Evolution des critères d'évaluation dans les essais cliniques

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Remerciements à

Jean-Yves Douillard, Lugano

Jean-Pierre Pignon, Eméilie Lanoy, Villejuif

1/ Discuss the conventional end-points for each type of evaluation phase in clinical trials

- Phase 0:
  - Exploratory studies in cancer patients with small doses of a given drug, 1st-in human trials
  - **Pharmacodynamic/pharmacokinetic studies**
  - Short treatment duration
  - No therapeutic benefit expected

- Phase 1:
  - Dose finding trials in all pre-treated tumor types
  - **Mostly focusing at safety according to dose level**
  - May be expanded to larger cohorts according to preliminary efficacy findings
  - May be done in drug combination study
  - Associated to pharmacokinetic/(dynamic) studies

1/ Discuss the conventional end-points for each type of evaluation phase in clinical trials

- Phase 2:
  - Selected patients with a given tumor type pre-treated or not
  - **Look at clinical efficacy most often Response Rate (RR) some time Progression-Free Survival (PFS)**
  - Provide additional safety data on larger cohorts
  - May be used for combination study
  - Either single arm or randomized
- Phase 3: The gold standard (?)
  - Comparative randomized trials vs. standard of care in various lines of treatment
  - Single agent or combination
  - **Primary end-point: Overall Survival (OS) or PFS**
  - Additional safety data
  - RR, Tolerance, QoL as secondary end-points
  - Often required for registration

1/ Discuss the conventional end-points for each type of evaluation phase in clinical trials

- **Phase 4:**
  - Most often in registered drugs according to the label
  - **Additional safety, long term risk and benefit**
- **Combined phase trials**
  - **Phase1/2 or 2/3 trials**
    - Successive phases with different end-points for each phase
    - Allow to select a better treatment arm and continue accrual
  - **Multi-arm/multi-stage trials**
    - Allow random allocation of experimental treatment vs. a control arm
    - Looking at dose, sequence of administration or impact of predefined biomarkers (Basket trials)

2/ Detail the strength and weaknesses of such end-points as well as the issue of surrogacy

- ORR, PFS and OS are the « Classical Endpoints" in randomized clinical trials
- The academic setting and a registration setting are different

- ORR and PFS have their limitations
  - Due to the imaging technology used
  - Due to variability among investigators, radiologists and independent review
  - Due to tested drugs
  - Reliability of RR may affect PFS

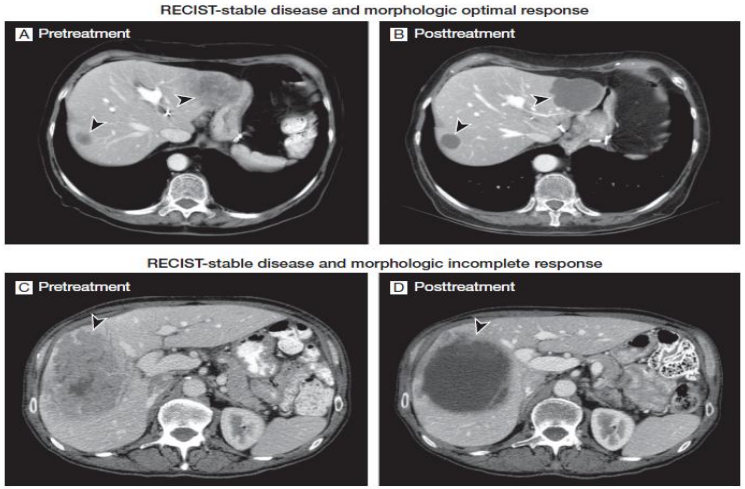
Weakness of Response rates: examples

- **Folfox in mCRC 1st line**

FOLFOX	ORR	PFS
NO16966	38%	8.5 m
TOURNIGAND	54%	8 m
OPUS (RASwt)	29%	5.8 m
PRIME (RASwt)	46%	7.9 m

- **Folfiri-Bevacizumab 1st line**

FOLFIRI	ORR	PFS
Mexico	53%	9.4 m
FIRE 3 (RASwt)	56%	10.2 m



Arrowheads indicate the tumor-liver interface. Morphologic optimal response is characterized by decreased attenuation and sharp tumor-liver interface (B); morphologic incomplete response is characterized by decreased attenuation but persistent ill-defined tumor-liver interface remaining after treatment (D).

2/ Detail the strength and weaknesses of such end-points as well as the issue of surrogacy

- **OS is a much stronger end-points not doubt-full**
  - Time to death irrespective of cause

- **However there are also some limitations**
  - All causes of death vs. cancer specific survival
  - Long duration of follow-up to have mature enough data
  - Impact of additional lines of treatment in metastatic setting
    - Motivates the need for surrogate end-points like DFS or PFS

Adjuvant chemotherapy in resected NSCLC: long term follow-up effect

	34 m	54-56 m	74 m	84 m	90 m	112 m
IALT	-	**0.86 P<0.03**	-	-	0.91 P<0.10	-
CALGB 9633	**0.62 P 0.014**	0.80 P 0.10	0.83 P 0.12	-	-	-
JBR 10	-	**0.61 P 0.04**	-	--	-	**0.78 P 0.04**
ANITA		**+ 8.6%**		**+8.4% 0.80 P 0.01**		

Besse B et al JCO 2008; 26: 5014-5017
Douillard JY JCO 2010; 28: 3-5

2/ Detail the strength and weaknesses of such end-points as well as the issue of surrogacy: Time dependent end-points definitions

- **Disease-free survival DFS**
  - Time to any event irrespective of cause (except lost of FU)
- **Relapse-free survival RFS**
  - Time to any event irrespective of cause, 2nd primary cancer ignored, lost of FU censored
- **Time to Recurrence TTR**
  - Time to any event related to the same cancer
  - 2nd primary, other primary ignored,
  - Death from other cancer, non-cancer related death, TT-related death censored
- **Time to Treatment Failure TTF**
  - Time to any event except non-cancer related death
  - Lost of Follow-up and non-cancer related death censored
- **Cancer-Specific Survival CSS**
  - Time to death due to the same cancer(original or same second primary)
  - Death related to other cancers, non-cancer, TT-related, lost of FU censored

2/ Detail the strength and weaknesses of such end-points as well as the issue of surrogacy

Time dependent end-points and the issue of surrogacy

- **Advantages of earlier time points: PFS and DFS**
  - Shorter FU and earlier conclusion
- **Risks of surrogate end-points**
  - Surrogacy never demonstrated for ever
  - More variability in the evaluation
  - Multiple time dependent endpoints (definition)

Endpoints in Adjuvant Treatment Trials: A Systematic Review of the Literature in Colon Cancer and Proposed Definitions for Future Trials

Cornelis J. A. Punt, Marc Buyse, Claus-Henning Köhne, Peter Hohenberger, Roberto Labianca, Hans J. Schmoll, Lars Påhlman, Alberto Sobrero, Jean-Yves Douillard

JNCI 2007; 13: 998-1003

The issue of surrogacy

- Surrogacy have been studied in a variety of tumor types and settings (Adjuvant and metastatic)

- Surrogacy of PFS or DFS for OS is not clearly established
  - It depends of the expected OS (long or short)
  - It depends also of available treatment in later line metastatic disease

DFS as a surrogate for OS in adjuvant setting of colon cancer

- **2005: IPD Meta-analysis[1]**
  - Trials from 1977-1999, N=20898, 18 trials, 33% stage II
  - Good correlation between 3y DFS and 5y OS

- **2011: new trials analysis[2]** (Capecitabine, UFT, Oxali, Irinotecan)
  - 12676 patients stage III, FU 6 years
  - DFS surrogate for OS confirmed in stage III (not stage II)
  - 6 year FU is recommended

1. **Sargent D. et al JCO 2005; 23: 8664-8670**
2. **Sargent D. et al Eur J Cancer 2011; 47: 990-996**

PFS as a surrogate for OS in Metastatic colon cancer

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer

Marc Buyse, Tomasz Burzykowski, Kevin Carroll, Stefan Michiels, Daniel J. Sargent, Langdon L. Miller, Gary L. Elfring, Jean-Pierre Pignon, and Pascal Piedbois

- **10 trials 5FU based, 3089 Patients (1981-1990)**
  - Good correlation between PFS and OS (HR threshold 0.86 to predict OS)

- **3 additional trial with Oxali, Irinotecan, 5FU (1995-1998)**
  - Good correlation between PFS and OS (HR threshold 0.77 to predict OS)

PFS as a surrogate for OS in Metastatic colon cancer

VOLUME 33 · NUMBER 1 · JANUARY 1 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Individual Patient Data Analysis of Progression-Free Survival Versus Overall Survival As a First-Line End Point for Metastatic Colorectal Cancer in Modern Randomized Trials: Findings From the Analysis and Research in Cancers of the Digestive System Database

Qian Shi, Aimery de Gramont, Axel Grothey, John Zalcberg, Benoist Chibaudel, Hans-Joachim Schmoll,

- **More recent analysis including biologicals (44% of pts)**
  - 22 First-line trials on 16762 patients (1997-2006)
  - Modest correlation between PFS and OS
- **Conclusion in the modern era of combined treatment**
  - In diseases where survival after PD exceeds 1st PFS, the correlation is modest
  - Substantial variability in OS is due to additional lines
  - Using OS is a challenging end-point to assess benefit to a single early line
  - **PFS remains a valid primary end-point for 1st-line mCRC**

DFS/PFS as a surrogate for OS in resected and locally-advanced NSCLC

- In lung cancer, outcome remains poor

	N patients	N events	DFS	N events	OS
Adjuvant					
CT vs Abst	5379	2525	6.4 y	2163	8.2 y
Locally Advanced			PFS		
RT/CT vs RT	2552	2391	8.1 m	2305	14.1 m

- Meta-analysis of 60 randomized trials, 15071 patients
  - Adjuvant: very good correlation CC 0.83
  - Locally advanced: very good correlation CC 0.85

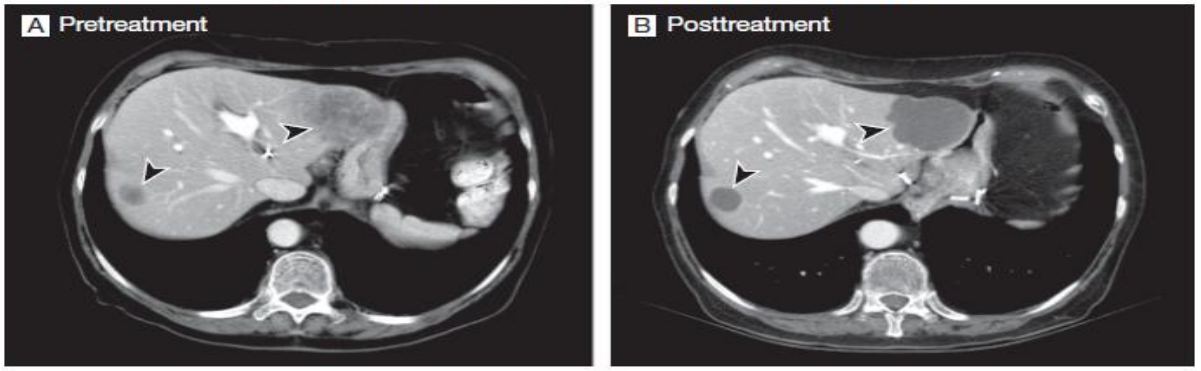
A Mauguen et al Lancet Oncol June 2013; 14: 7: 619-626

3/ Forsee how conventional end-points will need to be adapted to targeted therapies including immunotherapy

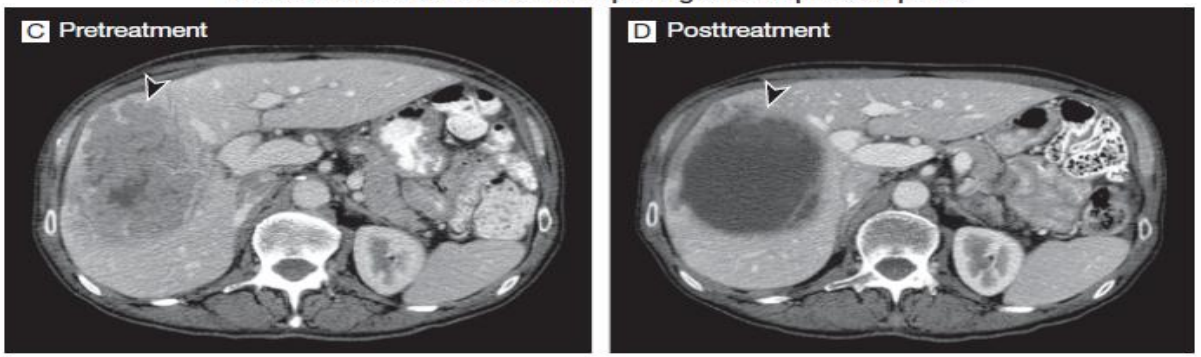
- **Targeted agents modify the morphology of lesion, not always in size**

  - **Colon cancer and bevacizumab**

RECIST-stable disease and morphologic optimal response



RECIST-stable disease and morphologic incomplete response



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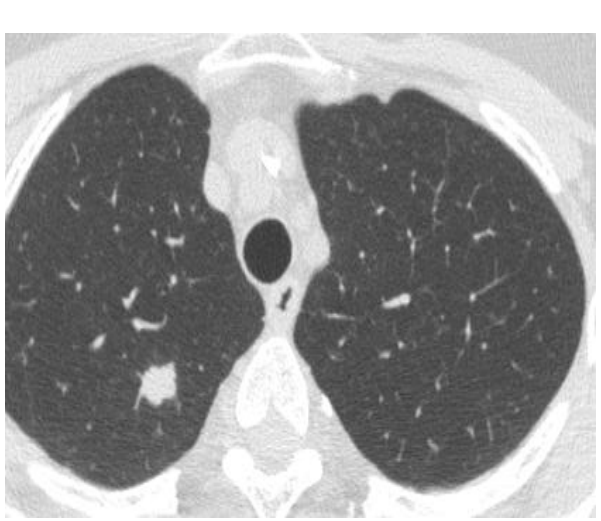
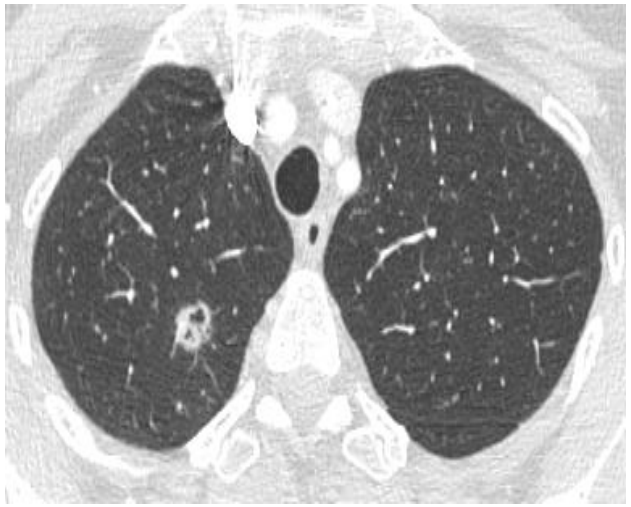
3/ Forsee how conventional end-points will need to be adapted to targeted therapies including immunotherapy

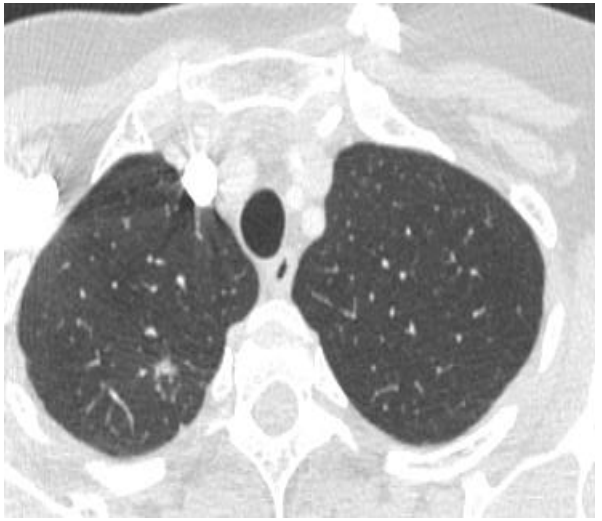
- **Targeted agents modify the morphology of lesion, not always in size**
  - **Lung adenocarcinoma and oral anti-angiogenic agent**



Pre-treatment



Cycle 2



Cycle 4

3/ Forsee how conventional end-points will need to be adapted to immunotherapy

- Under immune-check point inhibitors different profile of response may occur:
  - Objective response according to conventional RECIST
  - Stable disease according to conventional RECIST

  - Response after an initial increase in the size of lesion
  - Reduction of tumor burden on baseline target and appearance of news lesions

RECIST 1.1 and Immune-related RECIST criteria irRC

RECIST 1.1[1]

- **CR**: disappearance of all target lesions
- **PR: ≥30%** decrease in the sum of target diameters
- **PD:** >20% increase in the sum of target diameters as compared to the smallest diameter achieved
  - New lesion
- **SD:** no PR no PD

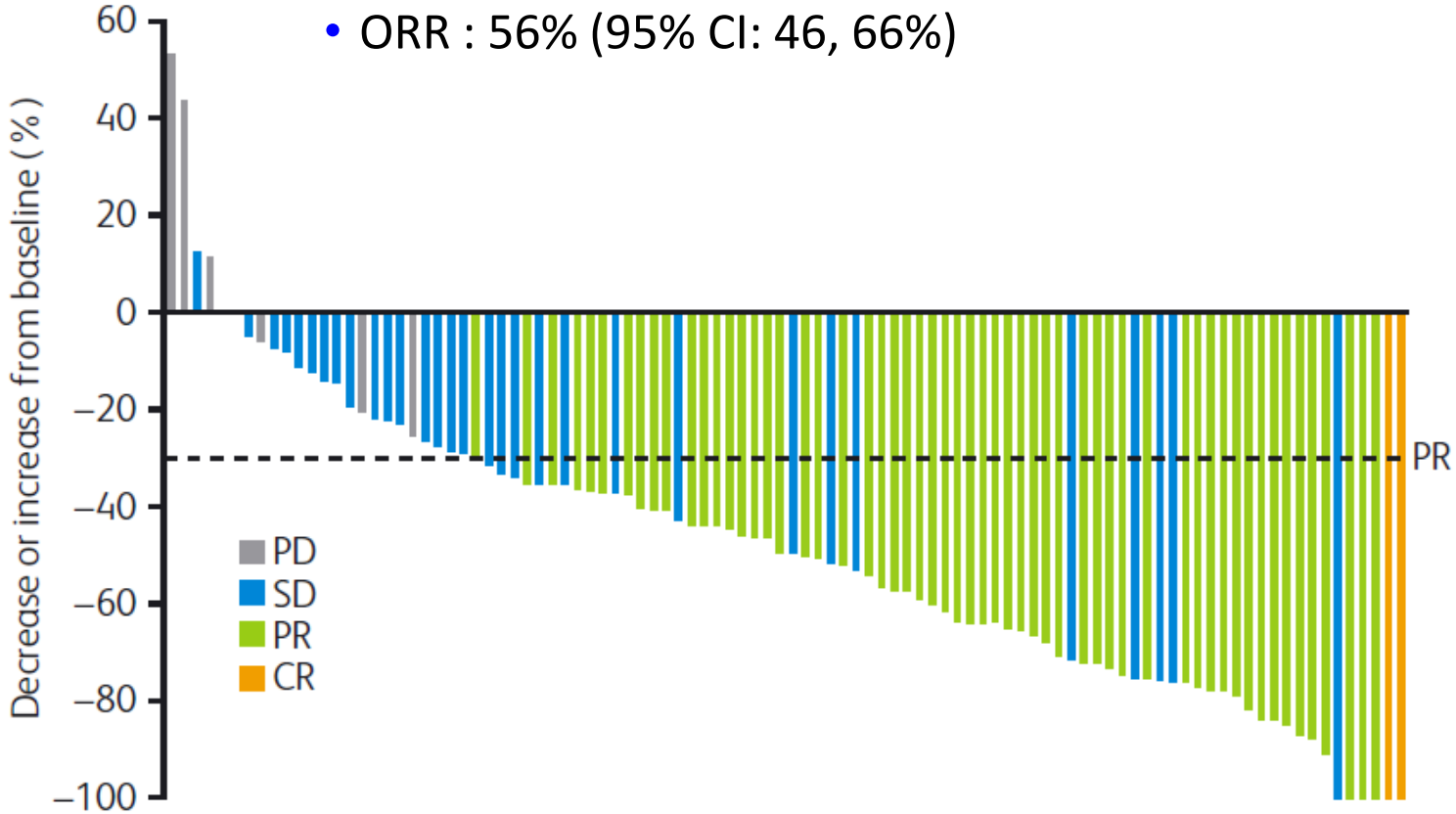
irRC[2]

- **irCR**: disappearance of all target lesions
- **PR: ≥ 50% decrease** in the sum of the products of the 2 largest perpendicular diameter (SPD)
- **PD: ≥ 25% increase** relative to nadir
- **SD: <50% decrease** or **< 25% increase**
- **NEW LESION**
  - **Measurable incorporated in tumor burden**
  - **Not measurable do not define progression**

1. **EA Eisenhauer et al Eur J Cancer 2009; 45: 228-247**
2. **JD Wolchok et al Cin Cancer Res 2009 December 1st; 15/ 7412-7420**

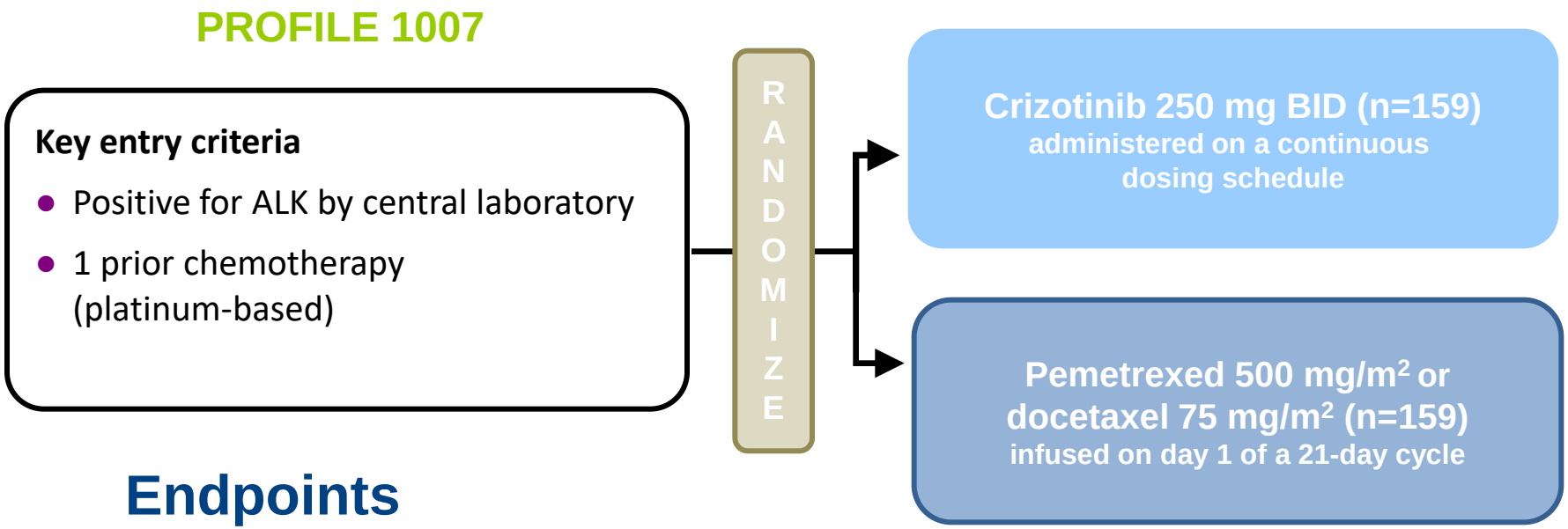
Exemples récents
ORR with Crizotinib
(105 patients EML4-ALK+)

- ORR : 56% (95% CI: 46, 66%)



PD: progressive disease SD: stable disease PR: partial response CR: complete response

Phase III trial with Crizotinib



Endpoints

1°: PFS (ITT population)

2°/Exploratory:

OS (ITT population)

PROFILE 1007: NCT00932893

US first FDA approval…

- Première présentation des résultats de l'essai Profile 1007: ESMO septembre 2012 mais:
- On 26 August 2011, Pfizer Inc. announced that the U.S. Food and Drug Administration (FDA) has approved XALKORI® (Crizotinib) capsules for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has ALK positive as detected by an FDA-approved test

Encore pire: l'immunothérapie

- Premières indications du pembrolizumab: essais randomisés…. Puis:

- The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®) on August 5 for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that has continued to progress despite standard-of-care treatment with chemotherapy.
- The FDA granted accelerated approval based on **early data from 174 patients with HNSCC enrolled in the nonrandomized KEYNOTE-012 trial.**
- **According to the FDA approval summary, 28 patients (16%) experienced a tumor response** following treatment with pembrolizumab. In 23 (82%) of those patients, the tumor response lasted for 6 months or longer, and several have lasted for more than 2 years.

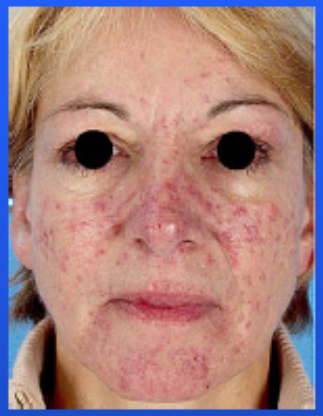
Problème spécifique des phases I

Paradigms challenged with Molecularly Targeted Agents (MTAs)

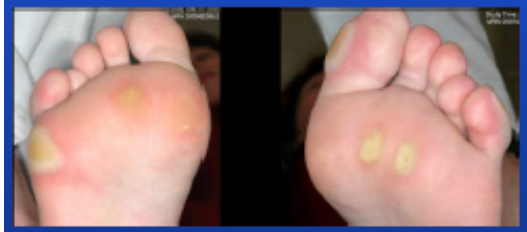
	Cytotoxic chemotherapy	MTAs
Administration	Usually administered for a pre-defined # of cycles Usually weak impact of chronic or moderate tox.	Till progression / resistance Likely prolonged (≈1 year) Evaluation of chronic or moderate toxicities is key
Dose-efficacy relationship	Linear RP2D often = MTD	Wider therapeutic range Broader range of RP2D
Dose-toxicity relationship	Linear	Not linear MTD not always reached
Cumulative / delayed toxicities	Evaluation less essential Often cause definitive treatment cessation	Crucial Cause dose-reduction or therapeutic pauses
Dose ajustement	on BW / BSA	Fixed administered dose

Problème spécifique des phases I

Moderate and late toxicities
Severity *vs* tolerability



Grade 2 folliculitis with EGFR-inhibitors

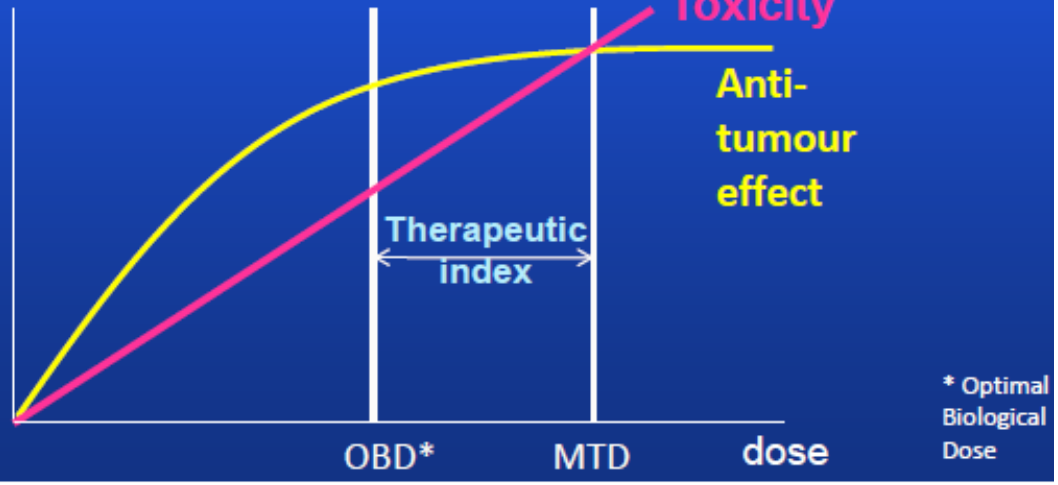


Grade 2 HFSR with sorafenib

Robert C, Semin Oncol 2012

Adverse event	Grade 2
Diarrhea	Increase 4-6 stools a day over baseline
Dry mouth	Moderate oral intake alterations, e.g. copious water, lubricants, diet limited to purees and/or other soft, moist foods

Tolerable?



Problème spécifique des phases I

The challenge of DLT/RP2D definition

Heterogeneity in DLT definition

Review of literature: SCOPUS search (Jan 2000 -> Apr 2010)

155 Phase I trials - MTAs only

Discrepancies in DLT definition
- items (organ-specific)
- severity (organ-specific)
- duration (4%)
- reversibility (12%)
- treatment delay (19%)
- dose intensity reduction (8%)

Le Tourneau et al, EJC 2011

Pilot study on late toxicities

Retrospective analysis
445 patients / 2 centres / 36 trials
2609 toxic events (skin, GI, renal only)

> 50% of the G3-4 toxicities
and
> 50% of the worst toxicities
occur after the 1st cycle,
i.e. after the DLT period

-> Suggestion of considering
acute *vs* chronic DLT

Postel-Vinay et al, JCO 2010

Pour les phases I

Recommendations (1)

1. **Dose-escalation**
   1. **Timing** of the dose escalation should still be based on data from C1 only and should not be delayed
   2. **Dose-increment recommendation** should take into account all available information, notably DLTs observed beyond cycle 1 in prior dose levels

2. **DLT assessment** needs to take into account selected lower grade toxicities leading to significant reductions in RDI (< 75%) , such as fatigue or some GI toxicities

Pour les phases I

Recommendations (2)

3. **All toxicities** should be comprehensively reported, even if not occurring during the DLT period

4. Any toxicity leading to a significant decrease in RDI should deserve particular attention

5. **Thorough assessment of the causality of AEs** is key, and should be done by using all available information, notably
   - effects of drug holidays or dose-reductions
   - correlation between disease evolution and symptoms evolution

Pour les phases I

Recommendations (3)

6. **Dose expansion cohorts** in phase I studies should focus on fine-tuning the dose-defining process

7. **The Recommended Dose** for further studies
   - should incorporate all available information, notably toxicities observed after C1
   - be based on achieving > 75% RDI

Problème spécifique des personnes âgées

Issue
RCTs remain gold standard when possible
Clinical trials should preferably integrate whole age range, including fit and frail older individuals
Elderly-specific clinical trials in older patients with cancer are required if standard therapy is different from that for younger patients
Trials of treatment strategy comparing different strategies (eg, therapy *v* best supportive care) should be encouraged
Randomized phase II or even single-arm phase II trials in specific subsets of older patients can provide insight into range of efficacy and toxicity in older populations but ideally should be confirmed in large phase III trials, which might be hard to perform for various reasons (eg, insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries in community can provide further insight for frail population with less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated into future trials in geriatric oncology
Regulatory authorities should require evaluation of efficacy and safety of new drugs in older and frail patients as well as in younger patients

Problème spécifique des personnes âgées

- Choix des critères de jugement nécessite une grande attention
- End points recommandés:
  - OS et DSS devraient être recueillis dans les essais où des personnes âgés sont inclus
  - Intérêt des composites
  - Qualité de vie et la préservation des capacités fonctionnelles doivent être utilisées plus souvent dans les essais cliniques

Problème spécifique des personnes âgées

- En principe, pas de limite sur l'âge dans les essais clinique Mais l'hétérogénéité des patients âgés (fragile vs non fragile) peut conduire à des biais de sélection
- Essais spécifiques pour des sous-groupes de patients âgés sont nécessaires
- La mise en place d'une évaluation gériatrique est cruciale pour mieux comprendre l'effet des traitements dans une population âgée

→ Nécessité d'une meilleure conception des essais cliniques pour comprendre l'impact des nouvelles thérapies chez les personnes âgées

Use and misuse of efficacy endpoints in phase III clinical trials

- **The choice of an appropriate endpoint is of paramount importance**
- **OS and PFS are the most frequent III in phase and should be selected based on tumor-type, natural history, late-line drugs availability**
  - Subgroup analysis may be hazardous and should be restricted to stratification factors
- **The use of new class of agents**
  - Would need better criteria (anti-angiogenics)
  - Are changing the rules for Immunotherapy with immune checkpoint inhibitors have been approved with small size trials including phase I/II

Les nouveaux problèmes

- Changer aussi les règles pour les phase I
- Et intégrer les personnes âgées dans la réflexion….