Tumor Growth rates to better capture therapeutic activity in cancer patients

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Statistical and biomedical models
for imaging in cancer
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Background

Current decision making (go/no go decision) in early drug development relies mostly on:

- RECIST for molecular targeted agents
- irRC for Immune checkpoint blockers (IO : immuno oncology)

Contextual difficulties of phase 1 trials:

- small number of pts
- molecular profile poorly known

Background

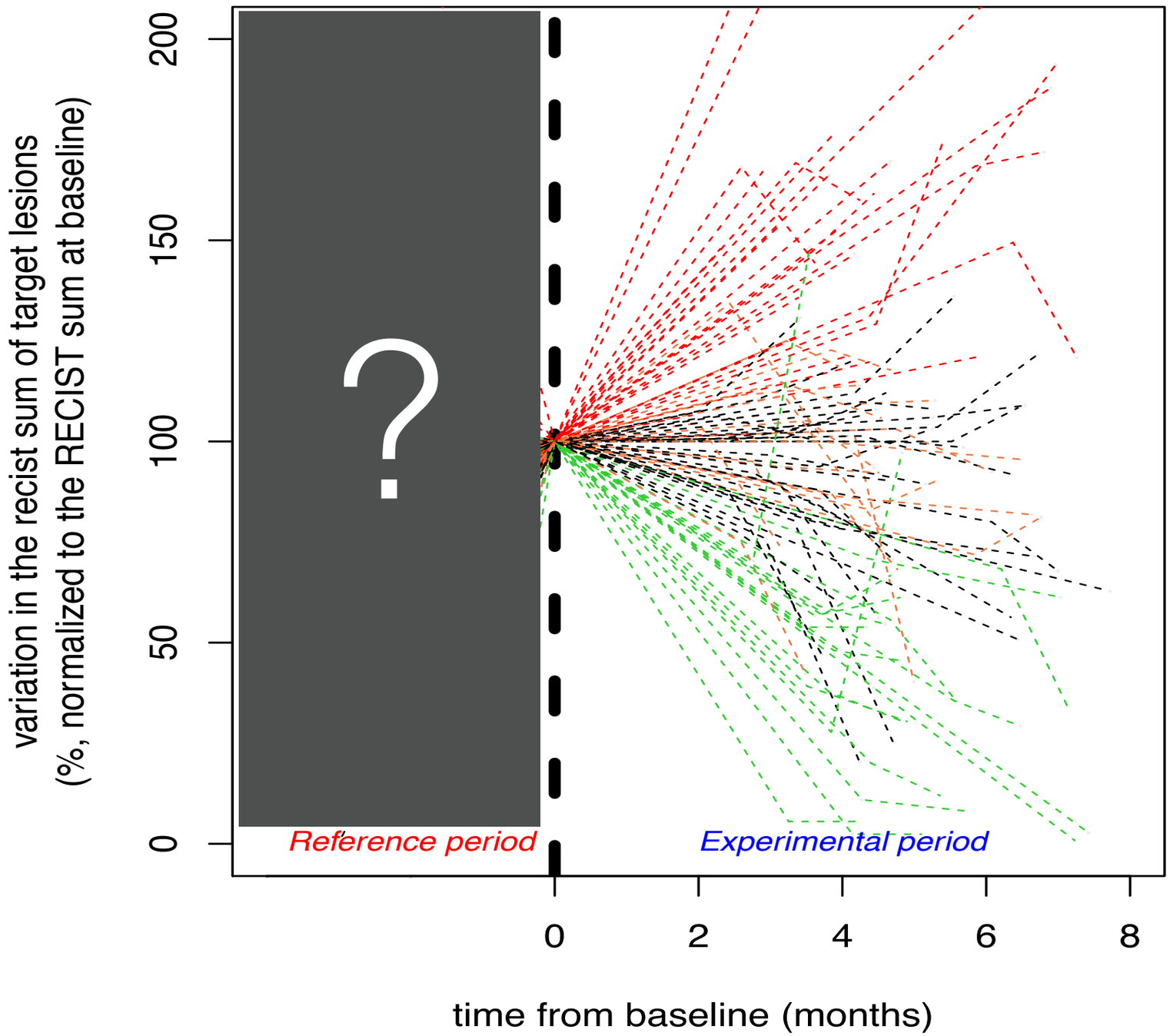
Difficulties related to RECIST:

- arbitrary cut-offs (-20%, +30%)
- most patients classified as Stable Disease (NOT informative group)
- Inconstant correlation with outcome (OS/PFS)
- No discrimination between treatment-effect and the course of the disease

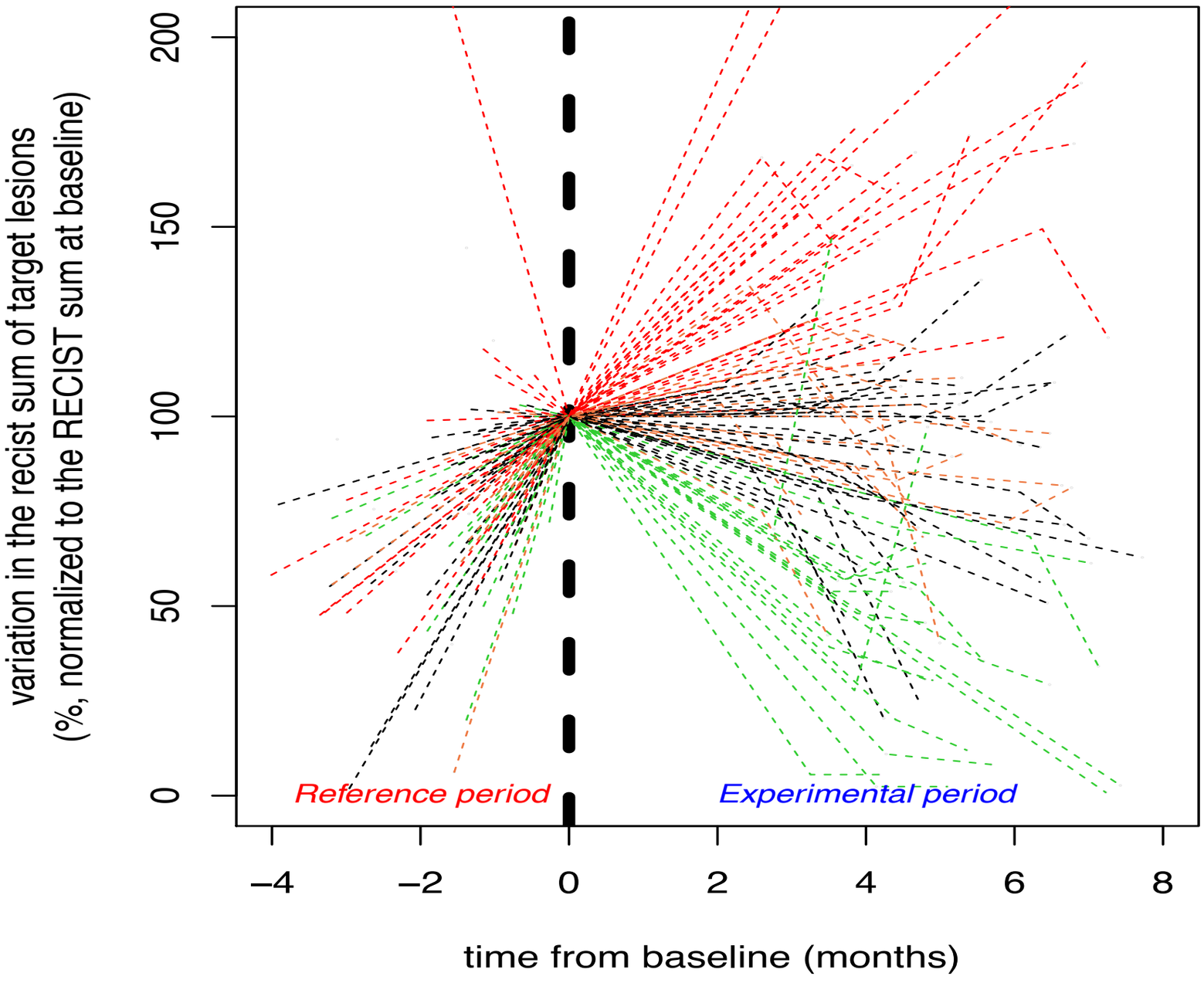
Difficulties related to the irRC :

- need two consecutive evaluations 4 wks apart (delay in evaluation)
- 2 dimensional (more complicated, more errors, require training)
- arbitrary cut-off
- validated in melanoma only

In the current situation (RECIST, iRRC), pre-treament tumor kinetics are unknown



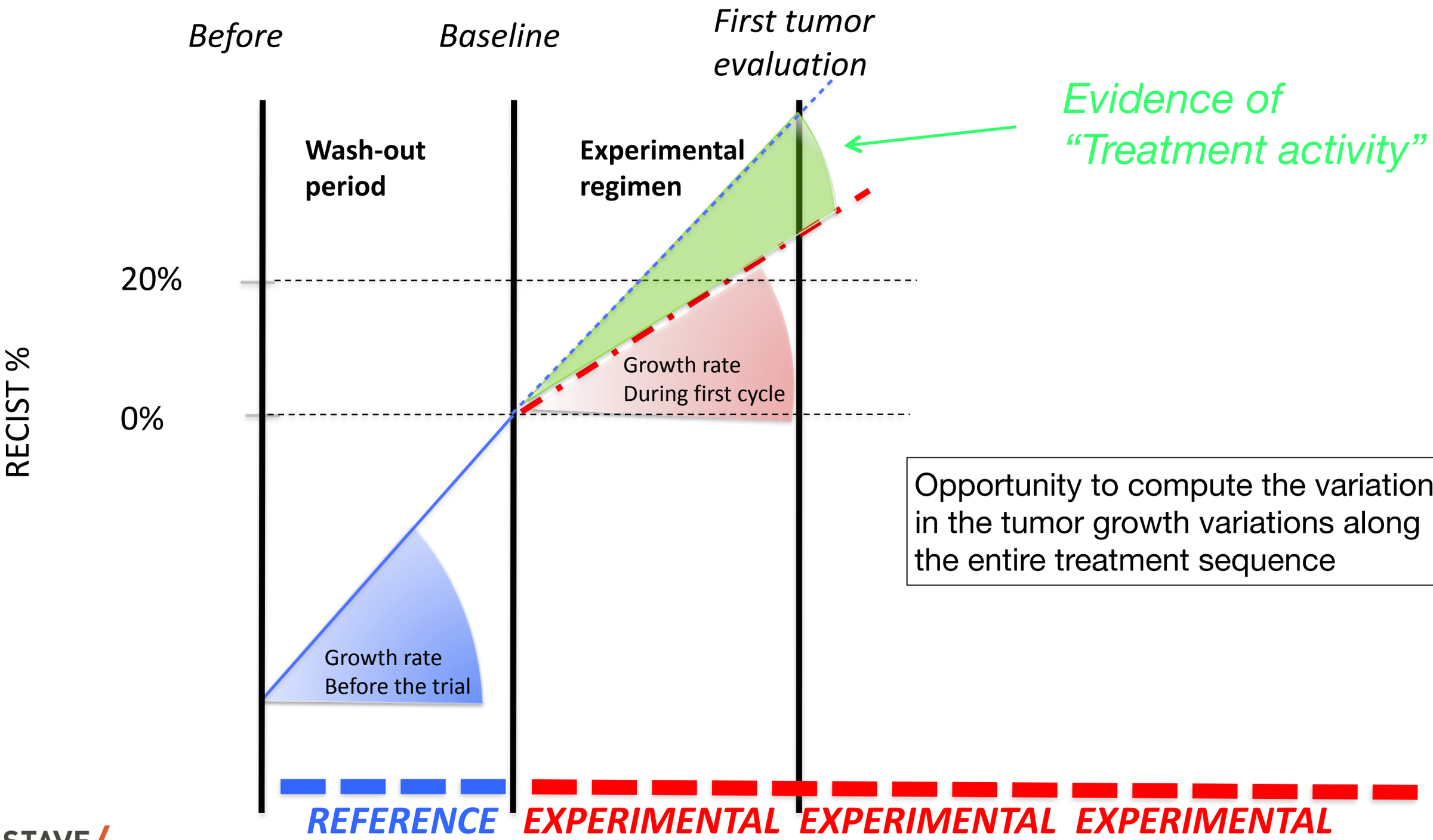
Pre-treatment heterogeneity is substantial



Question:

can we use the pre-treatment tumor kinetics to infer therapeutic activity ?

Integrating pre-treatment kinetics allows to infer the therapeutic activity of a given experimental

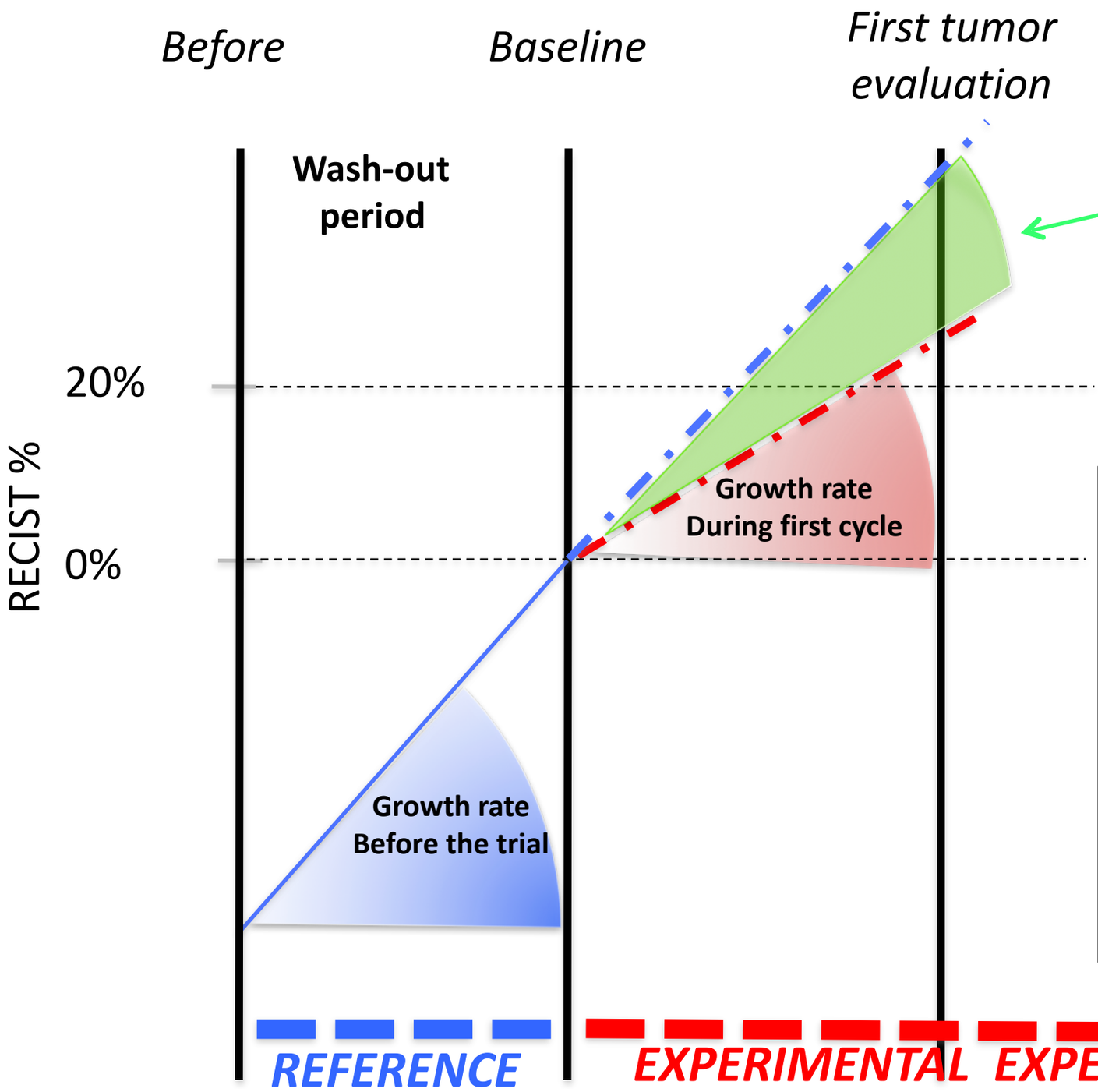


GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

github SOCIAL CODING

Gomez-Roca et al, Eur J Cancer 2011
Ferté et al, Clin Cancer Res 2014
Ferté et al, Eur Urol 2014

Hypothetical case #1 of a fast-growing tumor treated by an active drug



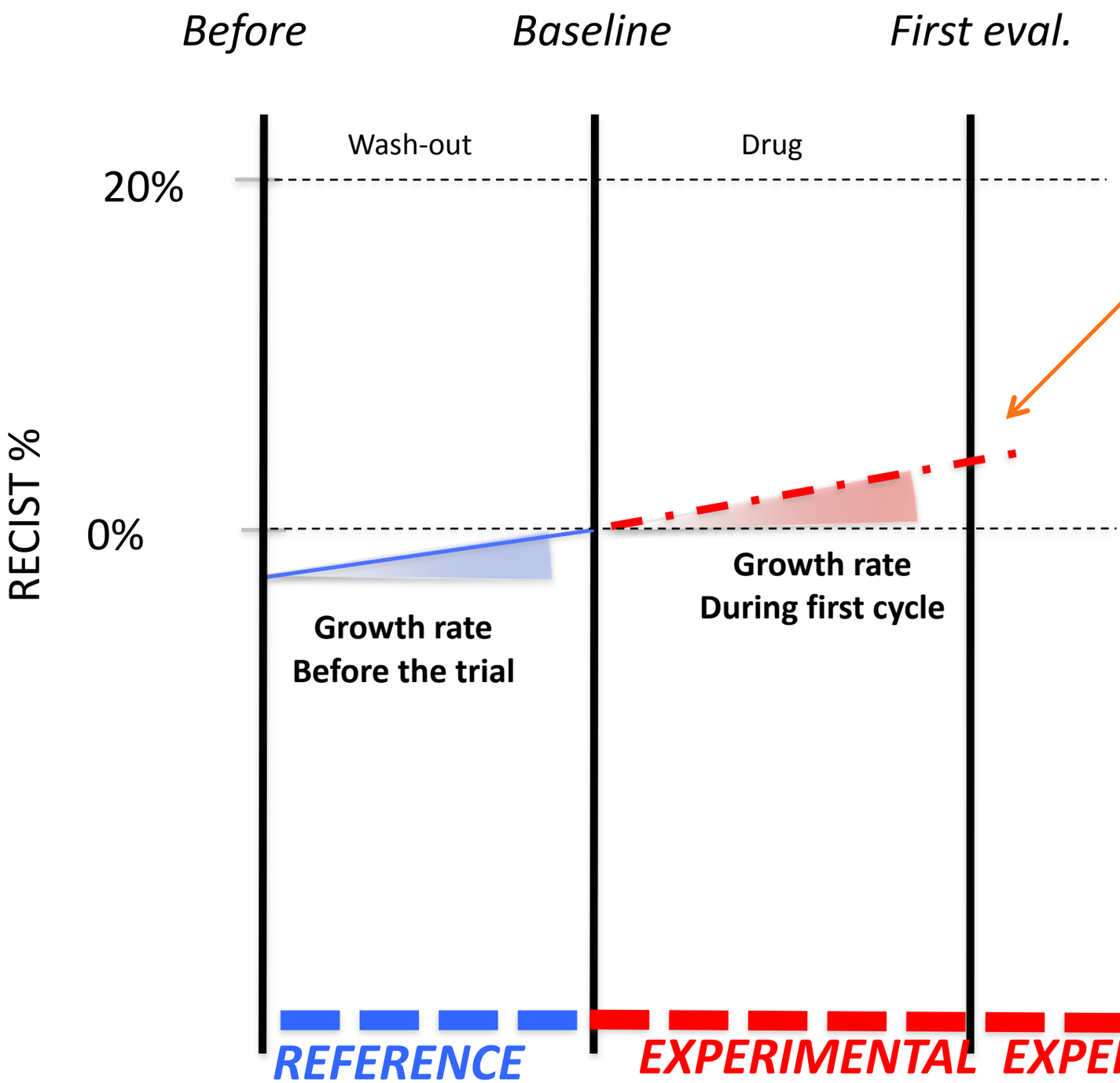
Evidence of "Treatment activity"

DECREASE in Tumor Growth Rate but RECIST >20%

→ Risk of discarding the patient of the trial for progressive disease, while there are signs of drug antitumor activity.

→ Risk of stopping the development of a potential active drug

Hypothetical case #2 of a slow-growing tumor treated by an inactive drug



No evidence of Treatment effect

Stability of the tumor kinetics and Stable Disease (as per RECIST)

→ Risk of assuming that the drug is benefiting to the patient, whereas there is a stability in the tumor growth kinetics without drug efficacy.

→Risk of retaining the patient retained in the trial with evident Safety, ethical, cost issues

Tumor Growth Rate (TGR)

- Tumor size (D) was defined as the sum of the largest diameters (RECIST sums).
- Let t be the time between each tumor evaluation.
- Tumor volume (V) was approximated by $V = 4 \prod R^3 /3$, where R= D/2.

$$TGR = dV / dt$$

$$= \ln(V_t/V_0) / dt$$

(assuming the tumor growth follows an exponential growth)

- TGR is expressed as an increase in tumor volume during 1 month.

applications in oncology

- molecular targeted agents

209 ph 1 pts
treated by MTA not
IO agents

136 + 902 ph 3 pts
treated by MTA not
IO agents

- immune checkpoints blockers (i.e. IO agents)

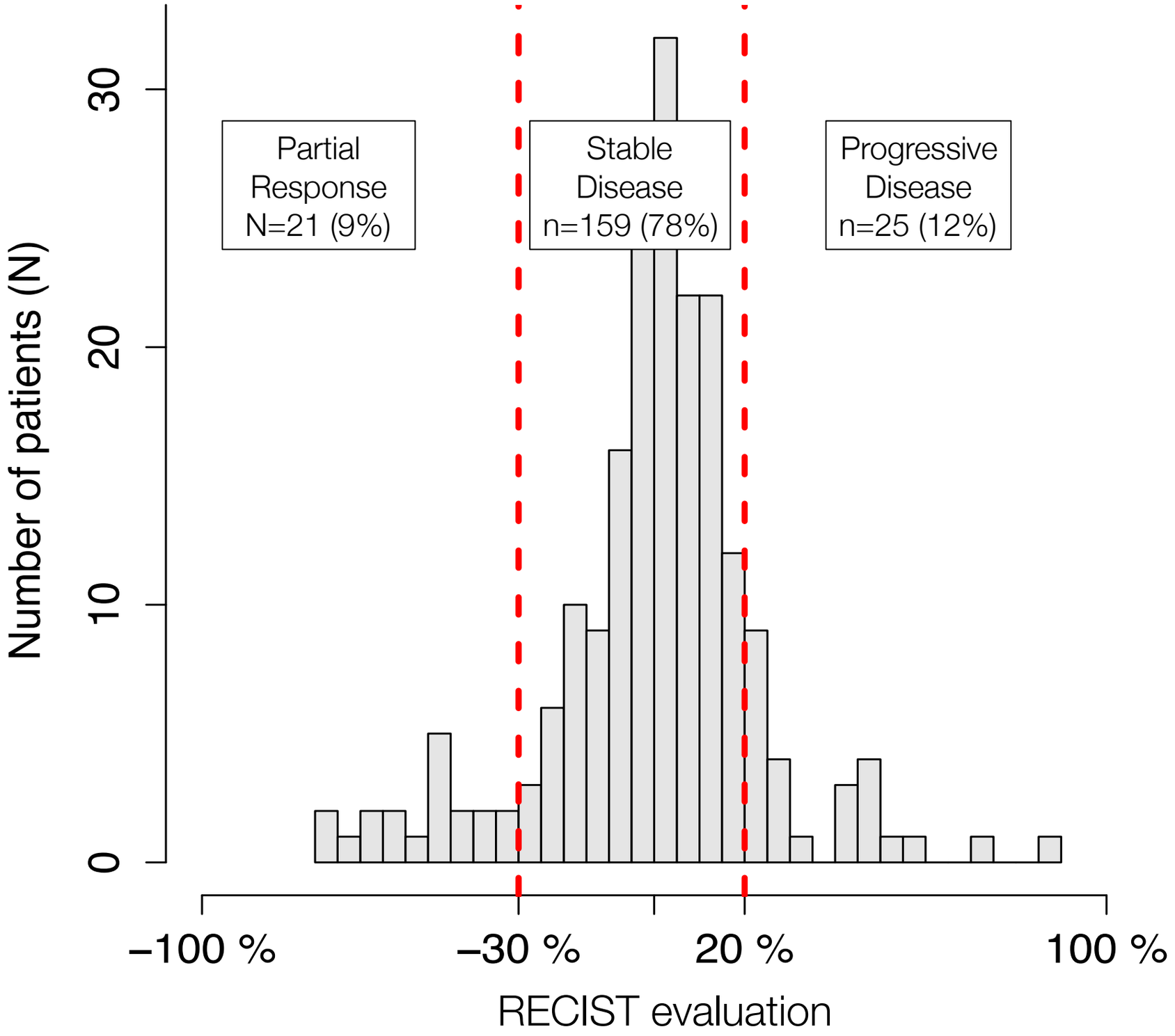
112 pts
treated by IO agents
not MTA agents

205 pts enrolled in 19 phase I trials at Gustave Roussy

- To describe the variation of TGR along the introduction of experimental therapeutics in phase I patients.
- To compute the associations between TGR, the most commonly used prognostic score (RMH) and the outcome.
- To evaluate the effect of treatment, prognostic scores, histology, and the number of previous treatment lines on TGR.

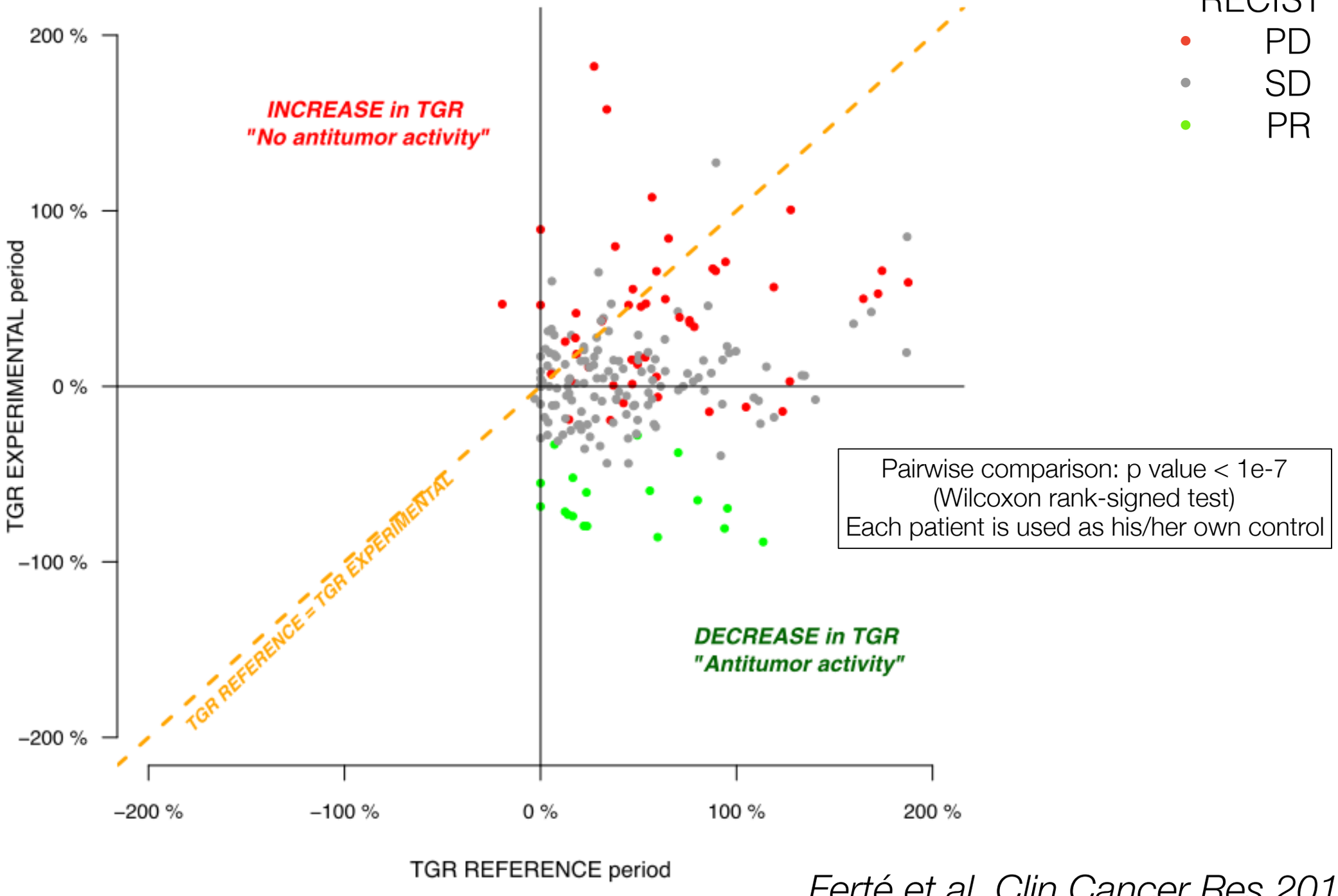
Ferté et al, Clin Cancer Res 2013

At the first evaluation, 78% of patients are classified as Stable Disease



Ferté et al, Clin Cancer Res 2013

At the first evaluation, 77% of patients (158 out of 205 pts) exhibit a decrease of TGR



Ferté et al, Clin Cancer Res 2013

Distribution of the RECIST score according to the variation of TGR

	Decrease of TGR	Increase of TGR	Total
Partial Response (PR)	19	0	19
Stable Disease (SD)	106	24	130
Progressive Disease (PD)	34	18	52
Total	159	42	201

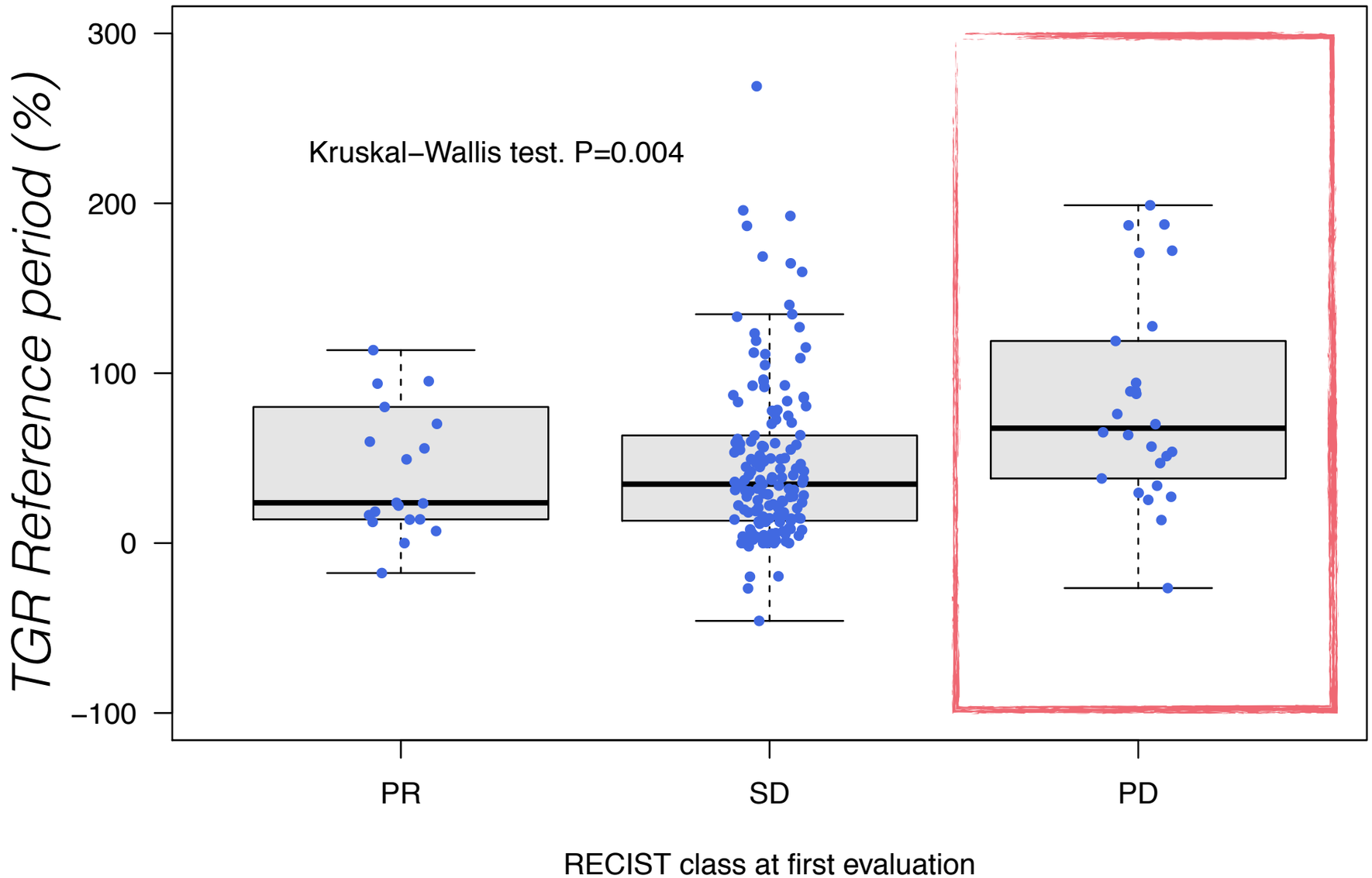
→ Most patients are classified as SD, which is NOT informative

→ “mis-identification” 140 out of 159 pts (88%) that exhibit a decrease of TGR

→ “mis-identification” 24 out of 42 pts (57%) that exhibit an increase of TGR

Higher TGR during reference period is associated with progression in patients treated by MTA

209 pts
treated by MTA
not IO agents



For MTA agents:

- **fast growing tumors before treatment are more prone to be progressive at the first evaluation**
- **integrating pre-treatment kinetics is relevant**

What about the occurrence of ‘new lesions’ ?

→ TGR is based on the sum of the RECIST diameters and thus has the same limitations than RECIST on ‘new lesions’. Similarly to RECIST, TGR does not capture new lesions.

→TGR provides information on the antitumor activity on the target lesions.

→New lesions observed at 1st evaluation are probably micro metastases already present before the treatment onset and may be driven by different biological state (i.e epithelial mesenchymal transition)

TGR decrease (REFERENCE - EXPERIMENTAL) is associated with PFS (multivariate analysis)

	Progression-free survival		Overall survival	
	hazard ratio 95% CI	P Value	hazard ratio 95% CI	P Value
Decrease of Tumor Growth Rate*	0.91 0.85 - 0.96	0.004	0.95 0.88 - 1.04	0.27
RMH prognostic score low score (0-1) vs. high score (2-3)	1.42 0.96 - 2.08	0.08	2.53 1.47- 4.34	0.0008

→ Every 10% decrease between TGR REFRENCE and TGR EXPERIMENTAL results in a 8% decrease in the progression hazard.

→The fact that the decrease in TGR is associated with PFS but not with OS suggests the prominent influence of the experimental regimen of the TGR.

Ferté et al, Clin Cancer Res 2013

The experimental regimen is the only variable independently associated with the decrease of TGR

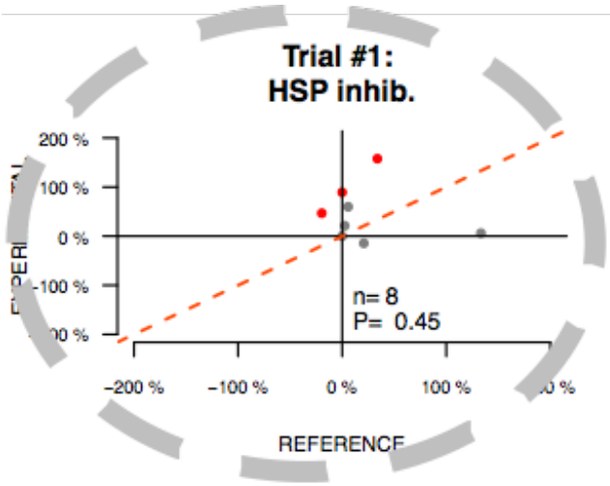
Variable	Coefficient (estimate)	Significance (P Value)	proportion of variance explained (R^2)
Trial (Overall variable)	-	<0.00001	31.1 %
Intercept (reference)	-0.46	0.79	
Trial #2: HSP inhib.	-2.36	0.07	
Trial #3: Cell-Cycle inhib.	1.42	0.24	
Trial #4: PI3K/Akt/mTOR inhib.	-2.49	0.07	
Trial #5: Antiangiogenic	2.89	0.05	
Trial #6: HDAC inhib.	2.13	0.04	
Trial #7: PI3K/Akt/mTOR inhib.	4.20	0.001	
Trial #8: MEK inhib.	5.36	0.0002	
Trial #9: Antiangiogenic	4.65	0.0001	
Trial #10: HER family inhibitor	3.30	0.003	
Trial #11: Antiangiogenic	4.35	0.00005	
Trial #12: PI3K/Akt/mTOR inhib.	4.95	0.00001	
Number of previous lines of chemotherapy (N)	0.04	0.82	0.01 %
RMH prognostic score low score (0-1) vs.high score(2-3)	0.04	0.95	0.02 %
Age (N)	-0.009	0.67	0.08 %

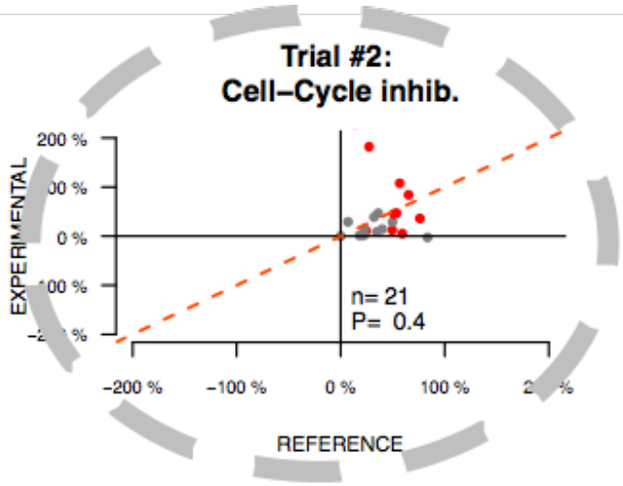
NB: No interaction was observed between the variables trial type, previous lines of chemotherapy, age and RMH (ANOVA, data not shown)

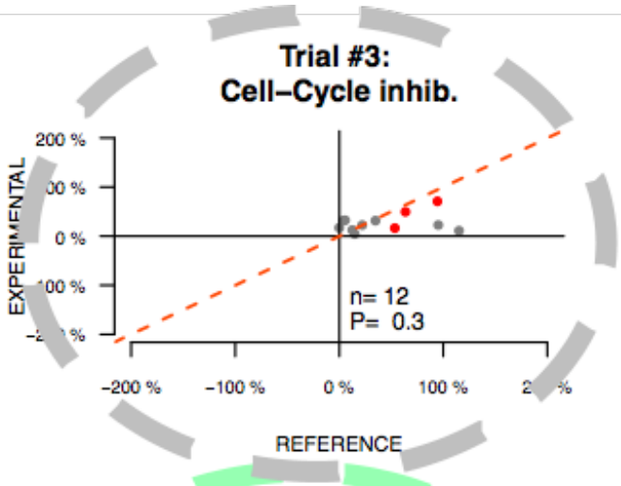
Ferté et al, Clin Cancer Res 2013

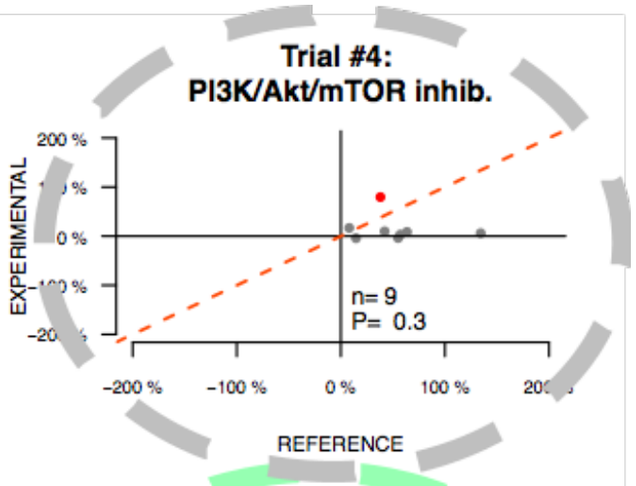
TGR profiling reveals trial specific patterns of drug activity

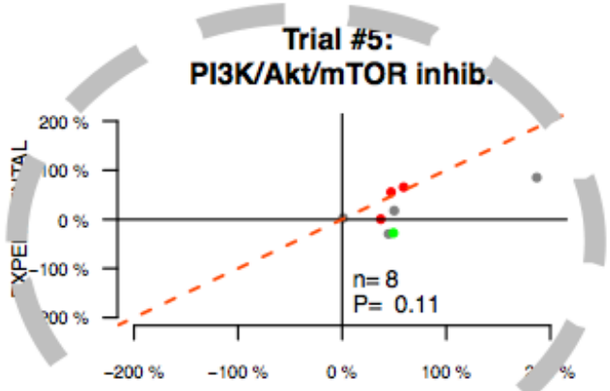
(green circles = trials with evidence of antitumor activity)

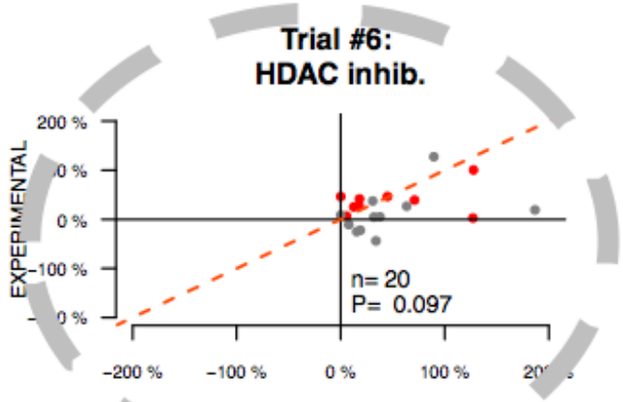


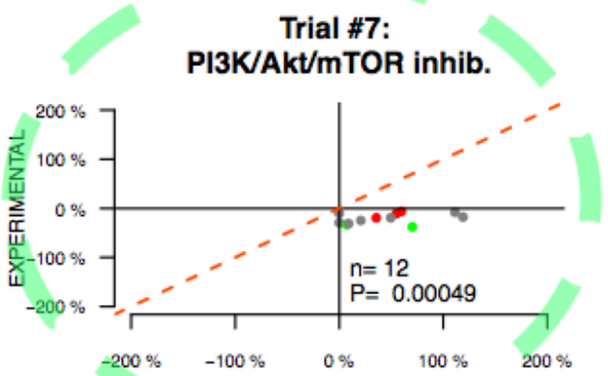


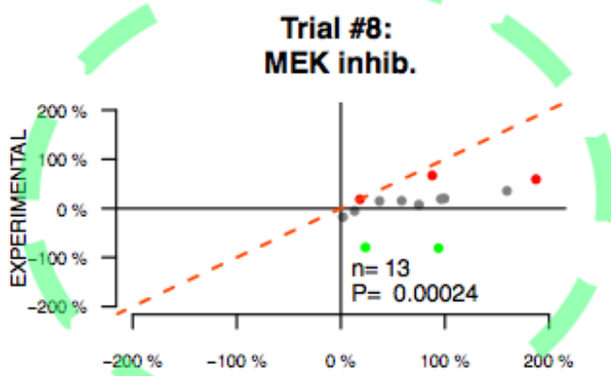


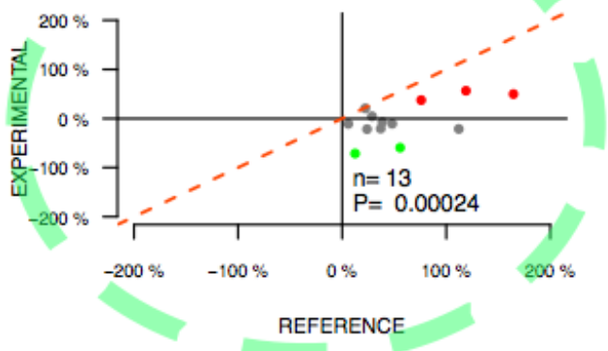


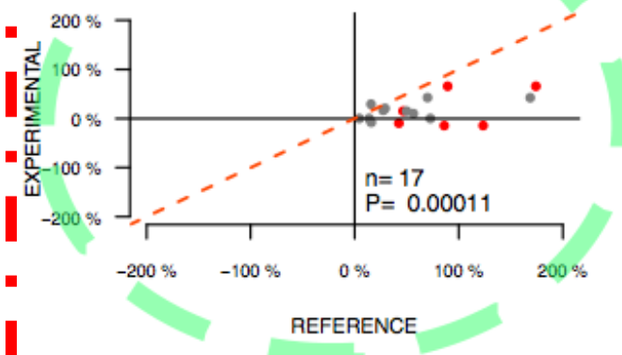


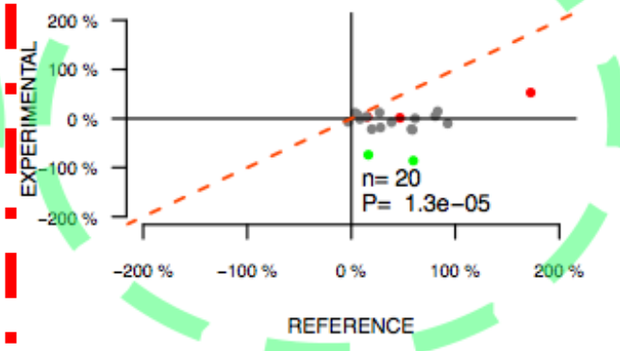


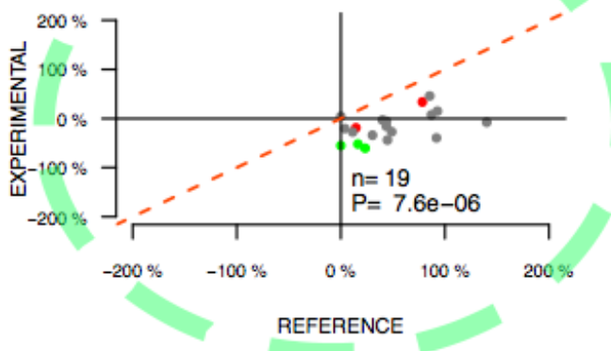












Terminated development
for lack of activity

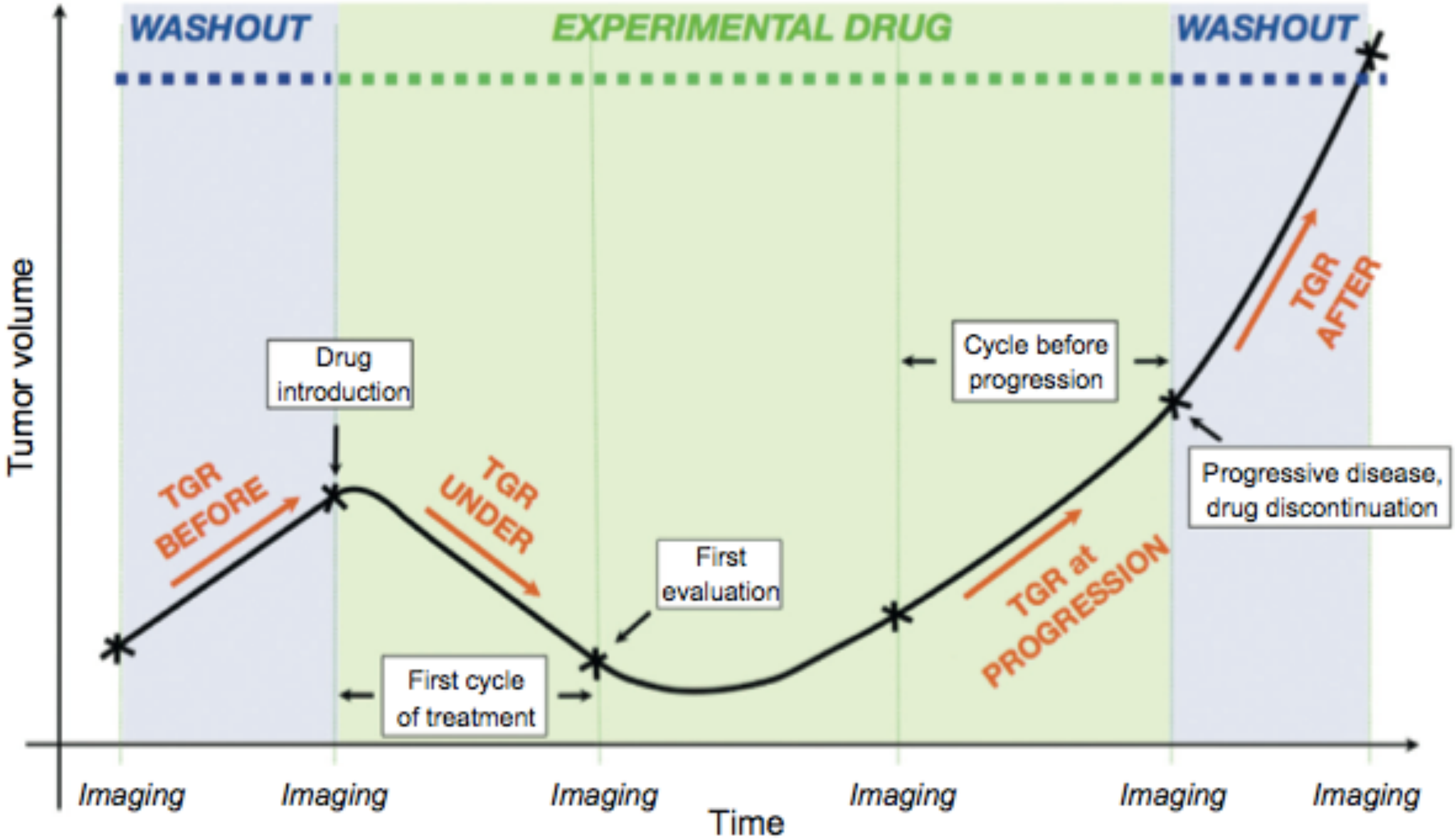
P values computed from pairwise wilcoxon signed-rank tests.
Only trials with n>8 pts were analyzed.

Ferté et al, Clin Cancer Res 2013

what about patients not treated in phase 1 trials ?

136 + 902 ph 3 pts treated by MTA not IO agents

Expand to specific treatment periods (pairwise comparisons)



Ferté et al, Eur Urol 2013

Tumor Growth Rate Provides Useful Information to Evaluate Sorafenib and Everolimus Treatment in Metastatic Renal Cell Carcinoma Patients: An Integrated Analysis of the TARGET and RECORD Phase 3 Trial Data.

TARGET phase III trial: Sorafenib vs. placebo

- IGR pts n=84 pts
- entire TARGET cohort n=902 pts

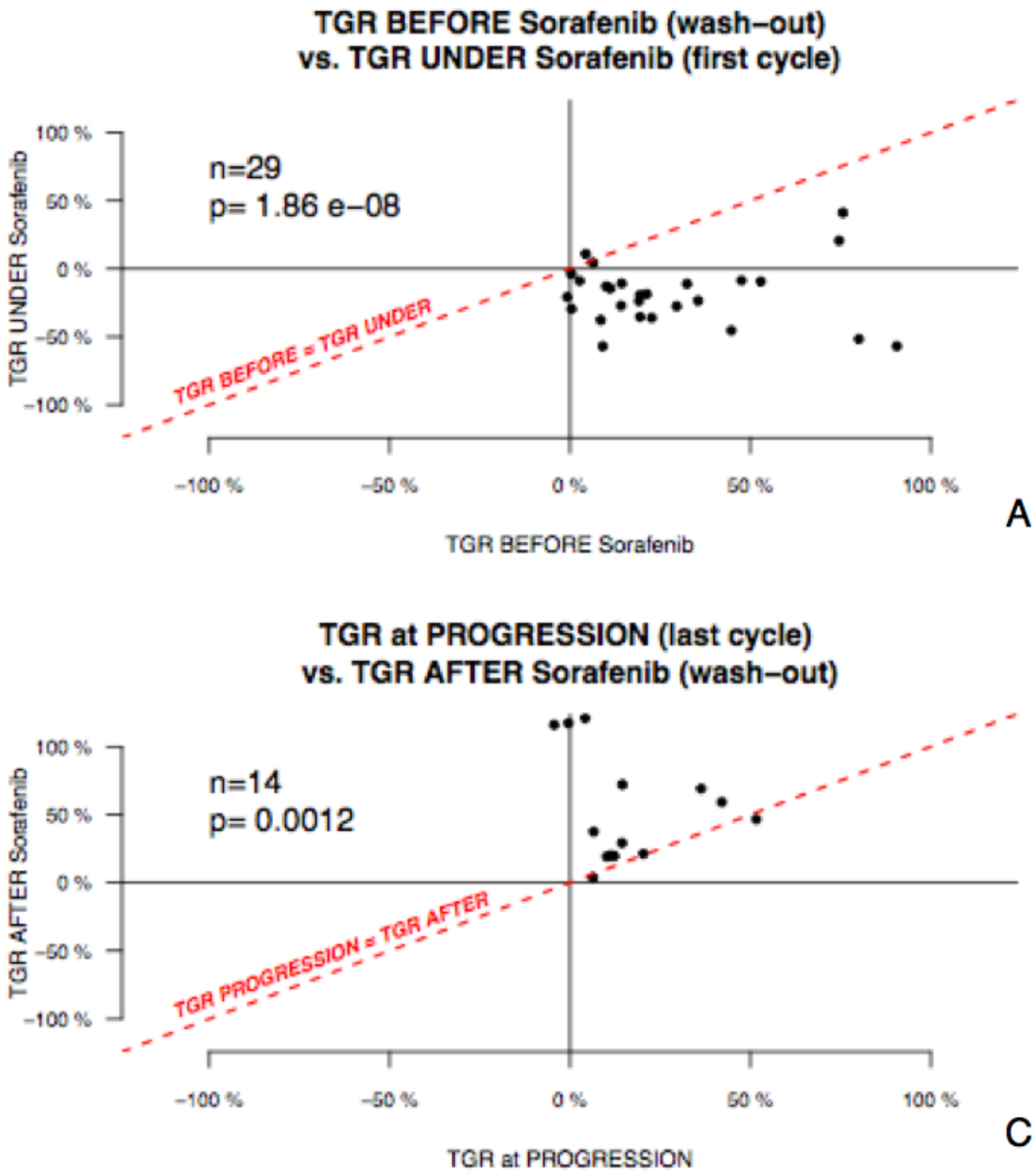
RECORD-1 phase III trial: Everolimus vs placebo

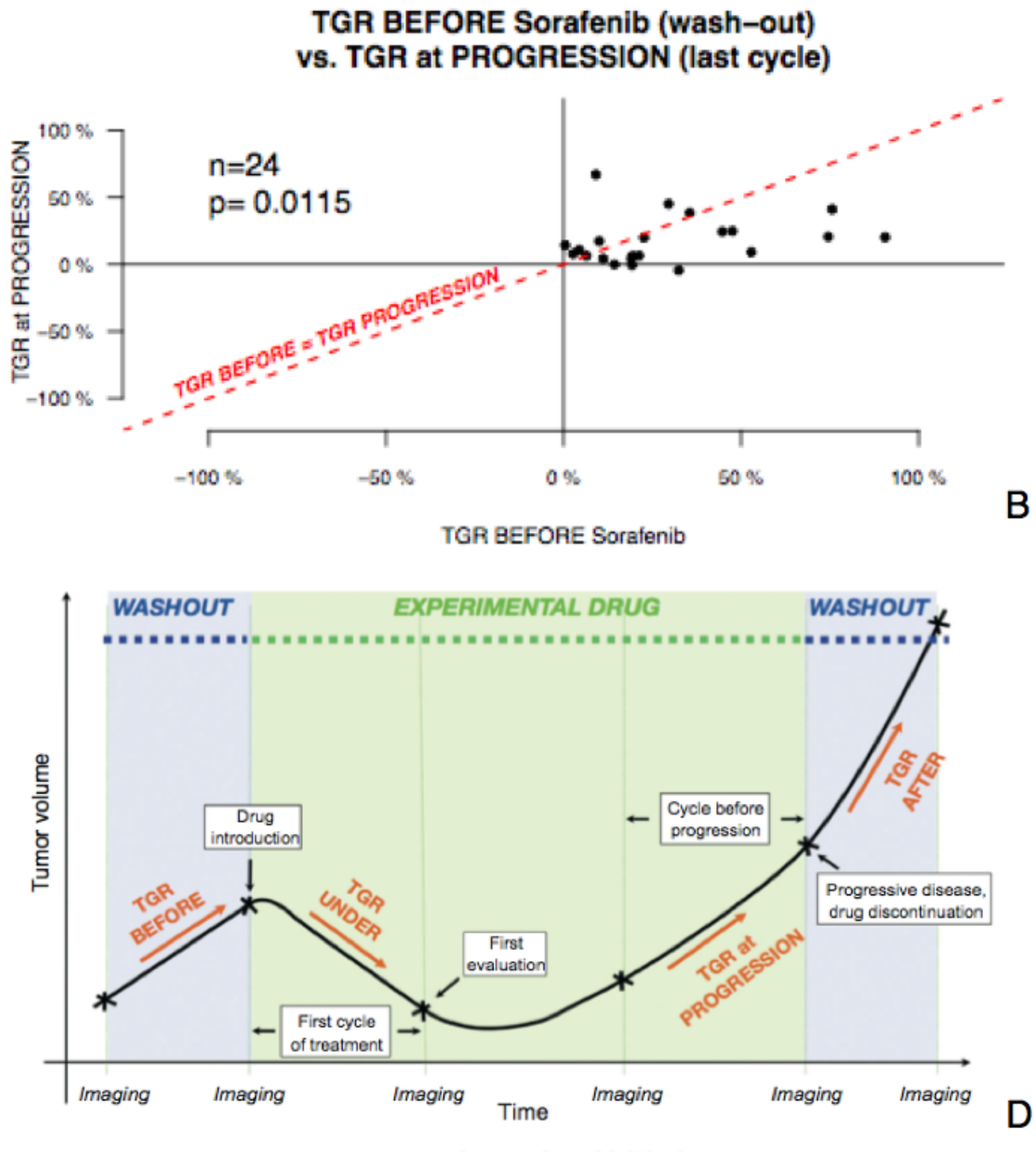
- IGR pts n=52 pts

Ferté et al, Eur Urol 2013

Pairwise comparisons of TGR in pts enrolled in the TARGET trial (sorafenib vs. placebo)

136 + 902 ph 3 pts treated by MTA not IO agents

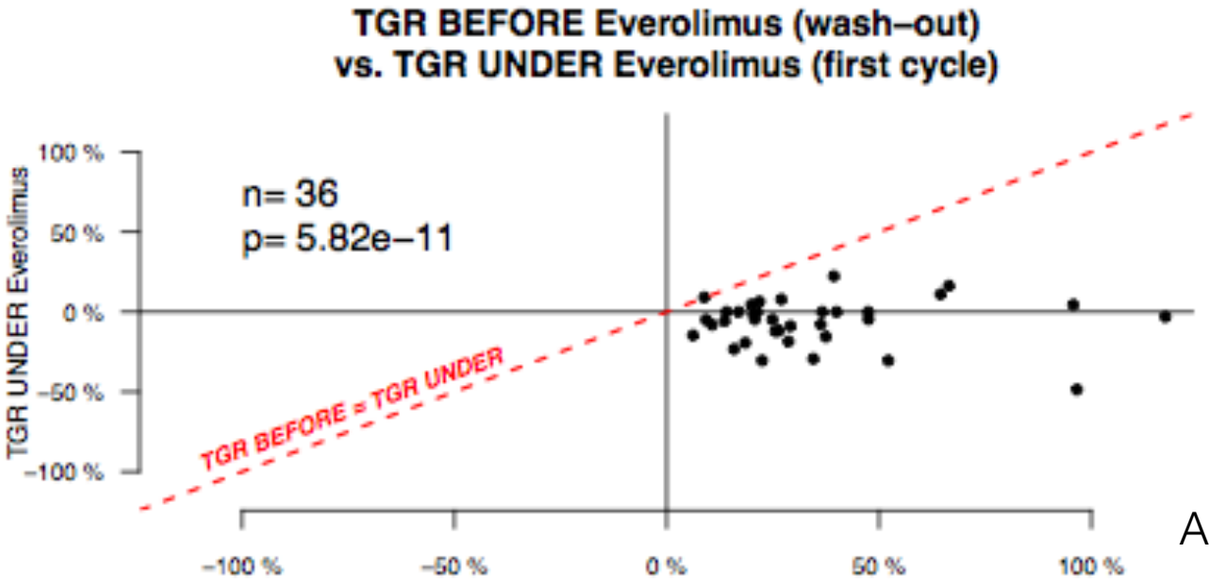




Ferté et al, Eur Urol 2013

Pairwise comparisons of TGR in pts enrolled in the RECORD-1 trial (everolimus vs. placebo)

136 + 902 ph 3 pts treated by MTA not IO agents



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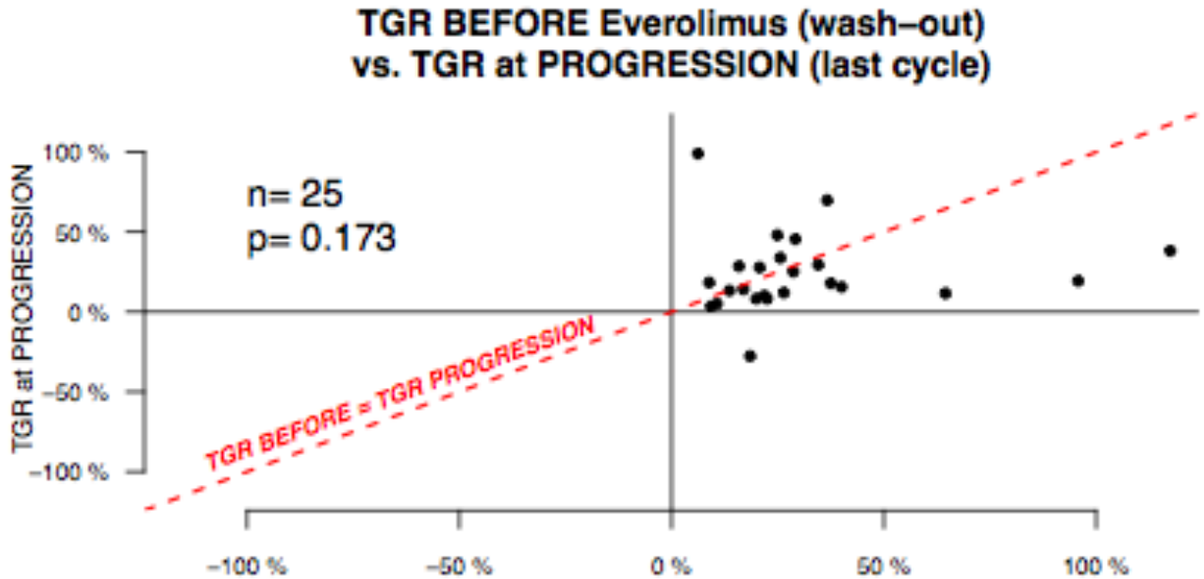

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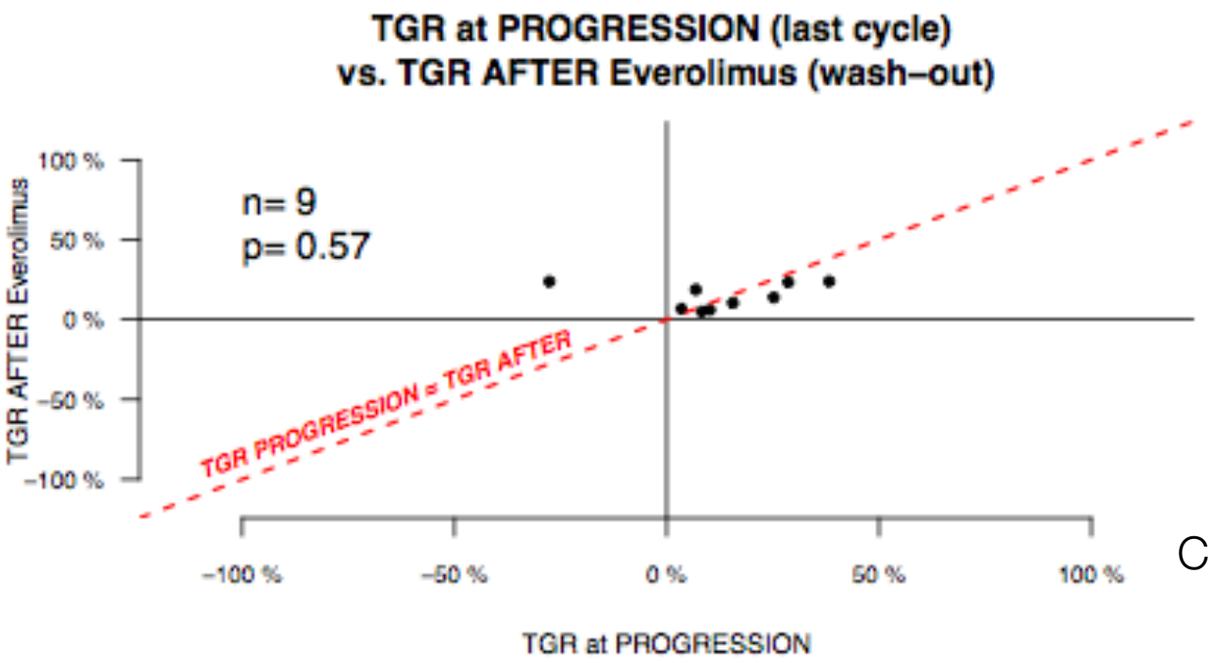

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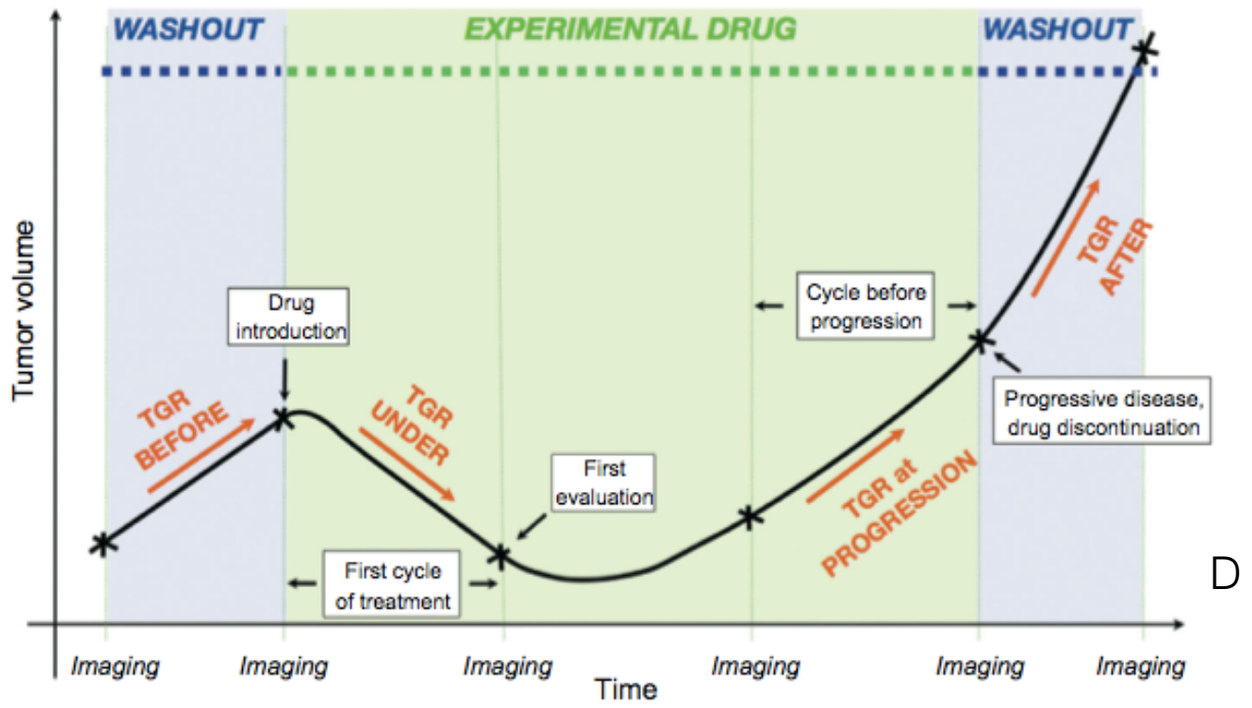


D

Ferté et al, Eur Urol 2013

what about immune checkpoint blockers ?

pseudoprogression under immune checkpoint blockers

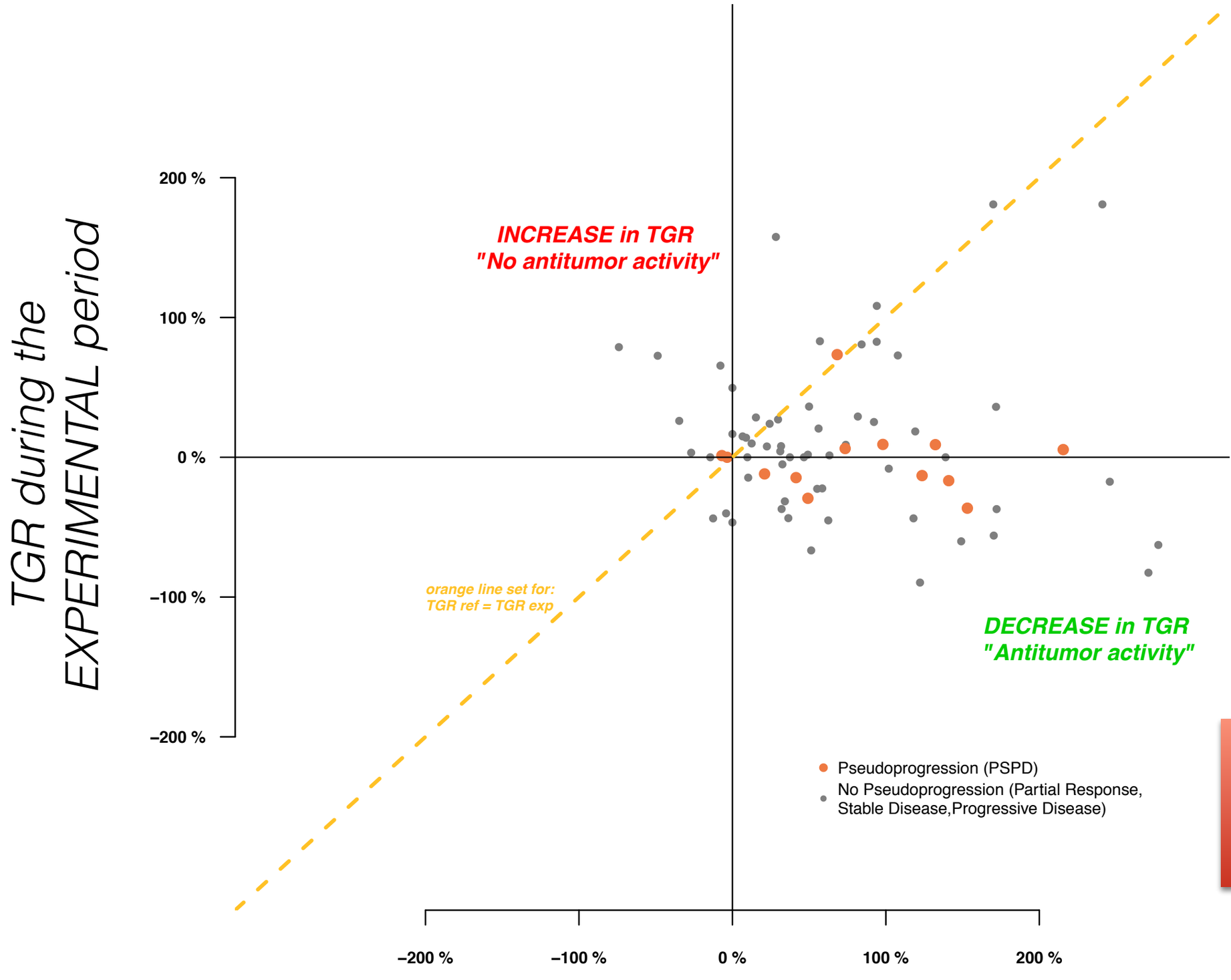
stable disease or partial response
after two consecutive observations per irRC

AND

who exhibited tumor progression
at the first evaluation (RECIST)

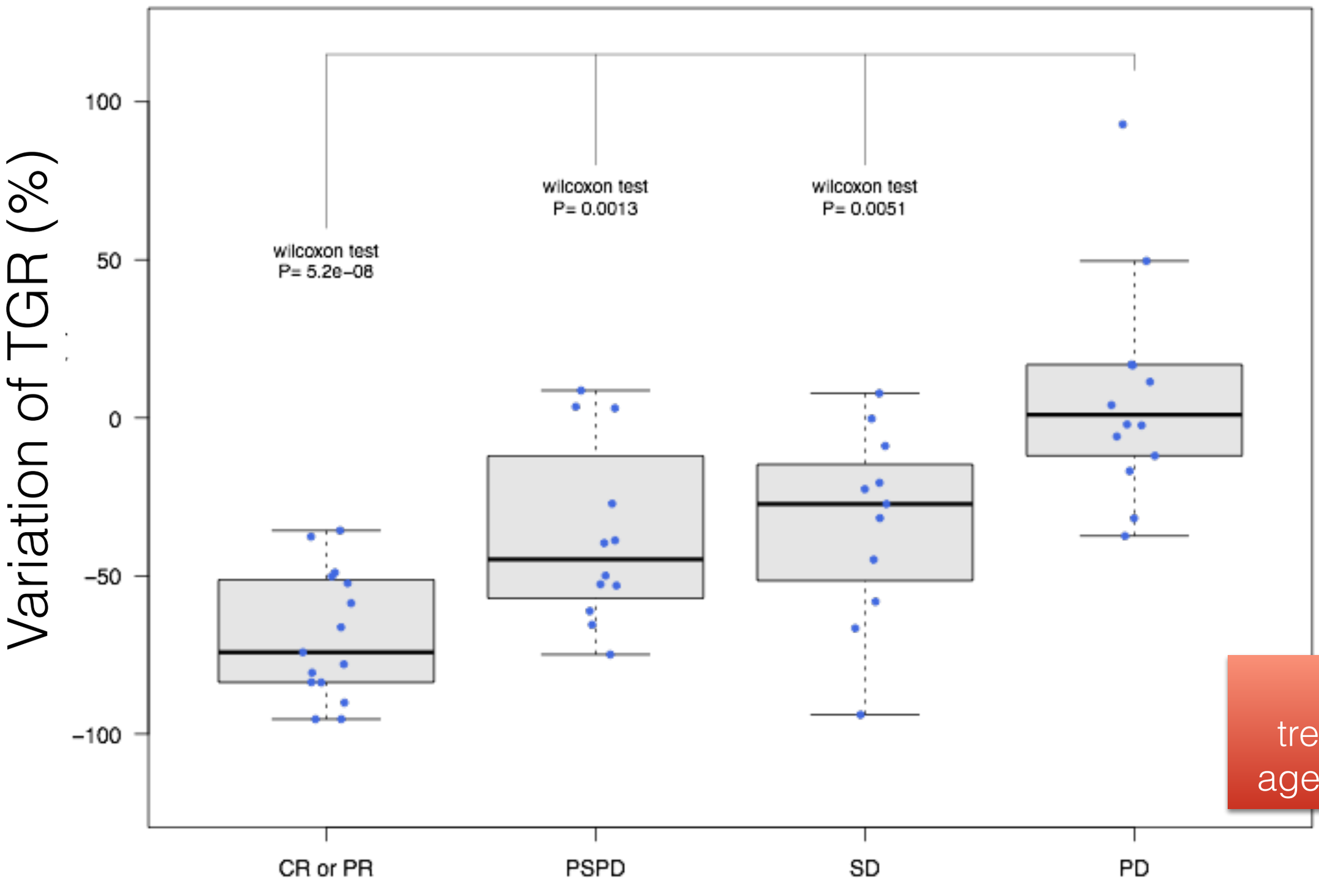
112 pts
treated by IO
agents not MTA

Most of PSPD patients exhibit a decrease of TGR between REFERENCE and EXPERIMENTAL periods



112 pts treated by IO agents not MTA

Variation of TGR between REFERENCE and EXPERIMENTAL periods



112 pts
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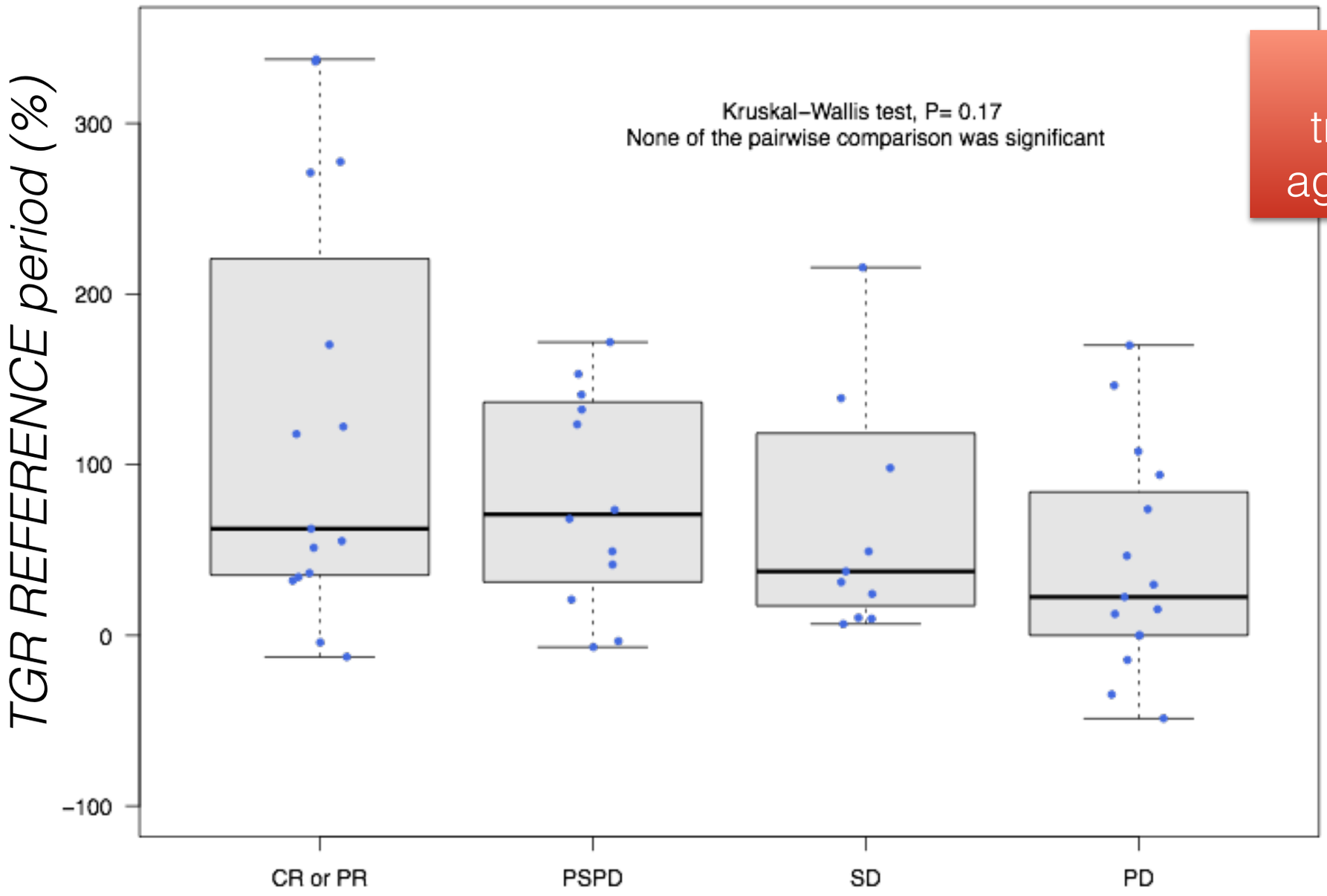
pre-treament TGR : not informative !

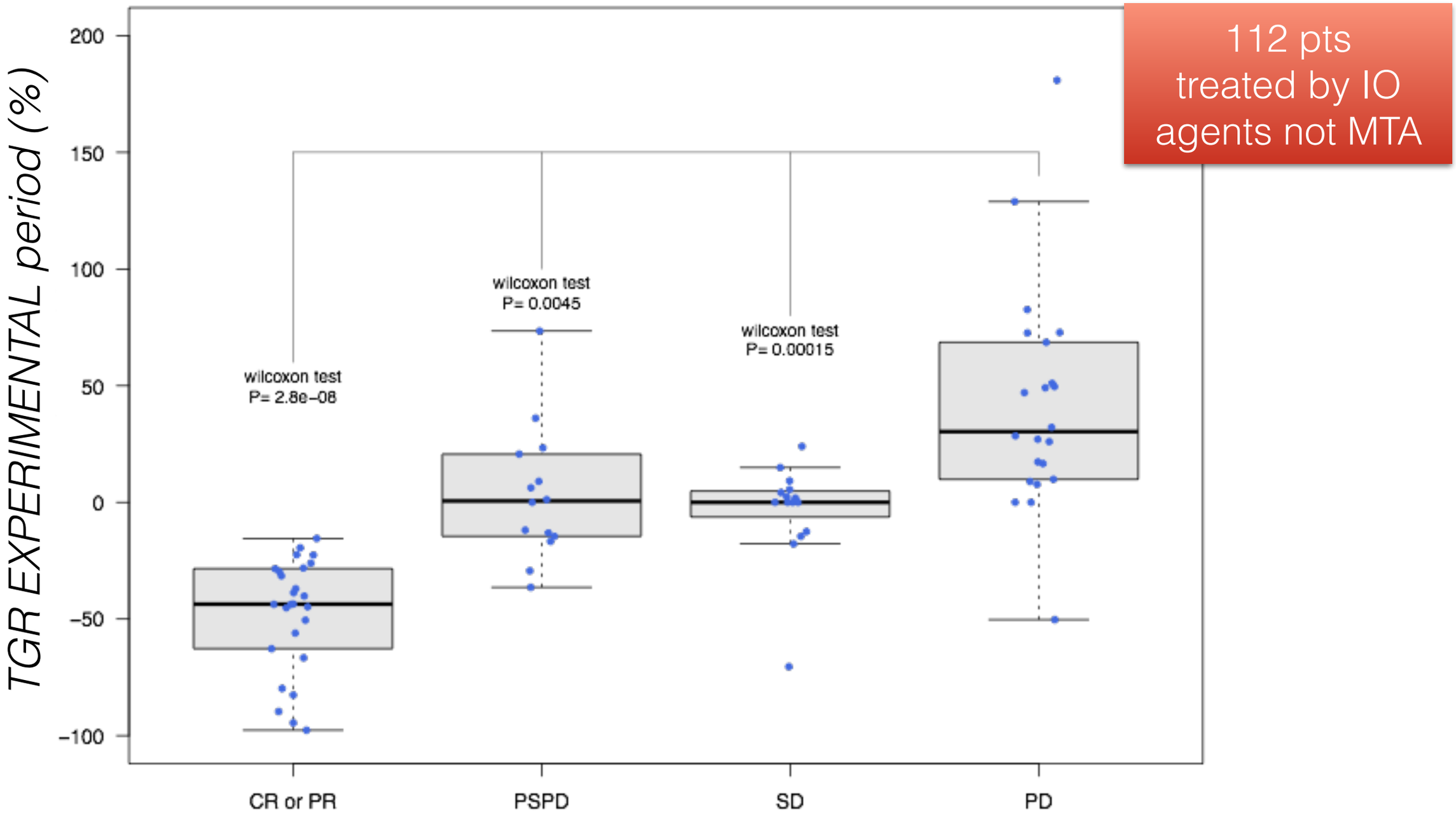


112 pts
treated by IO
agents not MTA

Different results from those observed with molecular targeted agents (Ferté et al, CCR 2014):

- is it related to the mechanism of action of immune checkpoint blockers ?
- is the TGR during the EXPERIMENTAL period responsible for the variation of TGR ?

TGR on treatment: informative !



112 pts treated by IO agents not MTA

NB: target lesions only

Conclusions

- For MTA agents only:

  - The variation of TGR (REFERENCE to EXPERIMENTAL periods) allows to early infer the therapeutic activity of drugs.

  - Higher TGR during the REFERENCE period is associated with higher risk of tumor progression.

- For Immune checkpoint inhibitors only, it seems that:

  - The TGR during the EXPERIMENTAL period only allows to early identify therapeutic activity of these drugs

  - The occurrence new lesions of new lesions at fist eval do not automatically mean absence of therapeutic activity of the drug.

Confirmatory studies are warranted

discussion

- Monitoring tumor kinetics along the treatment sequence is critical whatever the treatment type

- Tumor kinetics to provide insights of expected benefit of phase II-II (rather than predict survival)