Essais cliniques: nouveaux designs

Cours du *GOLF*
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Fabrice Barlesi, MD, PhD

Assistance Publique
Hôpitaux de Marseille

Centre de Recherche
en Cancérologie de Marseille

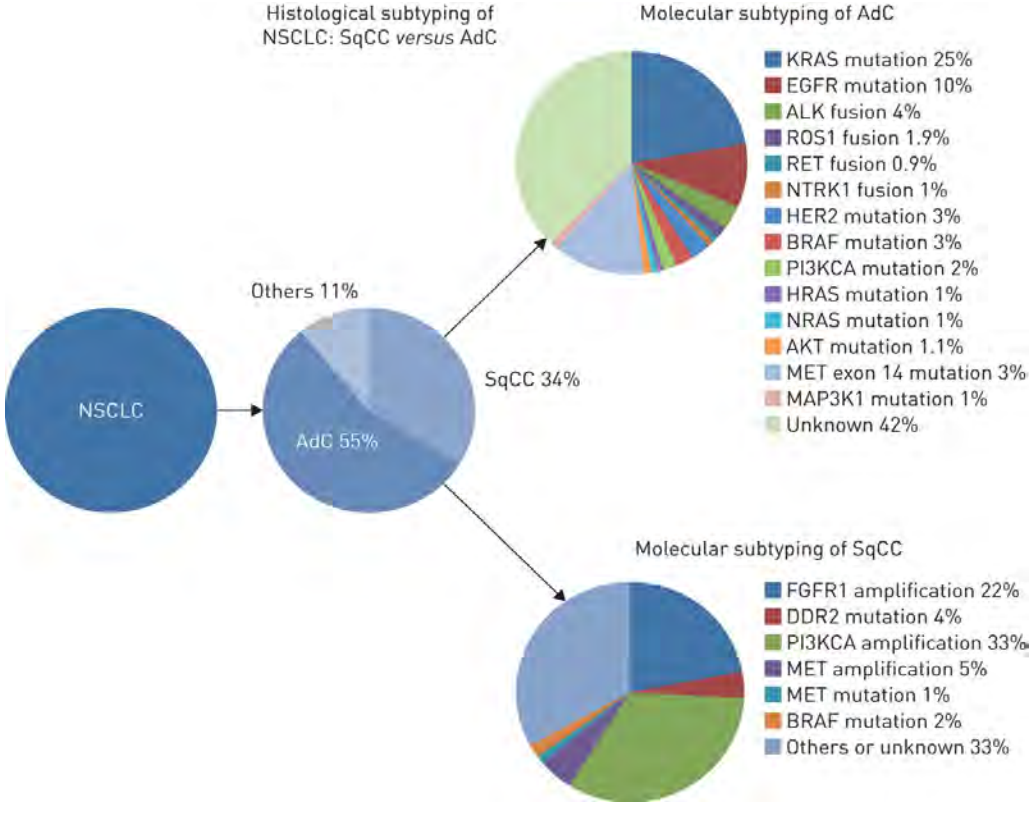
Aix*Marseille
université

Disclosures

- **Personal financial interests:**
  - Astra-Zeneca, Bayer, 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 ?

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



Bubendrof L, et al. Eur Respir Rev 2017

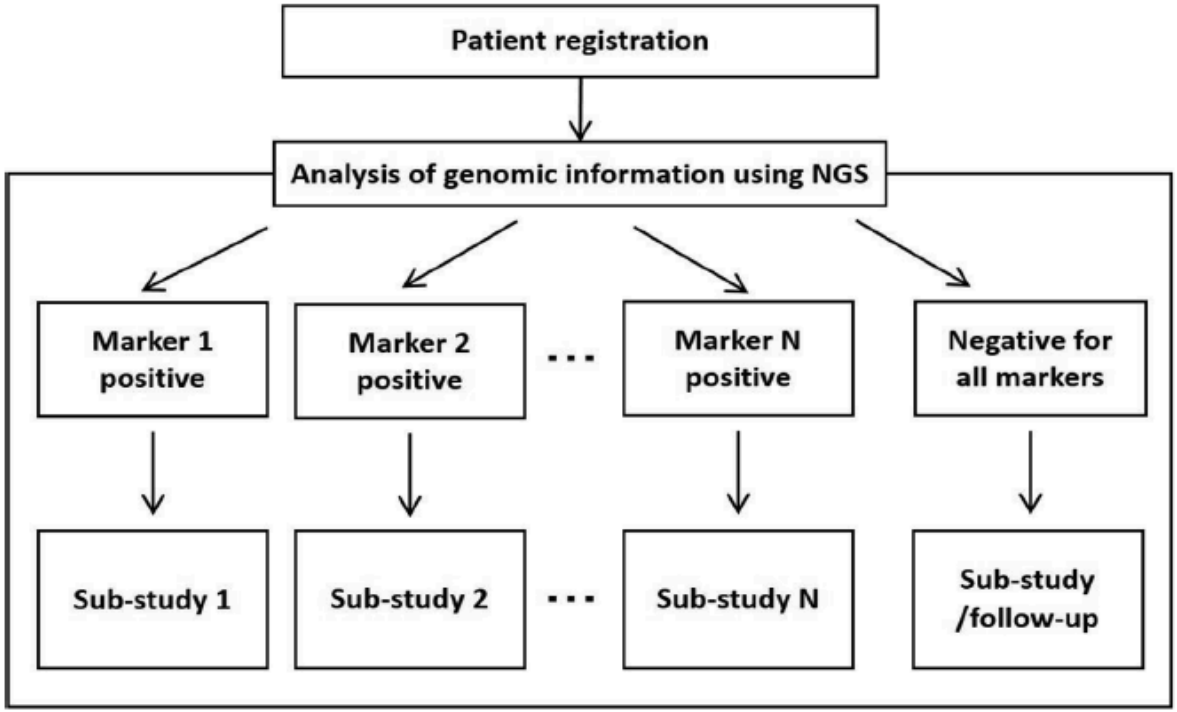
Pourquoi de nouveaux designs ?

- 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

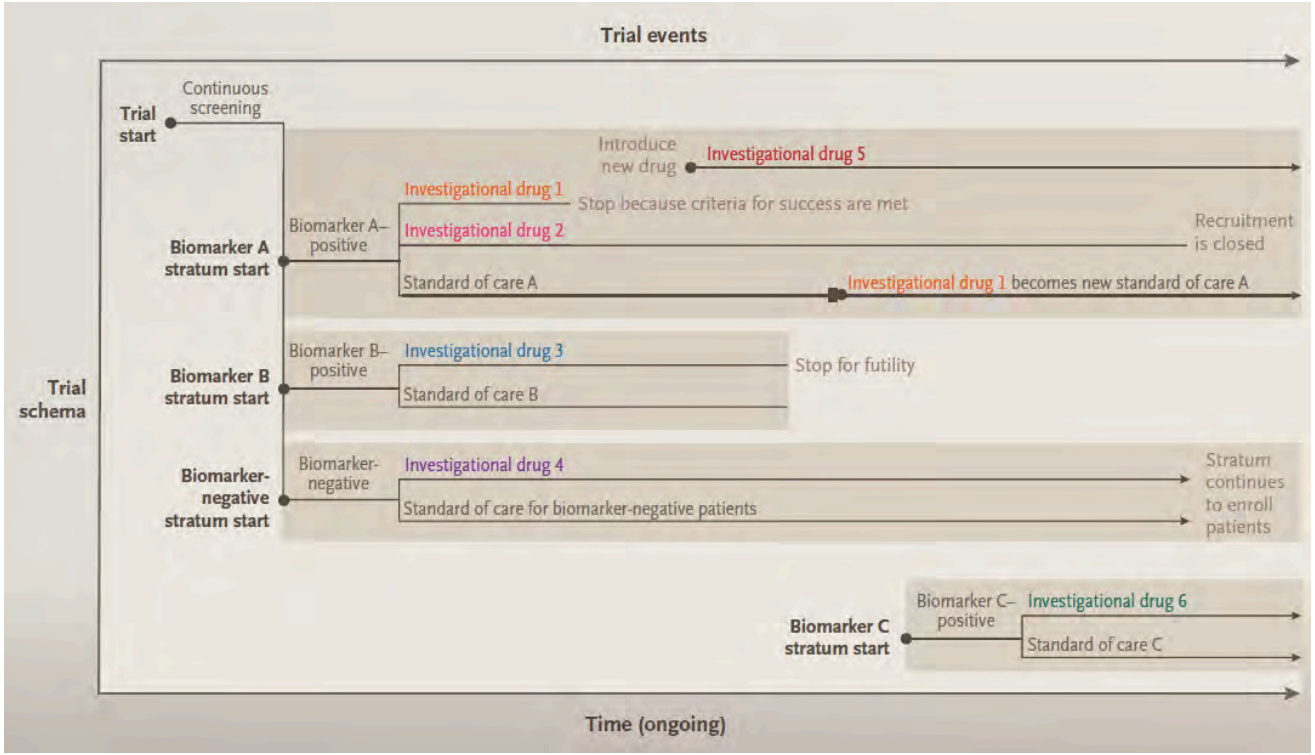
#1 Masterprotocols



- Masterprotocols, a comprehensive protocol created for evaluating multiple hypotheses

Hirokawa A *et al*, CCTC 2018

#1 Masterprotocols



- Masterprotocols
  - **Exploratory** are often composed of multiple single-arm sub-studies,
  - **Confirmatory** are composed of multiple randomized sub-studies

Woodcock J *et al*, NEJM 2017

#1 Masterprotocols

Areas of Innovation

Infrastructure
- Common screening platform for biomarker identification
- Governance
  - Steering committee
  - Adjudication committee
  - Data monitoring committee
  - Central institutional review board
- Trial networks and clinical centers
- Processes
  - Randomization
  - Data and safety capture and management
  - Quality-control oversight

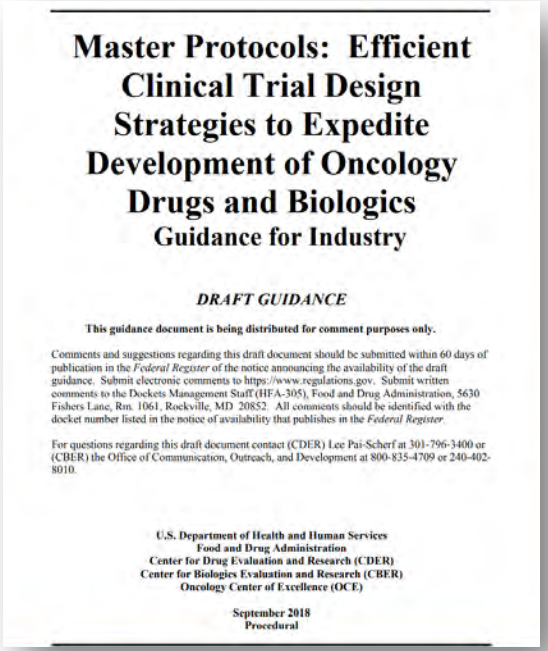
Trial Design
- Adaptive randomization and other adaptive design features
- Longitudinal modeling to determine probabilities of success or failure
- Shared control patients
- Natural-history cohort
- Biomarker qualification

- Masterprotocols

Woodcock J *et al*, NEJM 2017

#1 Masterprotocols

- Masterprotocol (FDA guidance)



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

Guidance for Industry

DRAFT GUIDANCE

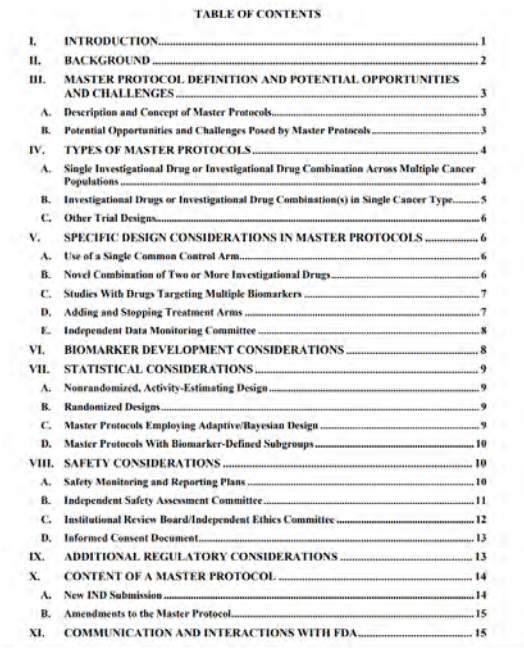
This guidance document is being distributed for comment purposes only.

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



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- Released on Sept. 28, 2018

www.fda.gov

#1 Masterprotocols

- 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)

#1 Masterprotocols

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

- Masterprotocols

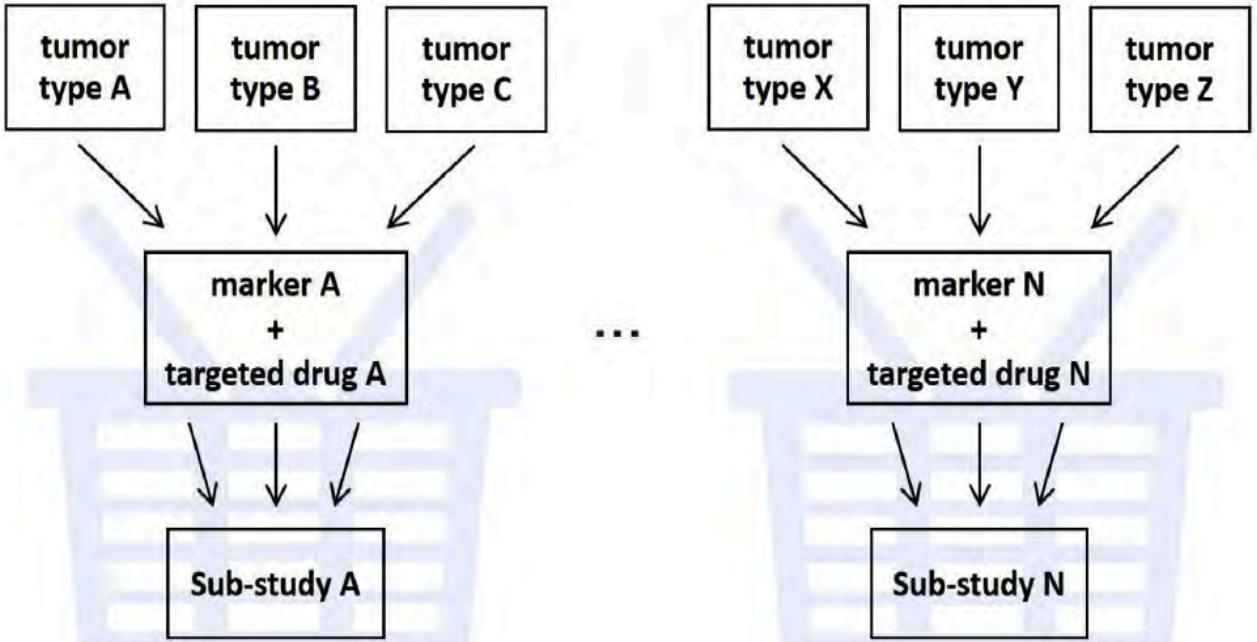
Woodcock J *et al*, NEJM 2017

#1’ Essais basket

- Explorer safety / efficacité d’une drogue

https://www.maisonsdumonde.com/FR/fr/p/panier-tresse-en-osier-h-38-cm-bazar-160228.htm

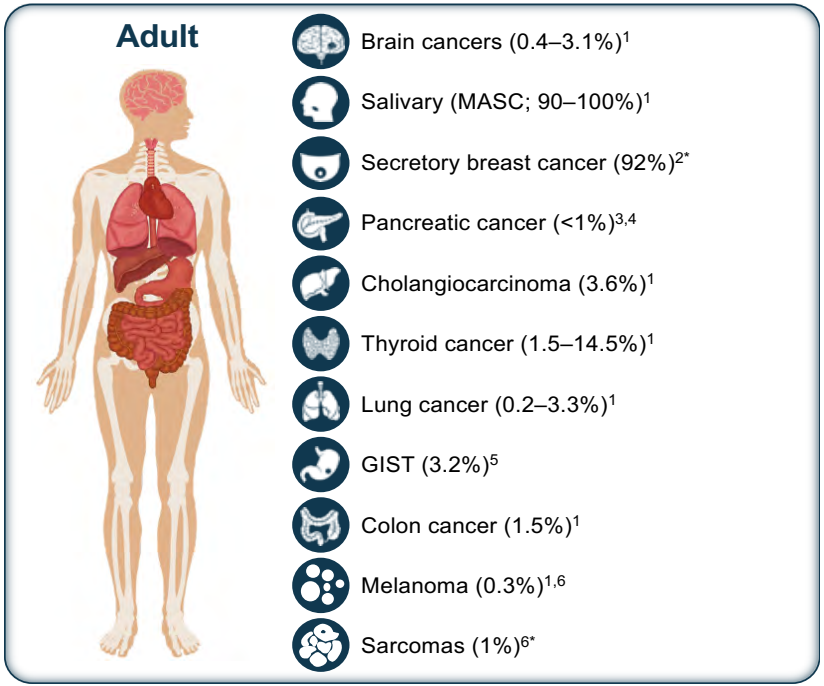
#1’ Essais basket

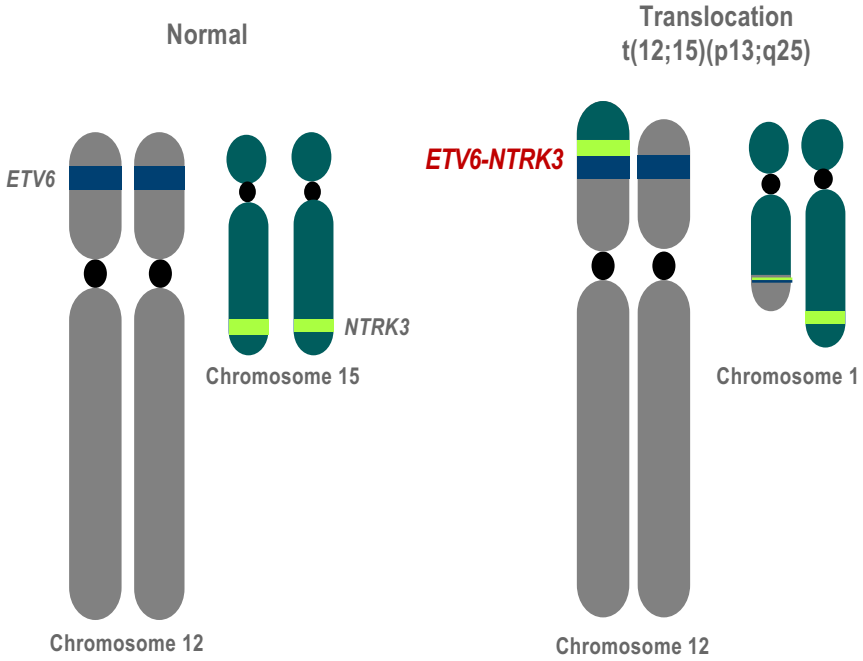


- Basket trials

Hirokawa A *et al*, CCTC 2018

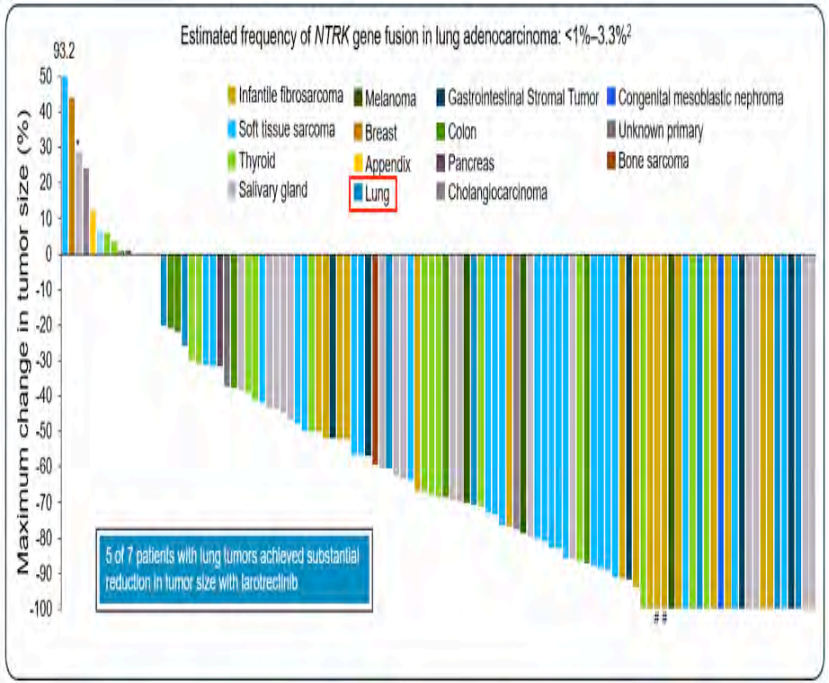
NTRK fusions

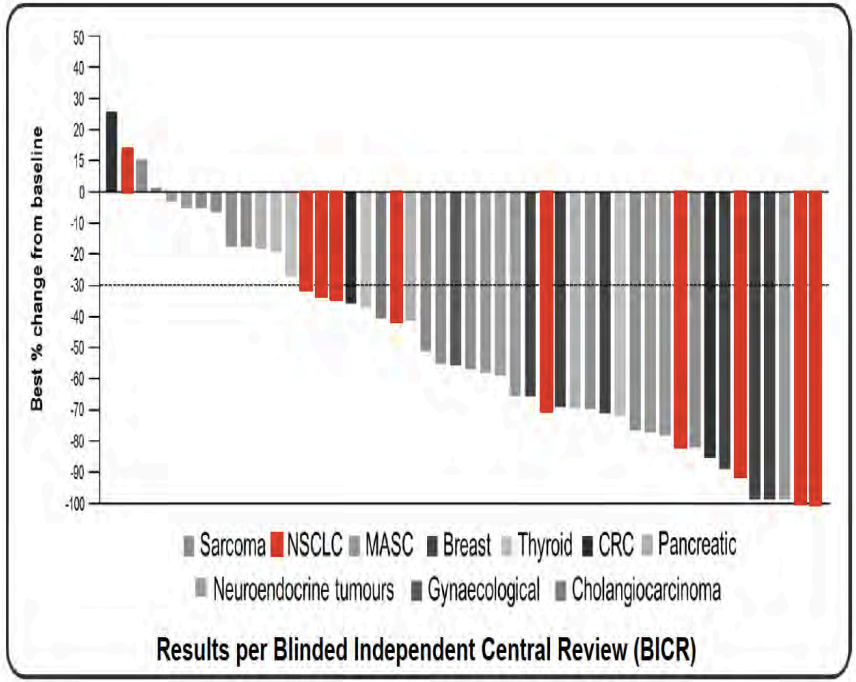




Adapted from Euhus D, et al. Cancer Cell 2002

NTRK fusions (Larotrectinib/Entrectinib)





Lassen UN, et al. ESMO 2018; Drilon A, et al. Cancer Discovery 2017; Doebele R, et al. AACR 2019

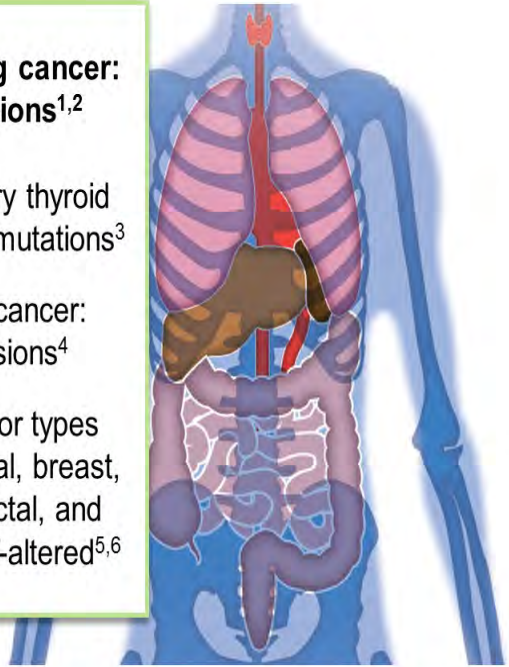
RET fusions

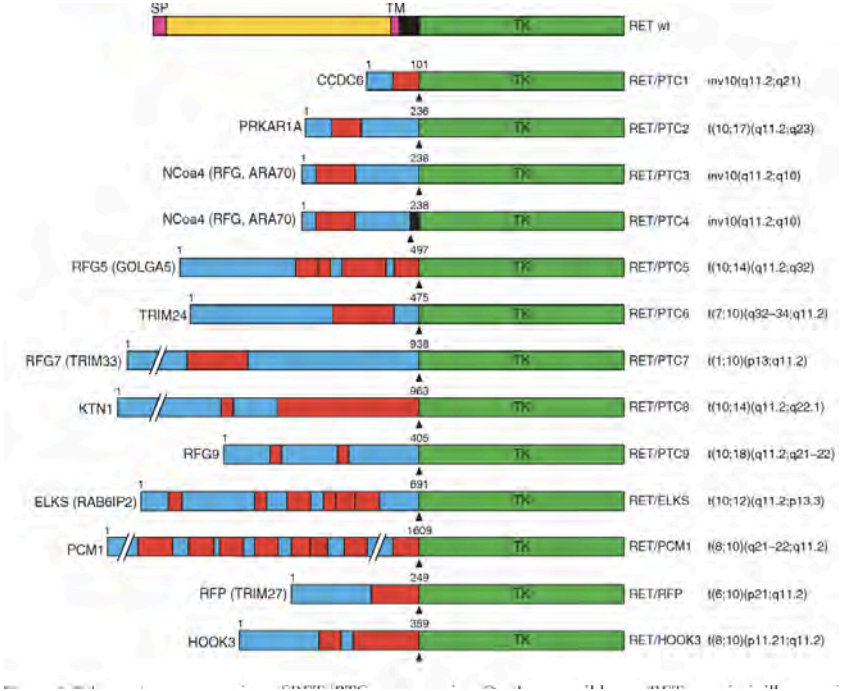
Non-small cell lung cancer: ~1-2% RET fusions[1,2]

Advanced medullary thyroid cancer: ~90% RET mutations[3]

Papillary thyroid cancer: ~20% RET fusions[4]

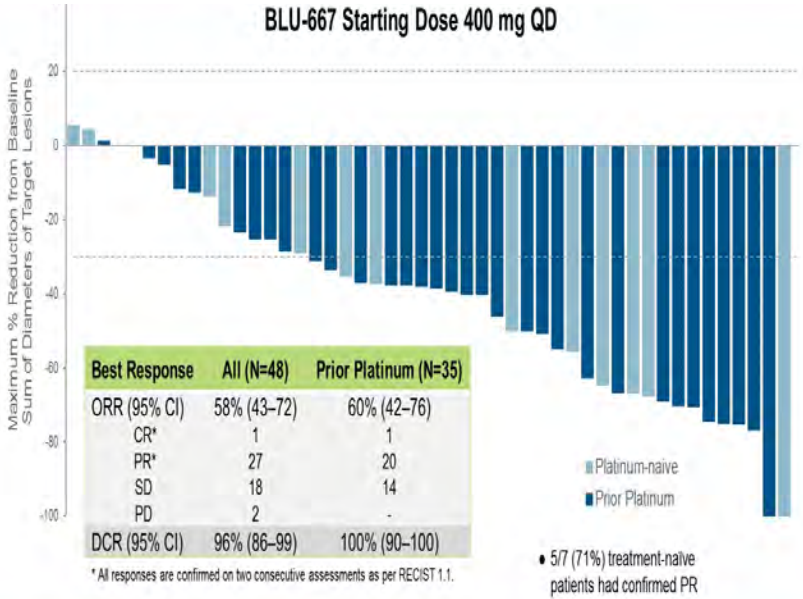
Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered[5,6]





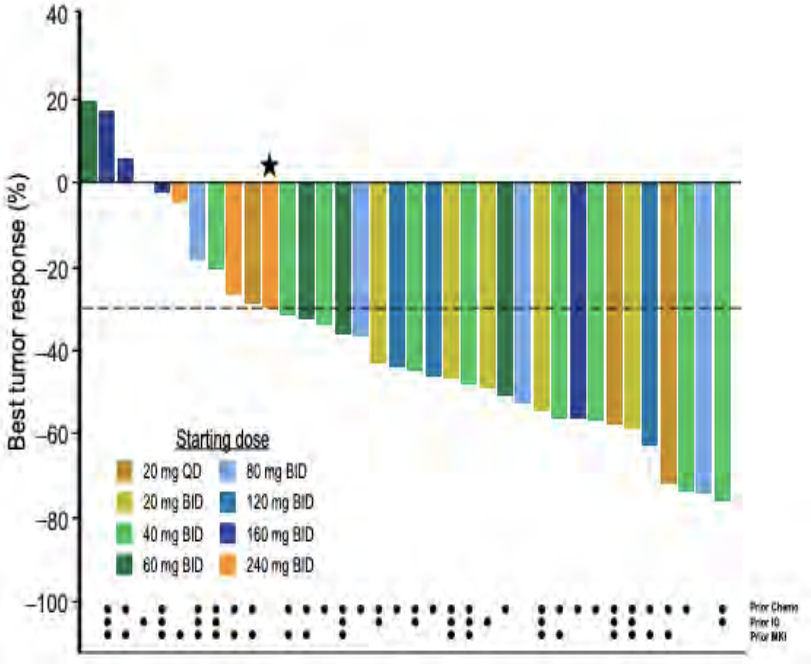
Adapted from Gainor J, et al. ASCO 2019; Santoro M. Cold Spring Harbor perspectives in biology 2013

RET fusions (BLU-667/LOXO-292)



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

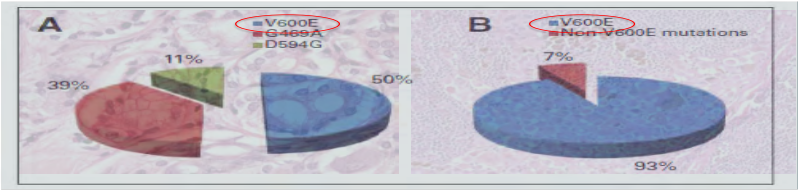
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.



Gainor J et al, ASCO 2019; Oxnard G et al, WCLC 2018

#1’ Essais basket

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



Lung adenocarcinoma Melanoma

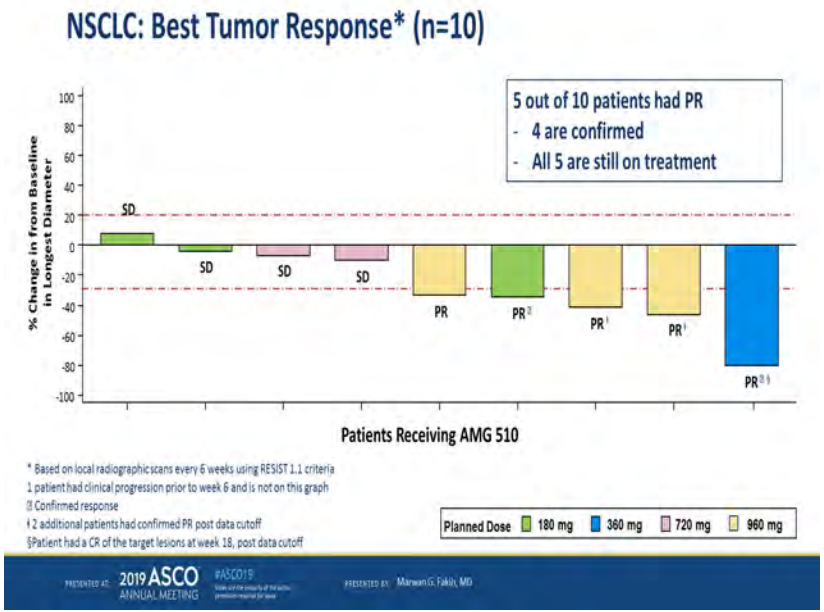
  - Diverses altérations avec des conséquences variables (*KRAS*)

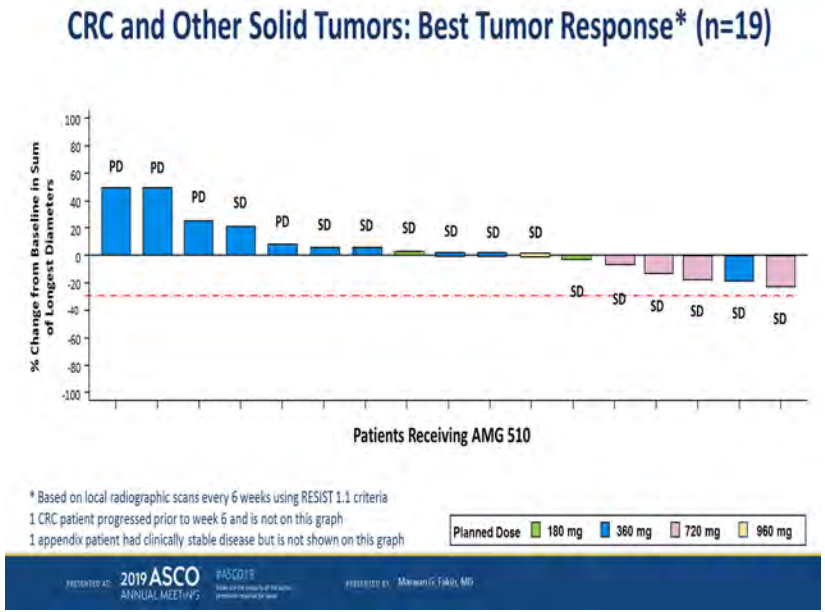
- Etapes initiales du développement (essais précoces) ?

- Basket trials: difficultés ?

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

KRAS G12C mutations (AMG510)





Fakih M, et al. ASCO 2019

#1’ Essais basket

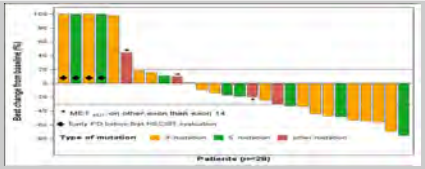
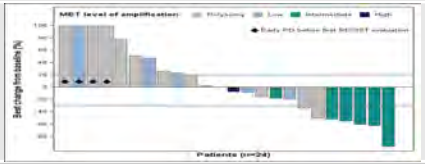
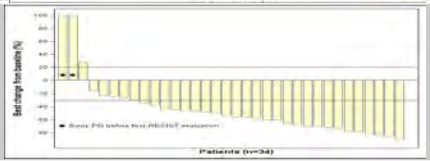
Localisation tumorale	ALK transloc.	ALK amp.	MET amp.	ROS1 transloc.	ALK mut.	MET mut.	Références
ALCL	50,0%						Merkel et al., 2011
Colorectal	2,4%		3,6%			3,3%	Lin et al., 2009 Lipson et al., 2012 Zen, 2008 Fumagalli, 2010
NSCLC			4,0%	3,5%			Bergethon et al., 2012 Takeuchi et al., 2012
Breast	2,4%						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

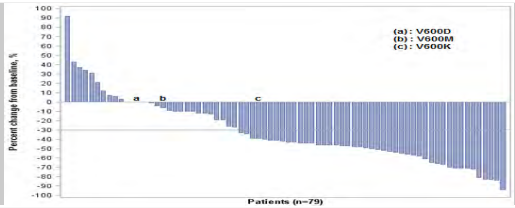
Available www.ecancer.fr

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. Ann Oncol 2019 (in press)

Acsé programs (ex. Vemurafenib/BRAFm)

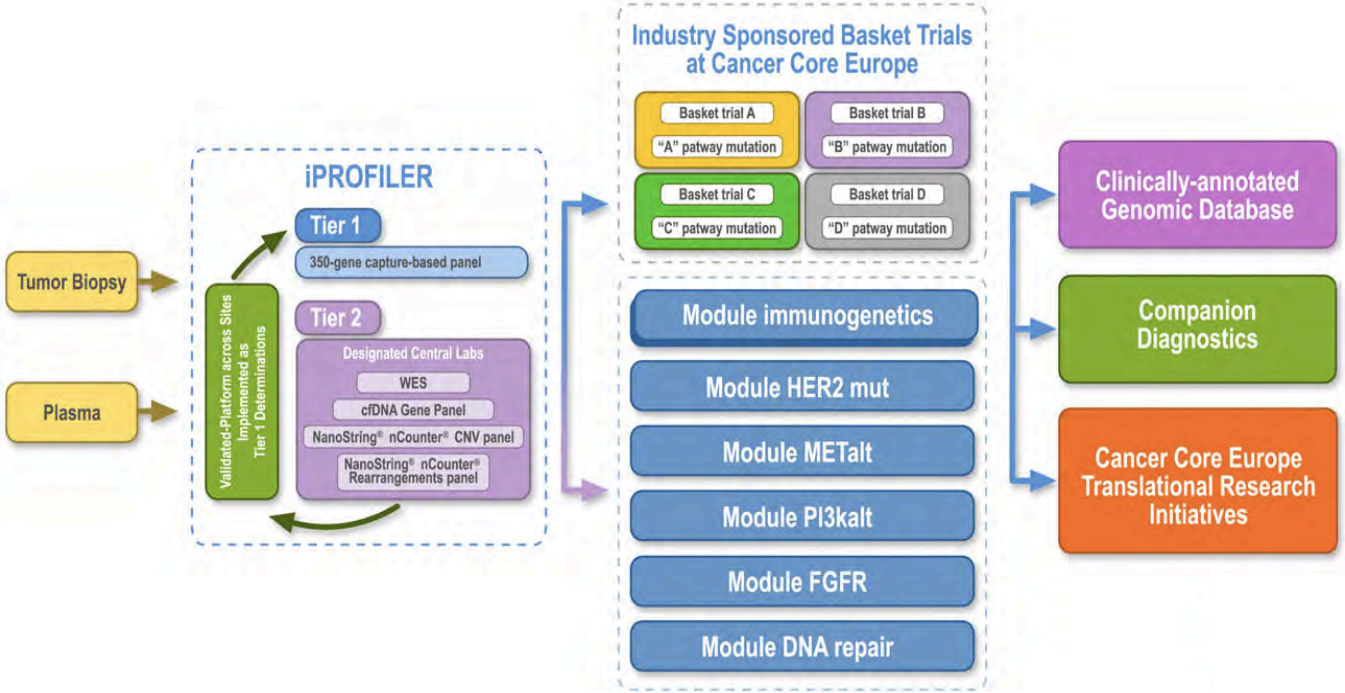
	Positive cases pts	Patients treated in the program	Efficacy (BOR)
BRAF V600	101	100	
BRAF non V600	17	15	**5% (study stopped)**

Mazières J, et al. WCLC 2018 (A)

2019’ FDA approvals

www.fda.gov

#1’ Essais basket



- Basket of Basket trials (Cancer Core Europe)

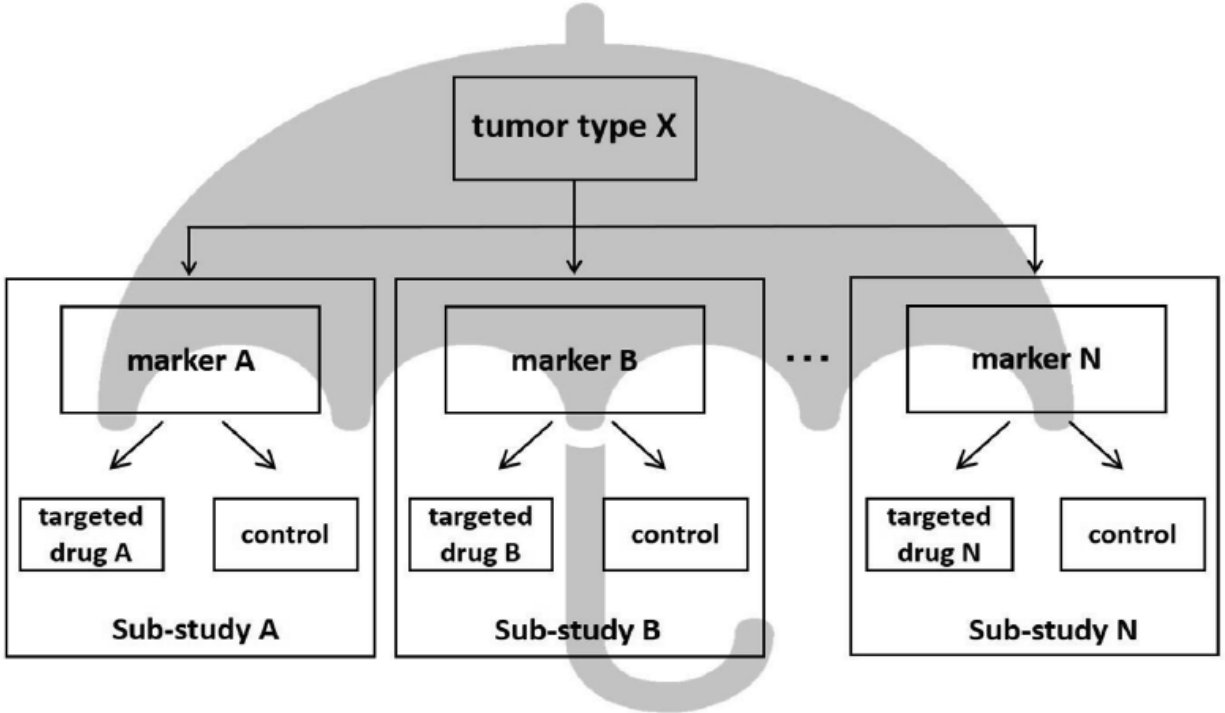
Garralada E, et al. Mol Oncol 2019

#1’’ Essais umbrella

- Explorer médecine de précision dans une tumeur donnée

https://www.amazon.com/totes-Womens-Clear-Bubble-Umbrella/dp/B01L9DKZ1A

#1’’ Essais umbrella

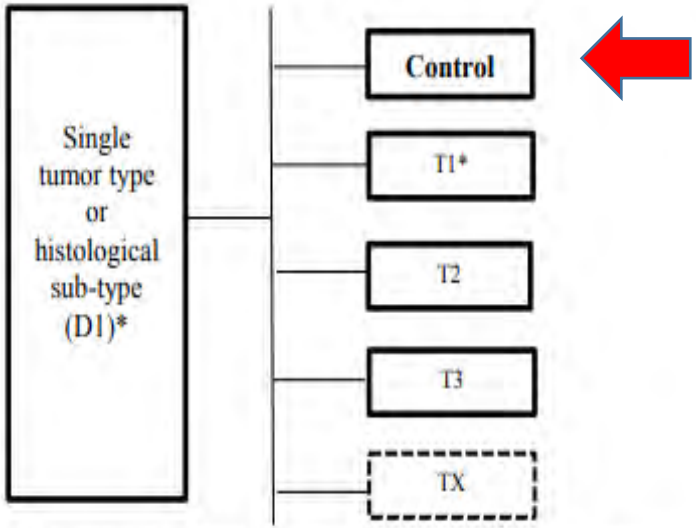


- Umbrella trials

Hirokawa A *et al*, CCTC 2018

#1’’ Essais umbrella

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

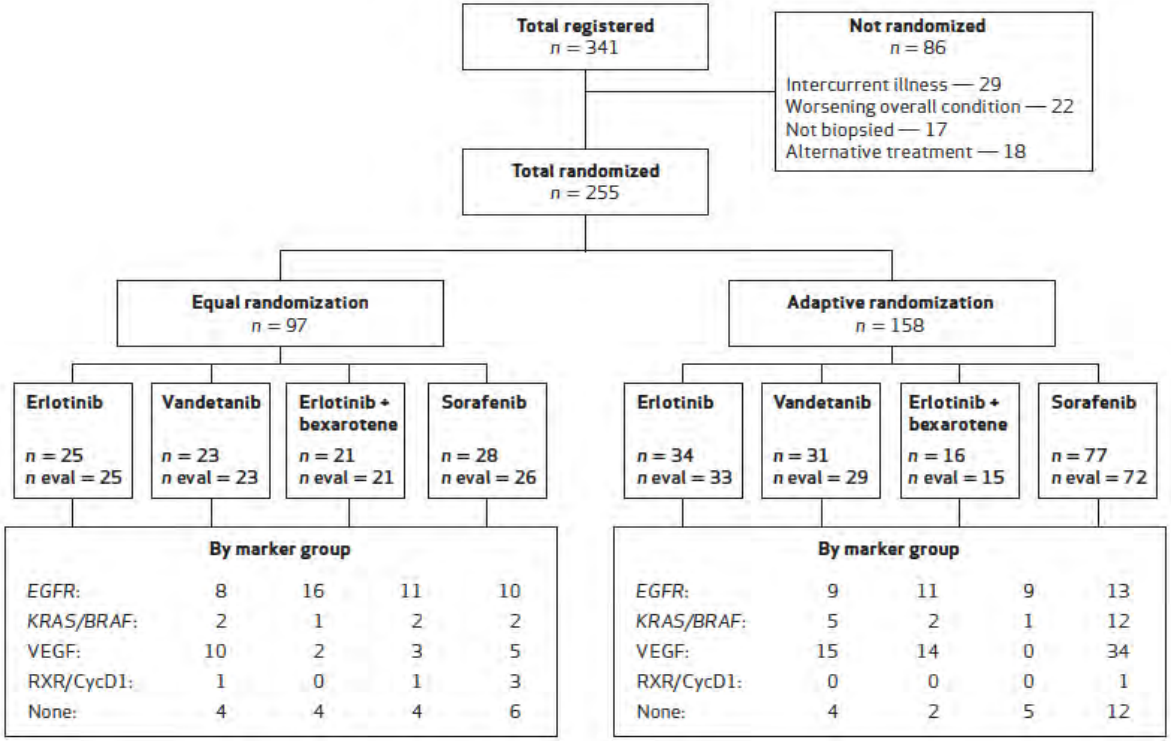


* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

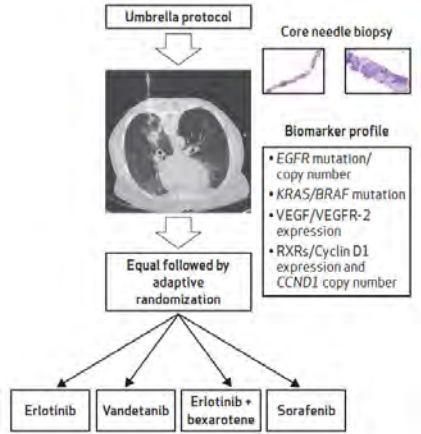
- FDA guidelines (Sep 28, 2018)

Available @ www.fda.org

#1” Essais umbrella

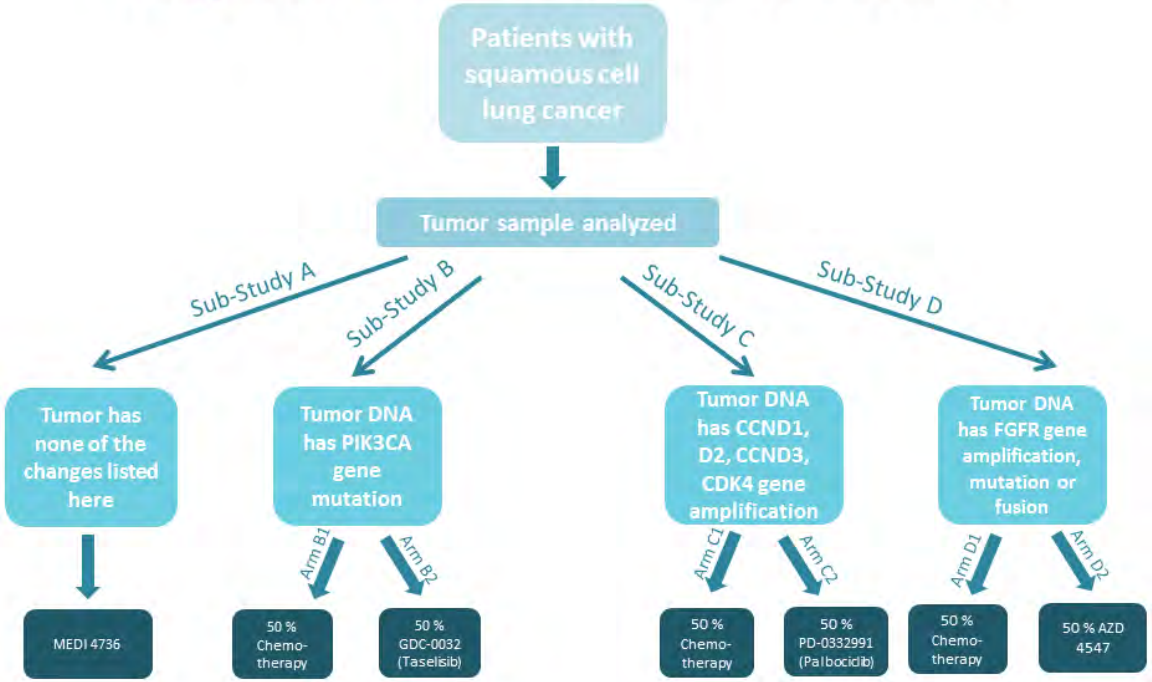


- Umbrella trials
  - Ex. Battle



Kim ES *et al*, Cancer Discov 2011

#1’’ Essais umbrella

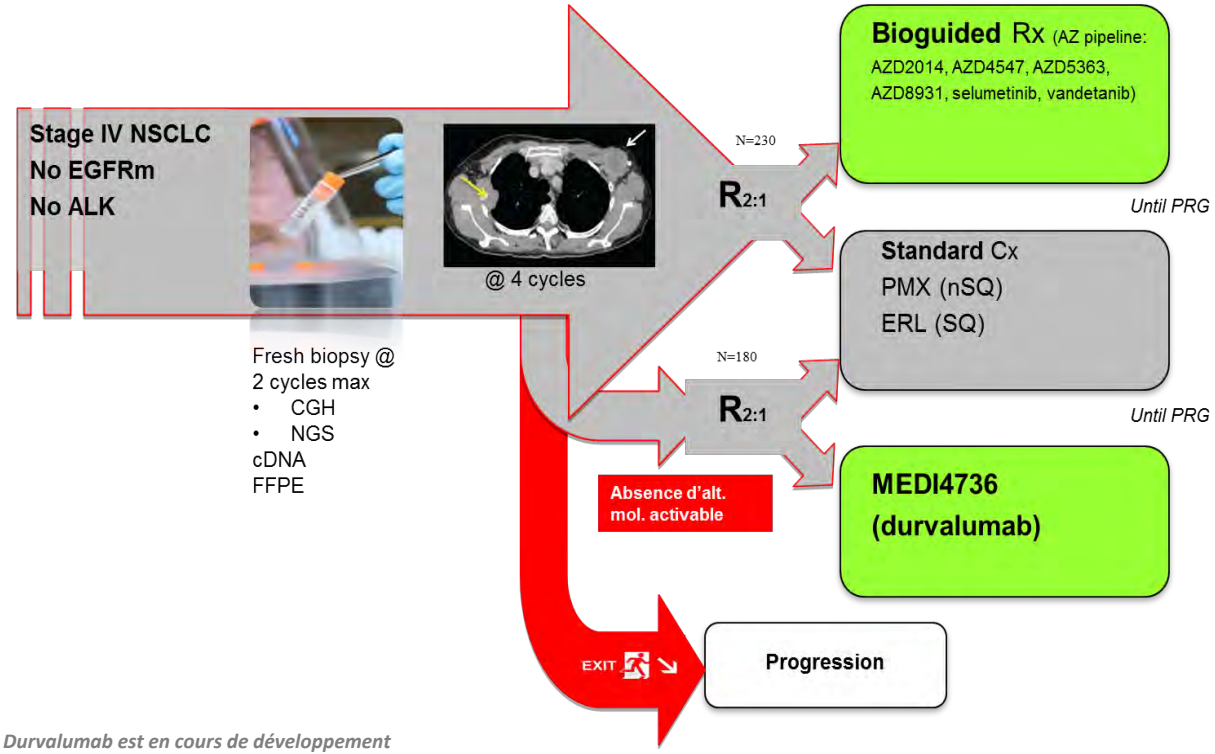


- NCI Lung MAP trial (SCC)

Durvalumab est en cours de développement

Downloaded from the NCI website

#1” Essais umbrella



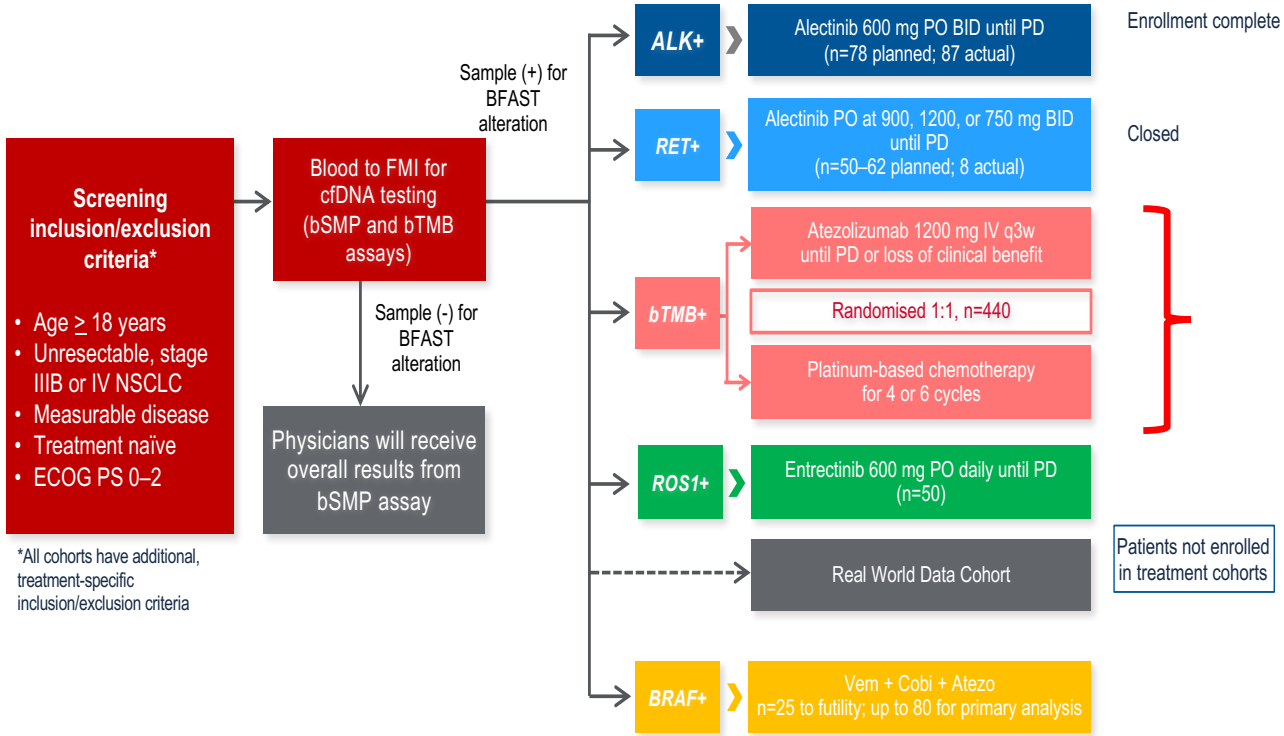
Durvalumab est en cours de développement

- Umbrella trials
  - Ex. SAFIR

IFCT Unicancer SAFIR 02 Lung trial

Pis: F Barlesi / B Besse

#1” Essais umbrella



- Umbrella trials
  - Ex. BFAST

BFAST trial

Gadgeel S, et al. ESMO 2019

#1’’ Essais umbrella

- 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

#1” Essais umbrella

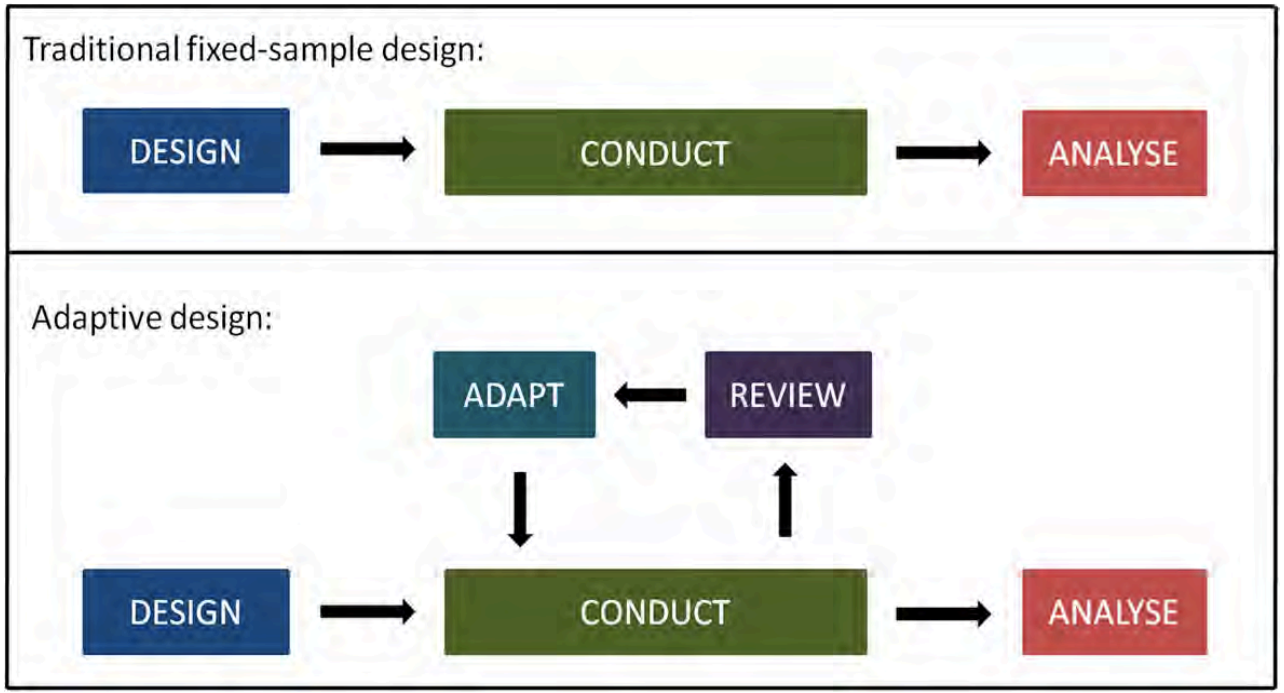
	MOSCATO, n (%)	SAFIR02lung, n (%)	MATRIX trial, n (%)	PROFILER n (%)	TARGET n (%)
Pts included	1036	977	3099	2676	100
Pts w actionable target (%)	411 **(39)**	350 **(36)**	731 **(23)**	1004 **(37)**	41 **(41)**
Pts w targeted Rx **(%)**	199 **(19)**	158 **(16)**	458 **(15)**	143 **(5)**	11 **(11)**

- 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; Rothwell D, et al. Nat Med 2019

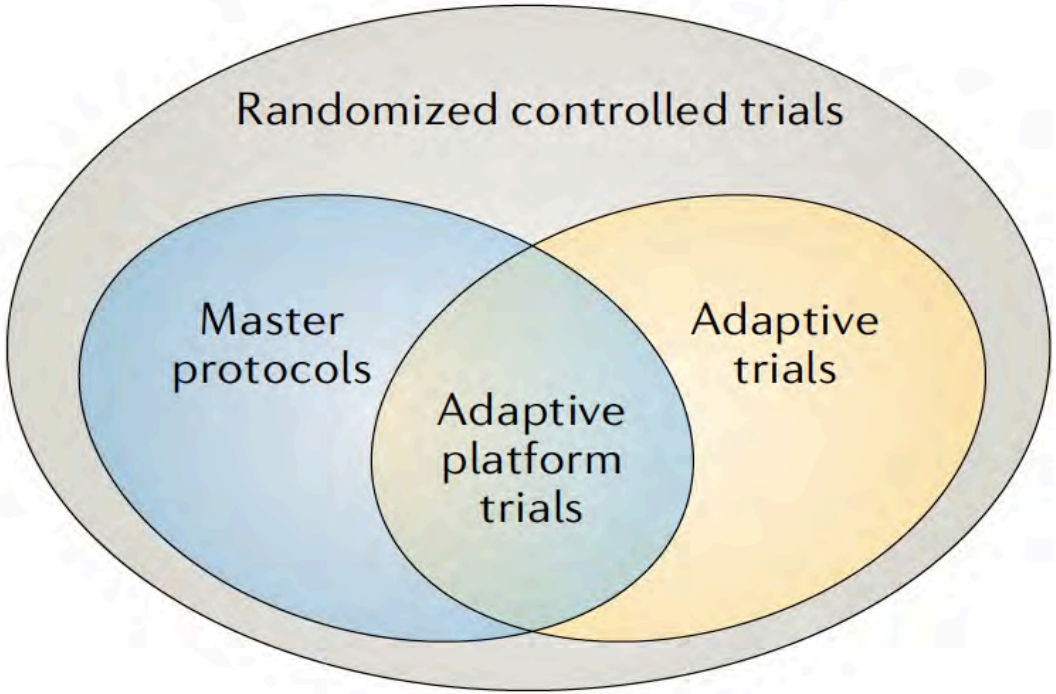
#2 Adaptative design



- Based on modifying parameters (drug, dose, schedule, sample size, …) according with observed outcomes

Pallman P, et al. BMC Medicine 2018

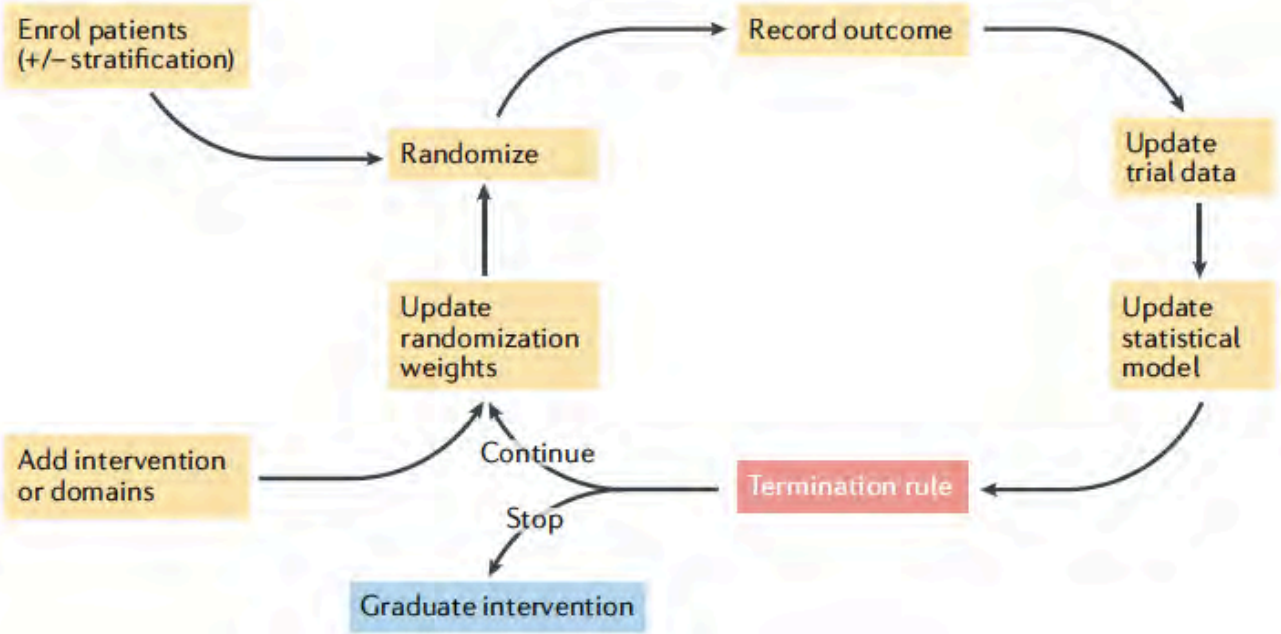
#2 Adaptative design



- Not exclusive

Pallman P, et al. BMC Medicine 2018

#2 Adaptative design



- Design adaptatif (principes)

Adaptative Platform Trials Coalition. Nat Rev Drug Discovery 2019

#2 Adaptative design

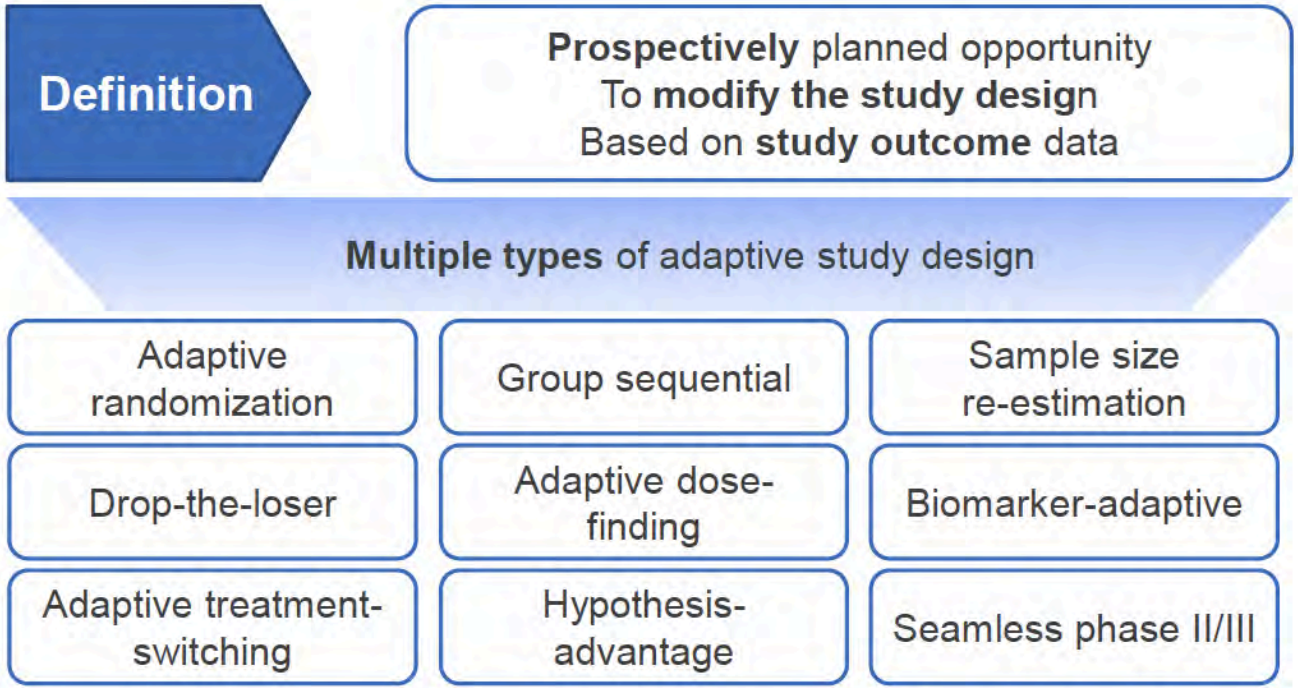
Box 1: What makes a randomised clinical trial adaptive?

- Key study design components can be adapted throughout the trial
- Trial planning involves several rounds of simulations
- Consequences and gains of possible trial adaptations need to be understood before initiation
- Statistical analysis plans are needed for both interim and final analyses
- Research question may change along with adaptations (for example, narrowing the population)
- Multiple trials (such as phase II and III) can seamlessly be combined in one adaptive trial
- New experimental treatments can be added rather than starting a new separate trial

- Design adaptatif

Thorlund K *et al*, BMJ Open 2018

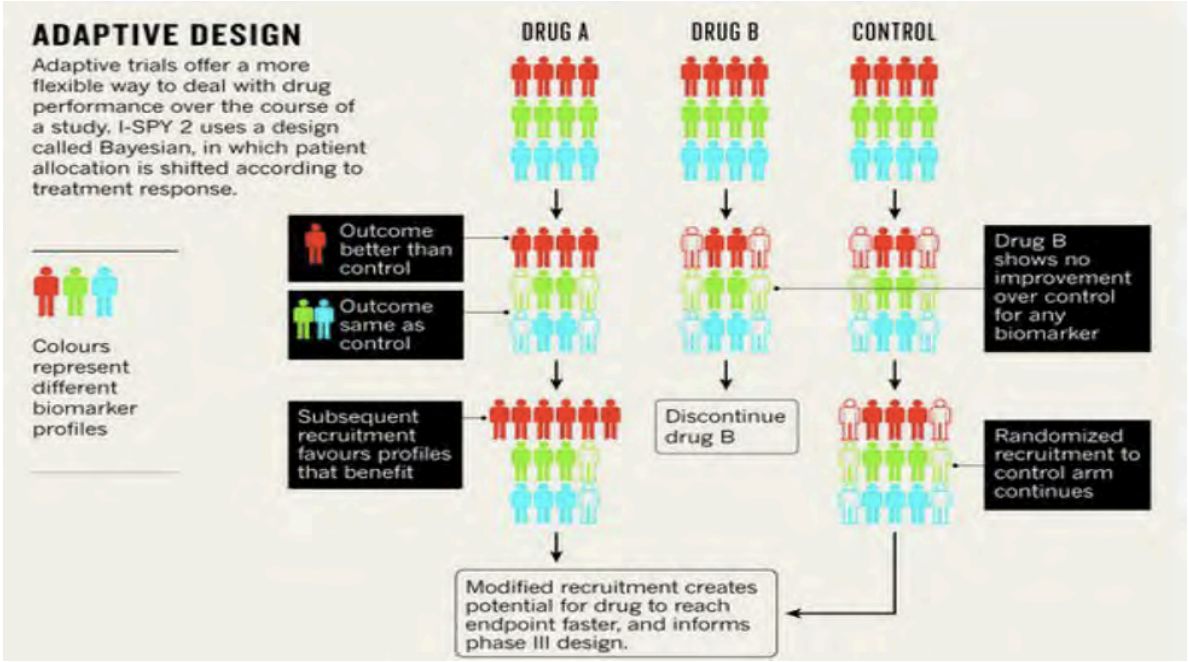
#2 Adaptative design



- Design adaptatif

ISPOR, 2017

#2 Adaptative design

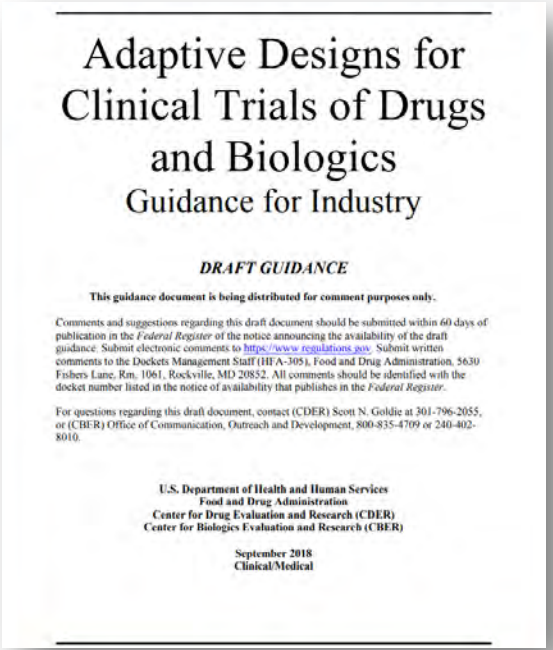


- Design adaptatif (consequences)

Eisenstein M *et al*, Nature 2014

#2 Adaptative design

- 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.

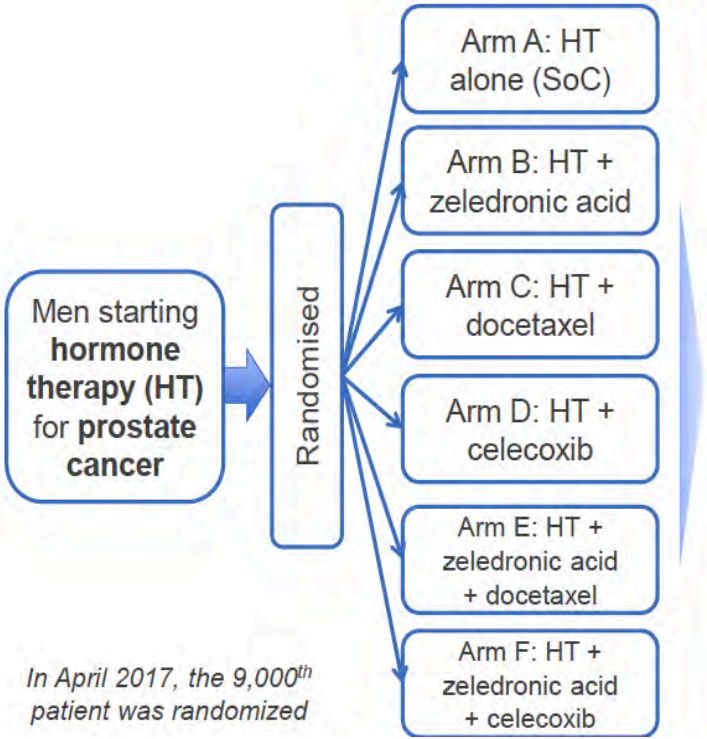
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical

- Released on Sept. 28, 2018

www.fda.gov

#2 Adaptative design

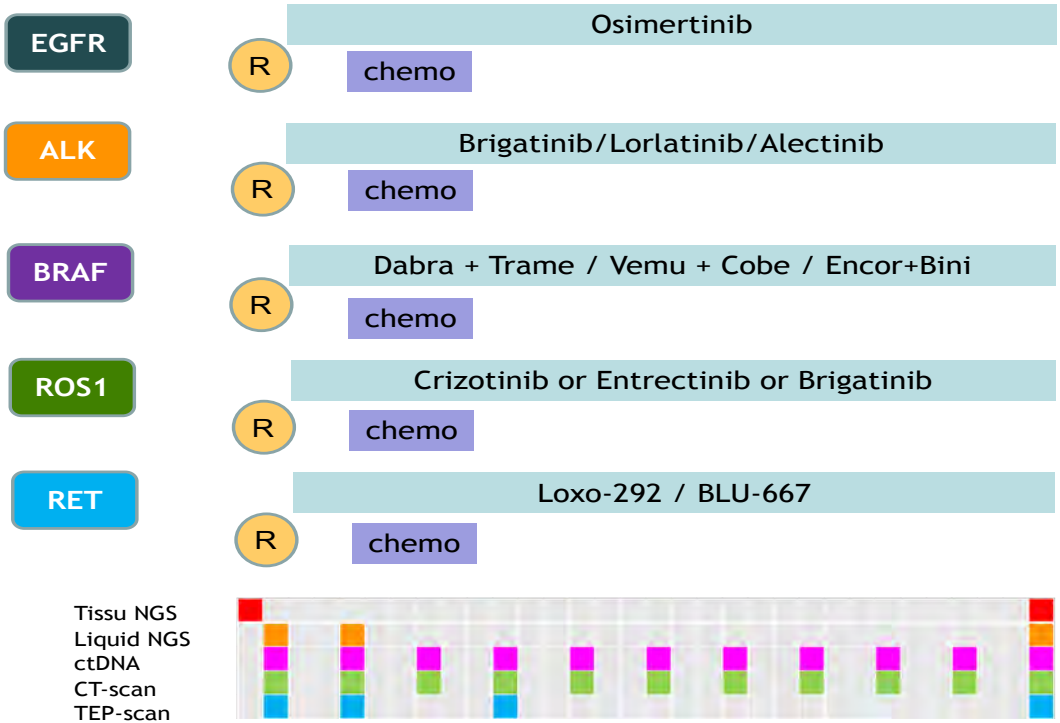


Date	Update
Apr 2011	Arms D & F closed based on interim analysis results
Nov 2011	Arm G (HT+abiraterone) added
Jun 2013	Arm H (HT+RT) added (in M1 patients only)
Jul 2014	Arm J (HT +enzalutamide +abiratorone) added
May 2015	Arm C results – +docetaxel improves OS => new SoC
Apr 2016	Arm B&E results – +zeledronic acid not improve OS
Sep 2016	Arm H closed based on interim analysis results
Sep 2016	Arm K (HT+metformin) added (in non-diabetics only)
Jul 2017	Arm G results +abiraterone improves OS

- Umbrella and adaptative trials
  - Ex. STAMPEDE

Design of the STAMPEDE trials and adaptations over the time; ISPOR 2017

#2 Adaptative design



- IFCT 19xx
  - Addicted tumors
  - Example of a possible design *(not currently approved)*

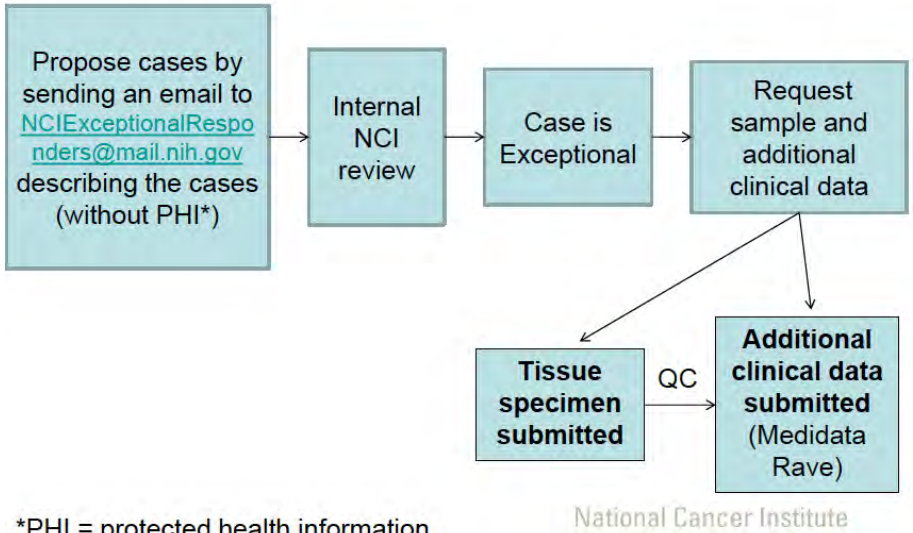
PI: F Barlesi / J Mazières

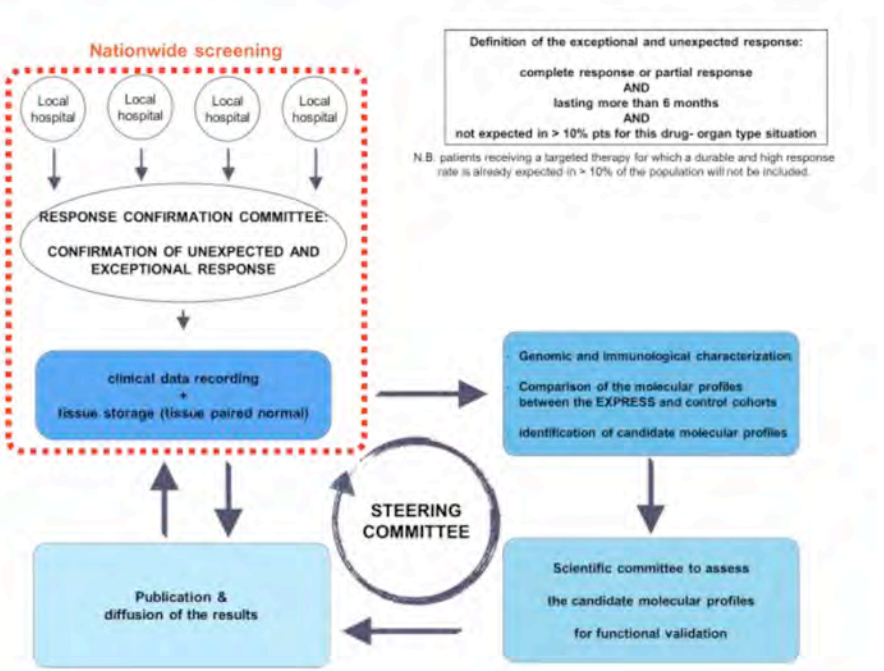
#3 Autres designs

- Multiples possibilités

https://www.journaldunet.com/management/direction-generale/1126607-comment-booster-la-creativite-de-ses-employes/

#3’ Target (retro-)discovery studies





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

#3’ 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: ___/___/____

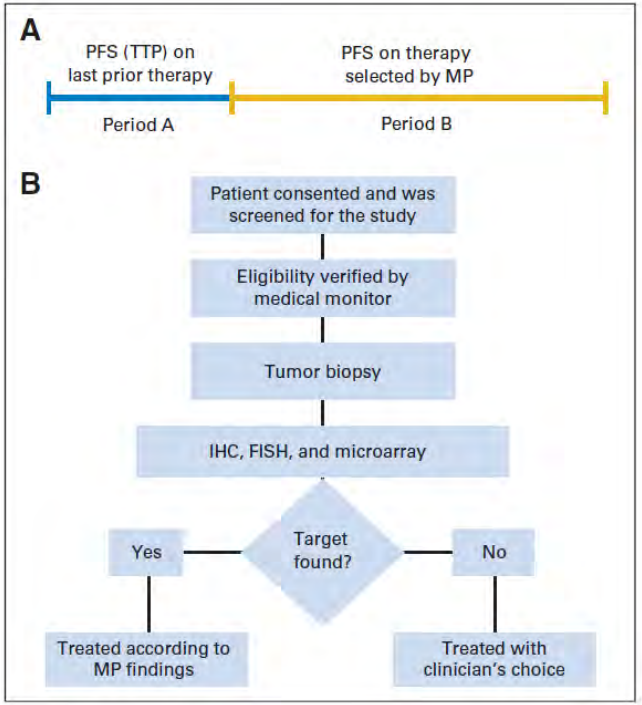
Précisez la localisation des métastases : _____

Express – Fiche de Screening V1.0 mars 2016

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

#3’’ 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

#3” PRG rate model (N of 1)

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

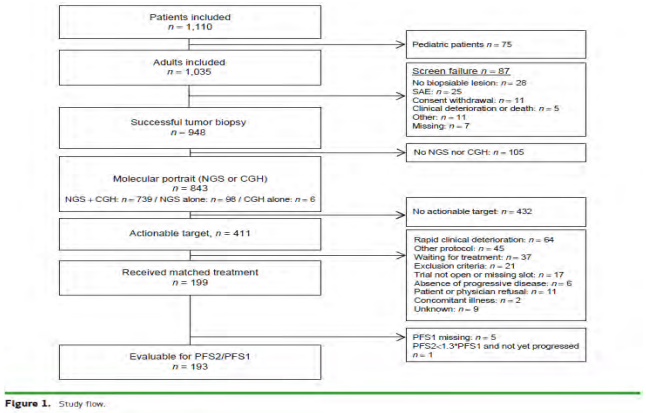


Figure 1. Study flow.

- Ratio > 1,3 chez 33% des patients

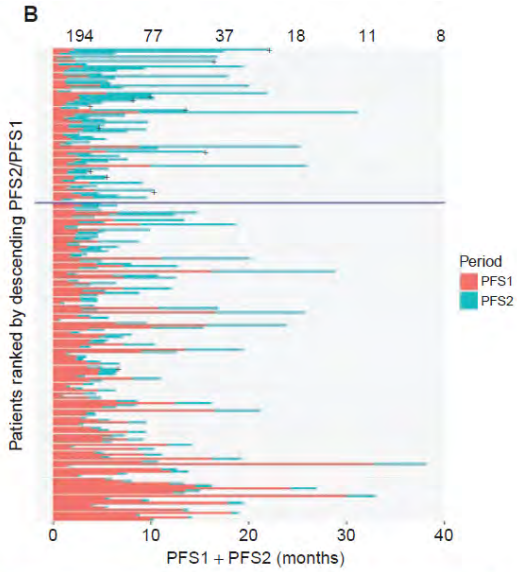


Figure 3. Efficacy on primary endpoint. **A**, Kaplan–Meier curve of PFS2/PFS1. Crosses denote censored data. Green line denotes PFS2/PFS1 > 1.3. **B**, Individual PFS1 and PFS2 times, ordered by descending PFS2/PFS1 ($n = 194$). Crosses denote censored data. Patients above the blue horizontal line have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

Massard C *et al*, Cancer Discov 2017

#3’’’ Window-of-opportunity trials

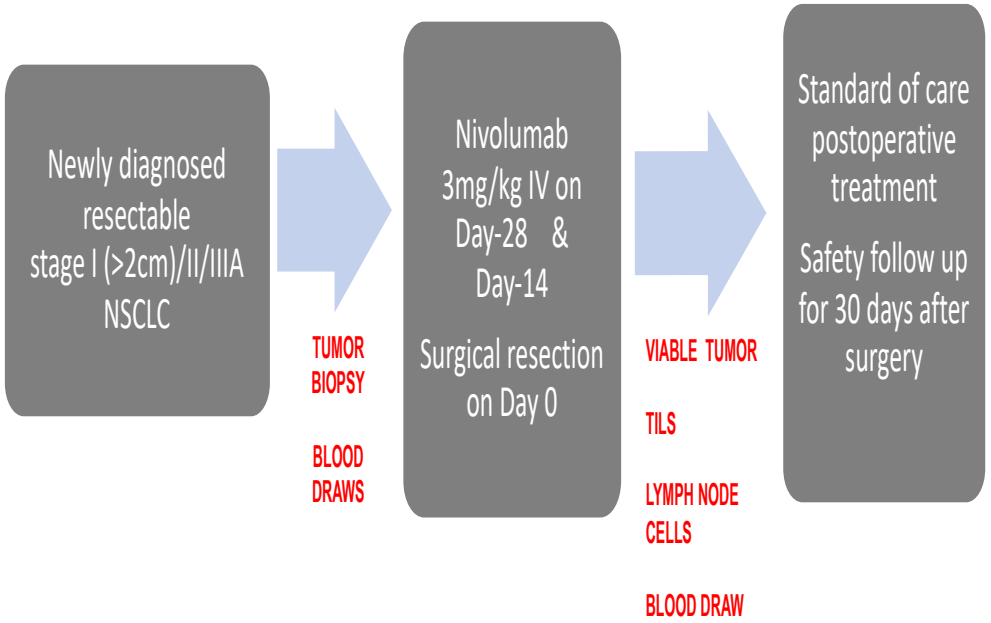
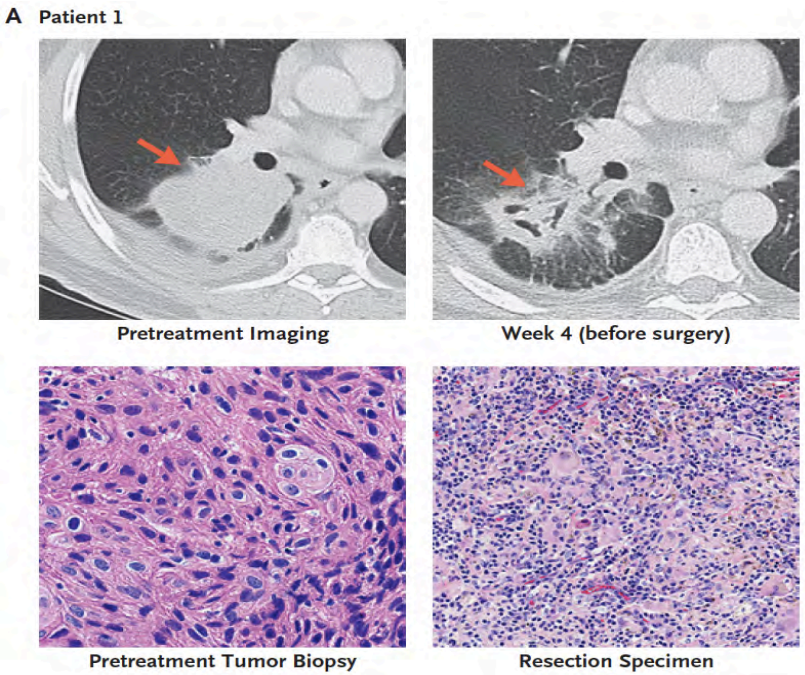


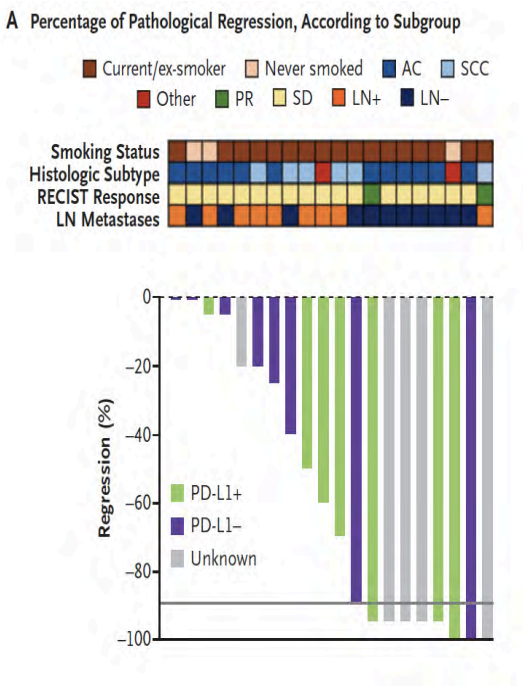
Table 1. Characteristics of the Patients at Baseline, According to Pathological Response.*

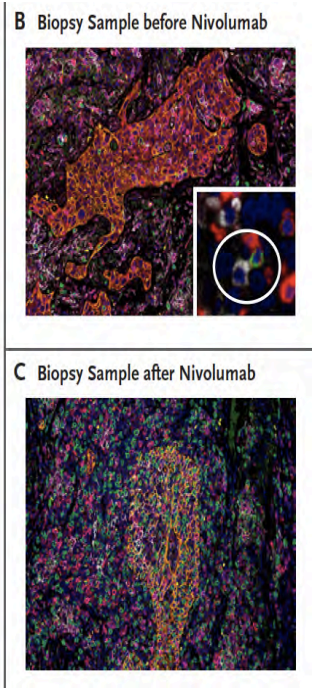
Characteristic	All Patients (N=21)	Patients with Major Pathological Response (N=9)	Patients without Major Pathological Response (N=11)†
Age at enrollment — yr			
Mean ±SD	66.9±8.3	67.7±8.3	65.8±8.5
Median (range)	67 (55–84)	66 (57–79)	67 (55–84)
Sex — no. (%)			
Female	11 (52)	6 (67)	4 (36)
Male	10 (48)	3 (33)	7 (64)
Histologic diagnosis — no. (%)			
Adenocarcinoma	13 (62)	6 (67)	6 (55)
Squamous-cell carcinoma	6 (29)	2 (22)	4 (36)
Other‡	2 (10)	1 (11)	1 (9)
Clinical disease stage — no. (%)§			
I	4 (19)	2 (22)	2 (18)
II	10 (48)	5 (56)	5 (45)
IIIA	7 (33)	2 (22)	4 (36)
Smoking status — no. (%)			
Never	3 (14)	1 (11)	2 (18)
Former or current	18 (86)	8 (89)	9 (82)

Forde P, et al. NEJM 2018

#3”’ Window-of-opportunity trials

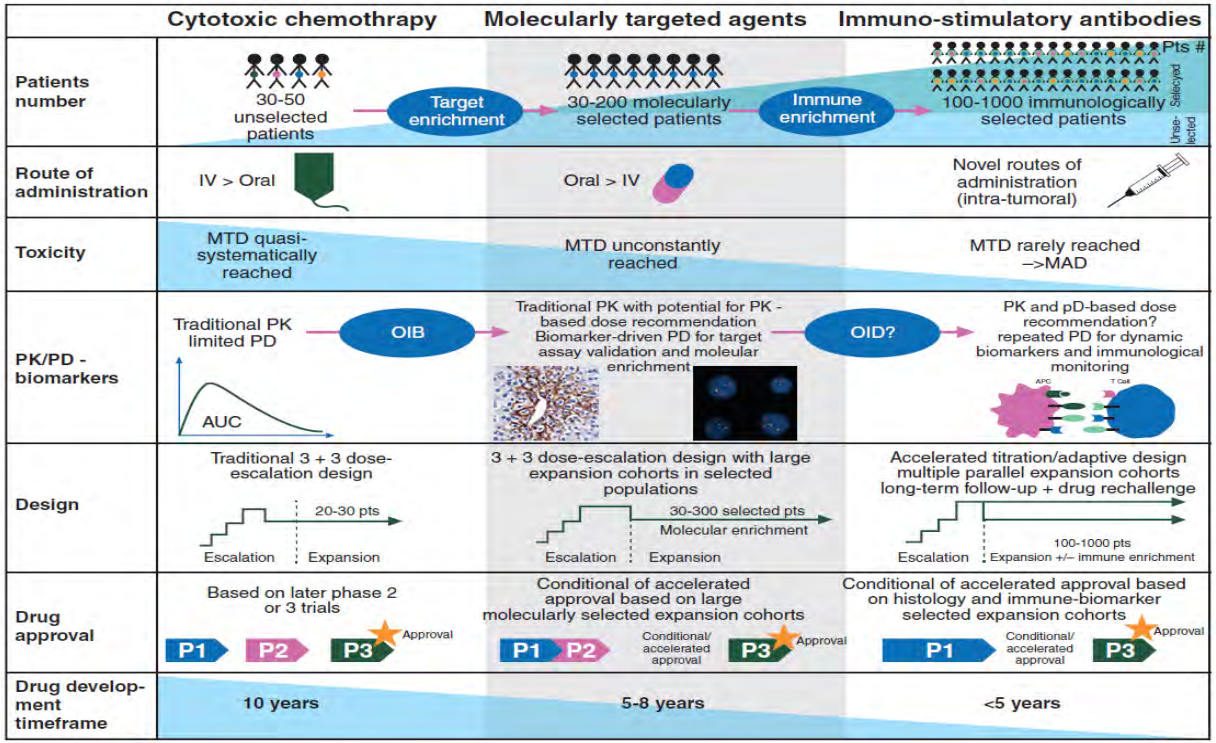






Forde P, et al. NEJM 2018

Conclusions: NG trials? Help to Succeed!



- Accelerated approval

Postel-Vinay S *et al*,

Ann Oncol 2016

Conclusions: NG trials? Costs!

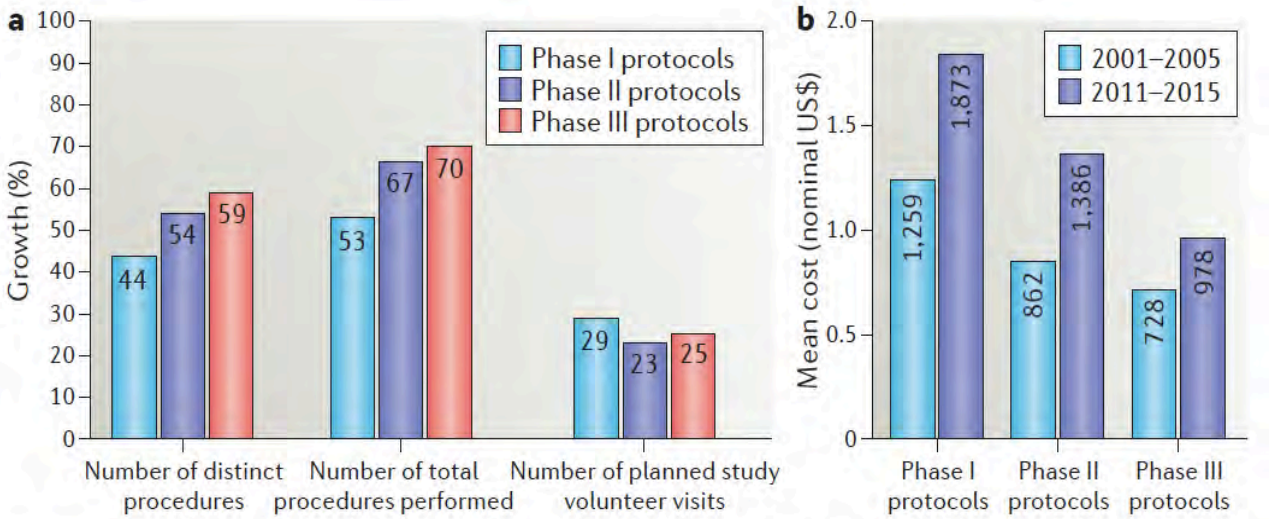


Figure 1 | **Trends in the complexity and costs of clinical trials. a** | Growth rates for protocol design metrics between 2001–2005 and 2011–2015. **b** | Cost per volunteer visit for the same two periods. Increases in protocol complexity have offset cost savings from procedural efficiencies and technology improvements. See Supplementary information S1 (box) for details.

- Increasing complexity and costs

Getz K & Campo R.
Nat Rev Drug Discov
2017

Conclusions: NG trials? Question!

- Approval *versus* Reimbursement

A suivre ! Save the date.

Merci

fabrice.barlesi@ap-hm.fr

@barlesi