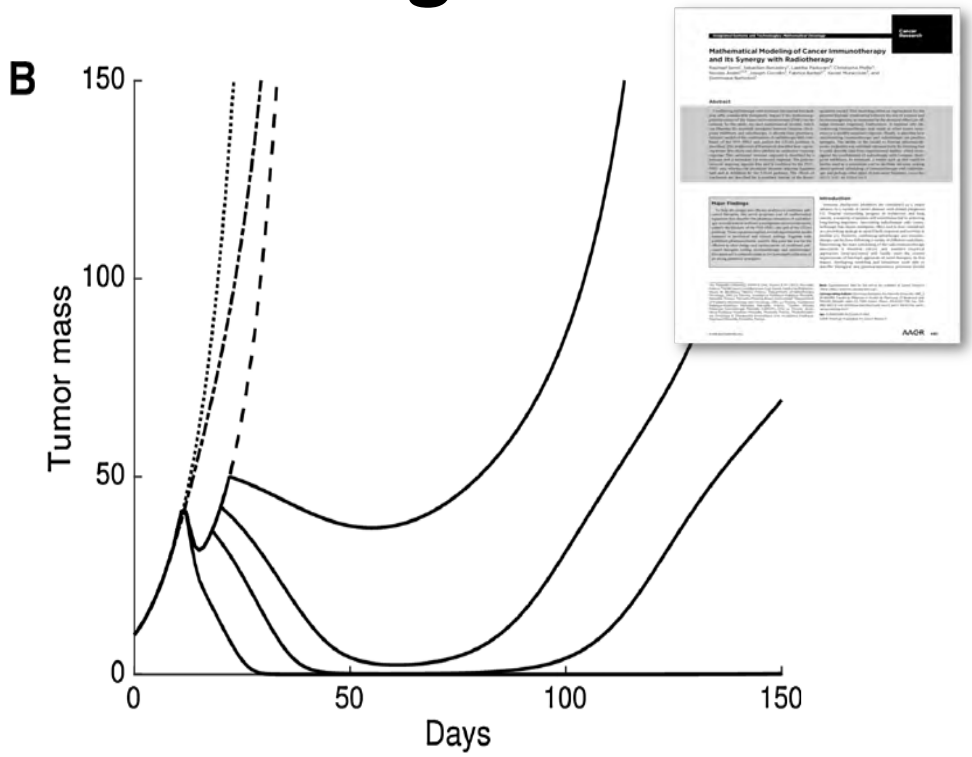
« There will be not enough money on this earth to test all the possible combinations »

Ira Mellman, Vice-President, Cancer Immunology, Genentech Inc.
AACR, New Orleans April 2016

NG trials design w math-modelling

- Combinaison RT / IO
  - Synergie et/ou effet abscopal

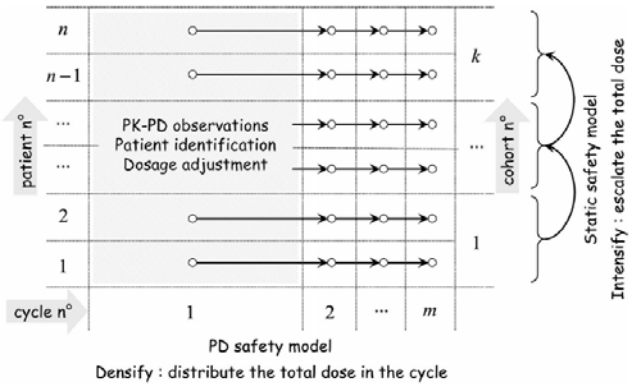
- Timing optimisé (modélisé) ?

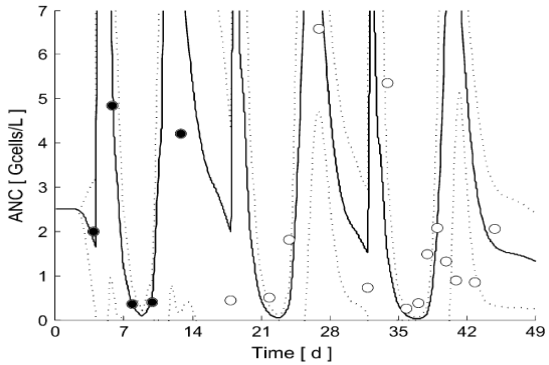


Serre R *et al*, Cancer Res 2016

NG trials design w math-modelling

- Modélisation PK (dose) / PD (toxicité et activité)





Breast Cancer Res Treat (2016) 156:331–341
DOI 10.1007/s10549-016-3760-9

CrossMark

CLINICAL TRIAL

Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients

Emilie Hénin[1,2] · Christophe Meille[3,6] · Dominique Barbolosi[3] · Benoit You[1,2,4] · Jérôme Guitton[1,2,5] · Athanassios Iliadis[3] · Gilles Freyer[1,2,4]

Received: 1 February 2016 / Accepted: 15 March 2016 / Published online: 22 March 2016
© Springer Science+Business Media New York 2016

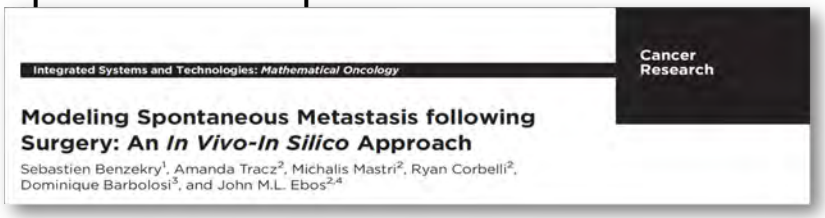
Abstract The MODEL1 trial is the first model-driven phase I/II dose-escalation study of densified docetaxel plus epirubicin administration in metastatic breast cancer patients, a regimen previously known to induce unacceptable life-threatening toxicities. The primary objective was to determine the maximum tolerated dose of this densified regimen. Study of the efficacy was a secondary objective. Her2-negative, hormone-resistant metastatic breast cancer patients were treated with escalating doses of docetaxel plus epirubicin every 2 weeks for six cycles with granulocyte colony stimulating factor support. A total of 16 patients were treated with total doses ranging from 85 to 110 mg of docetaxel plus epirubicin per cycle. Dose escalation was controlled by a non-hematological toxicity model. Dose densification was guided by a model of neutrophil kinetics, able to optimize docetaxel plus epirubicin dosing with respect to pre-defined acceptable levels of hematological toxicity while ensuring maximal efficacy. The densified treatment was safe since hematological toxicity was much lower compared to previous findings, and other adverse events were consistent with those observed with this regimen. The maximal tolerated dose was 100 mg given every 2 weeks. The response rate was 45 %; median progression-free survival was 10.4 months, whereas 54.6 months of median overall survival was achieved. The optimized docetaxel plus epirubicin dosing regimen led to fewer toxicities associated with higher efficacy as compared with standard or empirical densified dosing. This study suggests that model-driven dosage adjustment can lead to improved efficacy-toxicity balance in patients with cancer when several anticancer drugs are combined.

- Adaptation individuelle des doses de traitement à chaque cycle
  - Minimiser le risque
  - Maximiser le bénéfice

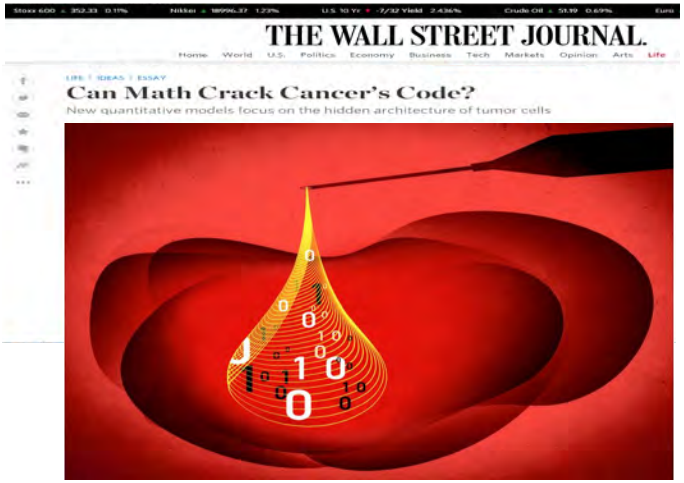
Henin E *et al*, Breast Cancer Res Treat 2016

NG trials design w math-modelling

- Modélisation des processus biologiques
  - Risque métastatique



  - Interaction moléculaire (Markov)
- Modélisation de l'impact des médicaments
- Modélisation des combinaisons
- …

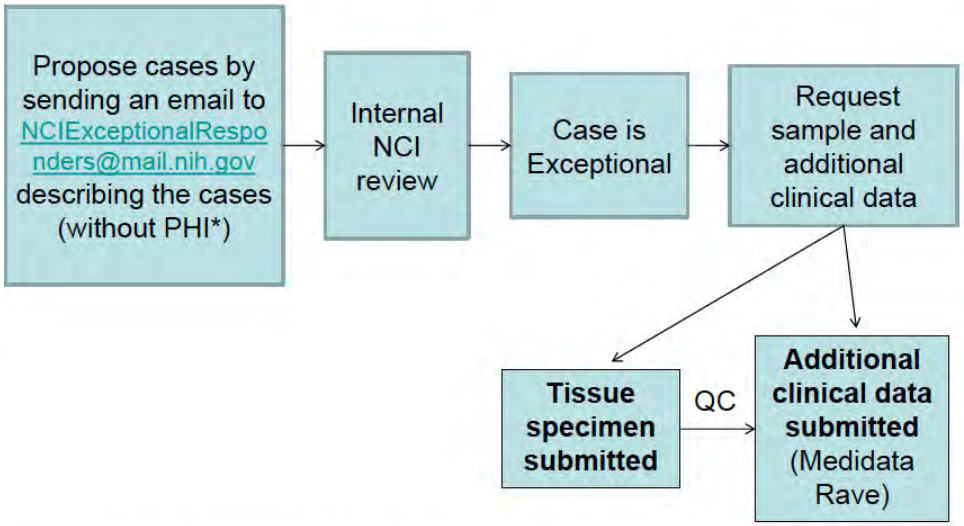


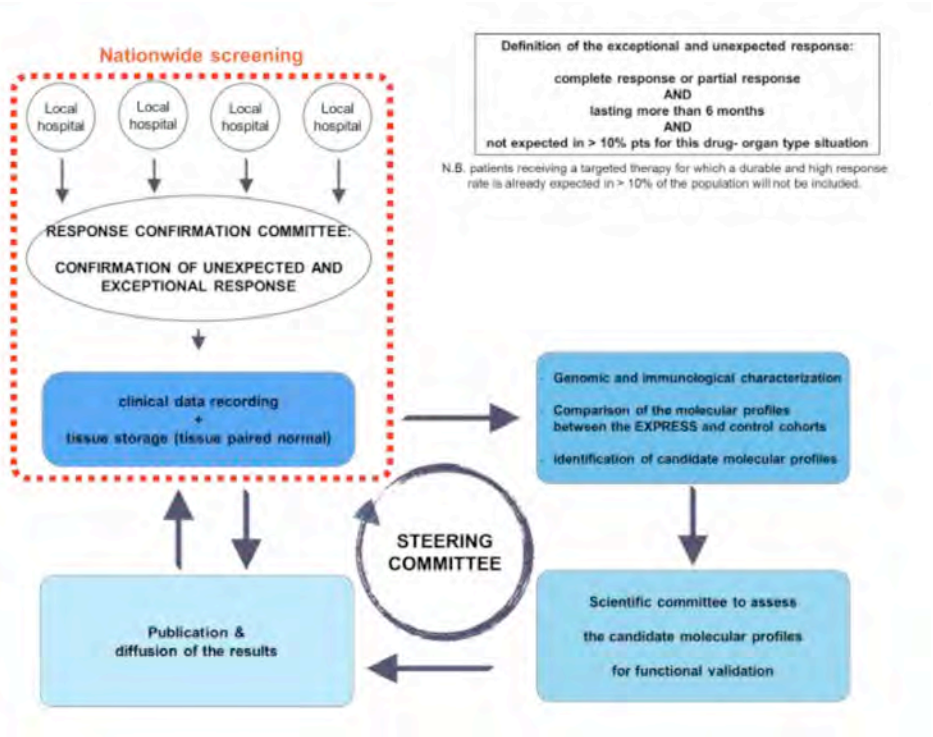
Impact #4

- 4ème défi: développer d'autres pistes

https://www.theodysseyonline.com/baby-steps-of-faith

NG Target (retro-)discovery studies





NCI exceptionnal responders initiative (available at NCI website); EXPRESS EXcePtional RESponSe (promotion Unicancer, PI: C Ferté)

NG Target (retro-)discovery studies

- **EXPRESS**
  - RC ou RP (RECIST)
  - DOR > 6 mois
  - Attendue < 10% des patients
  - Fax / email: express@unicancer.fr

EXPRESS
EXceptPtional RESponSE

Madame, Monsieur,

Vous souhaitez présenter le dossier de votre patient « Répondeur Exceptionnel » au Comité de Revue des Réponses (CO-Rev), dont le rôle est de valider le caractère exceptionnel de la réponse selon les critères de l'étude EXPRESS. Nous vous proposons de remplir les renseignements suivants et de les adresser à Madame Veronica Pezzella :

Soit par fax au n° 01 71 93 61 67

Soit par mail à express@unicancer.fr

Vous serez contacté par un membre de l'équipe Express d'Unicancer par retour de mail. La date de la prochaine session du CoRev vous sera communiquée pour que vous présentiez le dossier de votre patient. N'hésitez pas à contacter Madame Pezzella au 01 44 23 04 77 pour toute question.

FICHE DE SCREENING

Informations du patient :

Sexe : .....

Date de naissance : ----/-----/------

Coordonnées du médecin du patient :

Dr : _____

Tél : _____

Mail : _____

PATHOLOGIE

Type de tumeur (merci de cocher la case correspondant)

Cancer du Sein ☐
Cancer broncho- pulmonaire ☐
Préciser sous type histologique : _____
Cancer colorectal ☐
Cancer de l'ovaire ☐
Cancer du rein à cellules claires ☐
Mélanome Cutané ☐

Autre, précisez : _____

Type histologique :

Date de diagnostic initial: ____/____/_____

Date de diagnostic de la maladie avancée/ métastatique: ____/____/_____

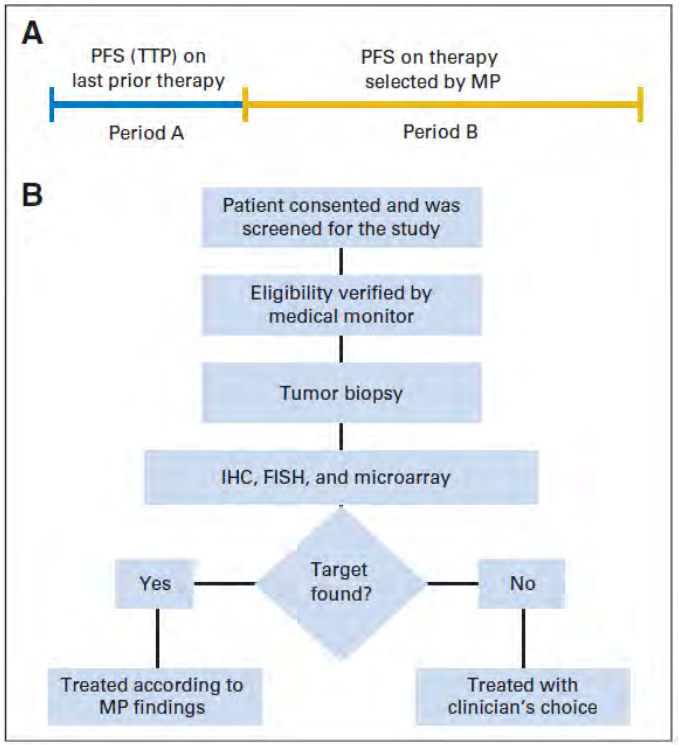
Précisez la localisation des métastases : _____

Express – Fiche de Screening V1.0 mars 2016

EXPRESS EXcePtional RESponSe (promotion Unicancer, PI: O LeSaux & A Italiano)

NG trials: PRG rate model (N of 1)

- Le patient est son propre contrôle
  - Au travers de diverses lignes de traitement
  - Traitements bio-guidés ou pas
  - PFS traitement précédent / PFS traitement actuel



Von Hoff D *et al*, J Clin Oncol 2010

NG trials: PRG rate model (N of 1)

- Le patient est son propre contrôle
  - Intérêt renforcé par MOSCATO

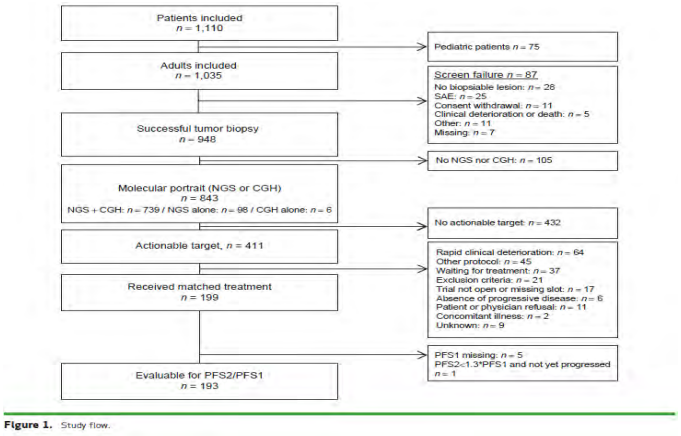


Figure 1. Study flow.

- Ratio > 1,3 chez 33% des patients

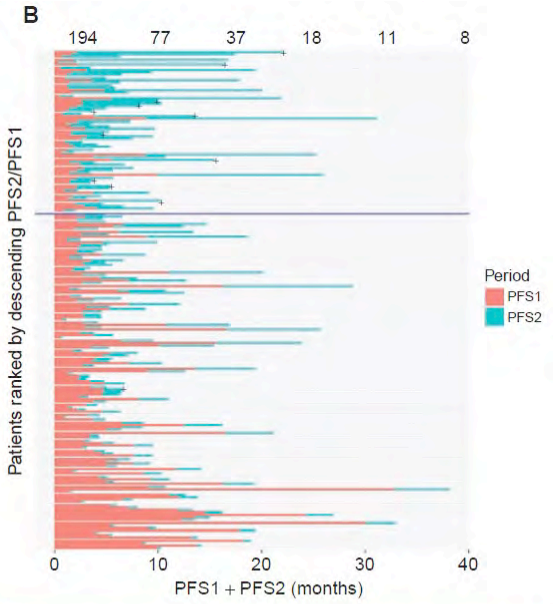
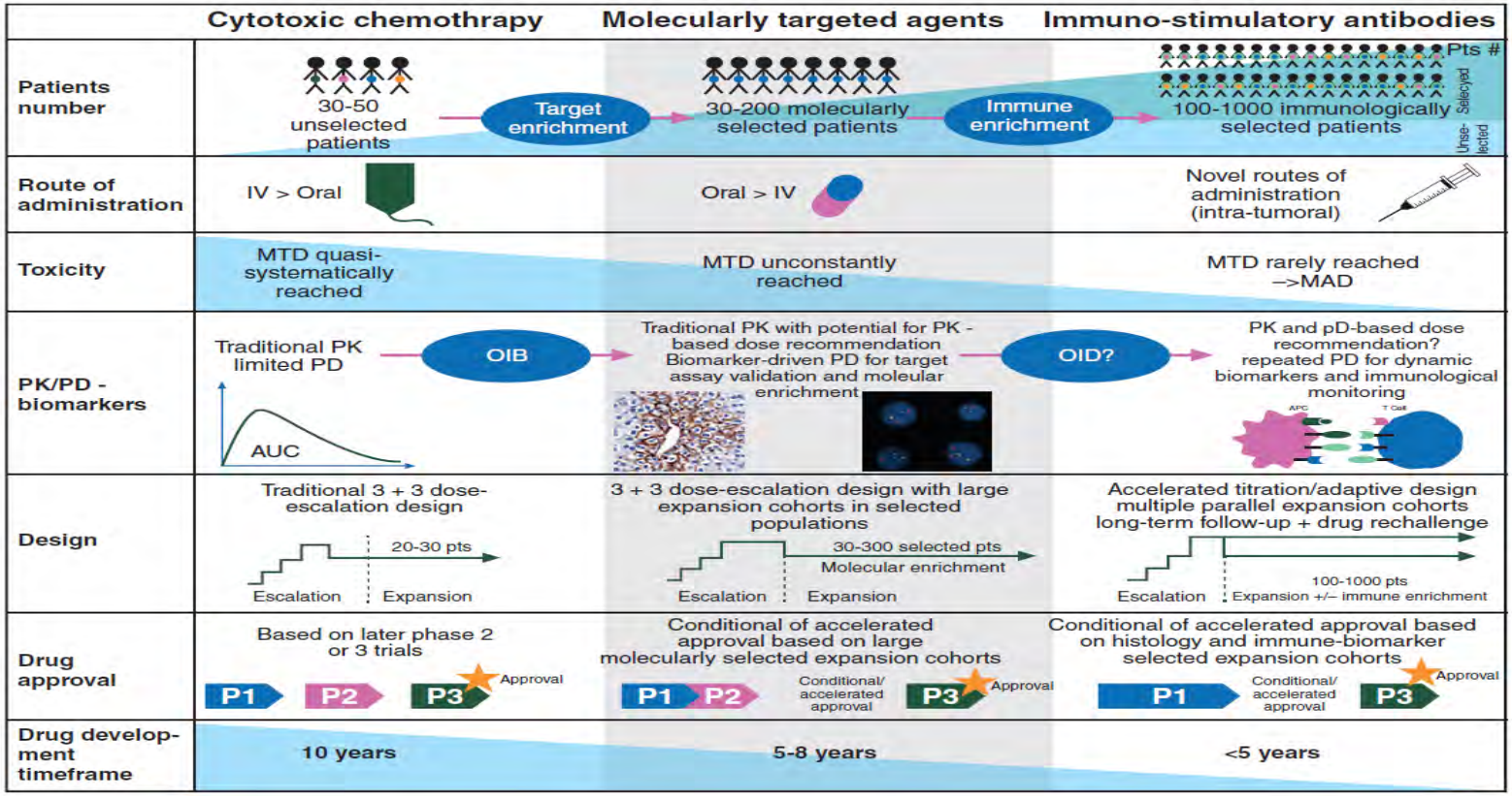


Figure 3. Efficacy on primary endpoint. **A**, Kaplan–Meier curve of PFS2/PFS1. Crosses denote censored data. Green line denotes PFS2/PFS1 > 1.3. **B**, Individual PFS1 and PFS2 times, ordered by descending PFS2/PFS1 ($n = 194$). Crosses denote censored data. Patients above the blue horizontal line have PFS2/PFS1 > 1.3.

Massard C *et al*, Cancer Discov 2017

NG trials ?



Postel-Vinay S *et al*,

Ann Oncol 2016

NG trials !

Merci

fabrice.barlesi@ap-hm.fr

@barlesi