Sciences Economiques et Sociales de la Santé
& Traitement de l'Information Médicale

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Paradigmes statistiques pour les essais cliniques moléculaires et l'analyse des biomarqueurs prédictifs en oncologie

mai 2019

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Paradigmes statistiques pour le design d'essais cliniques moléculaires et l'analyse des biomarqueurs prédictifs en oncologie

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Many types of biomarker-based trials already in 2011-13

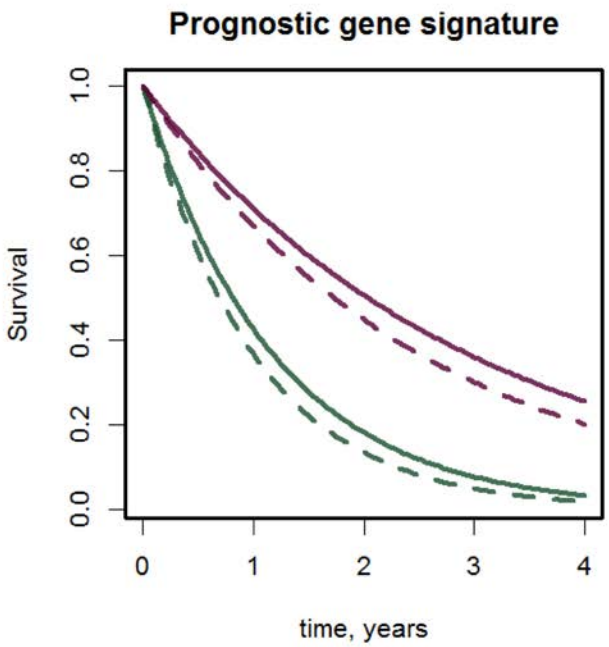
Table 2. Trial designs using biomarkers.

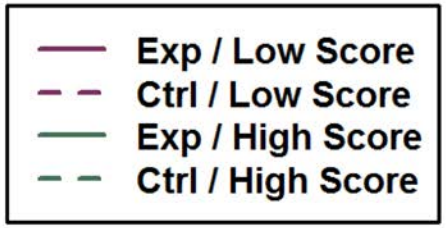
Trial phase	Treatment	Biomarker type	Validated biomarker	Trial design	Examples
	Standard	Prognostic	No	Retrospective series	MammaPrint™ in early breast cancer Oncotype DX® in early breast cancer
	Standard	Predictive	No	Retrospective analyses of randomized trials	Oncotype DX in early breast cancer (SWOG-8814) *KRAS* mutations in advanced colorectal cancer (CRYSTAL) *EGFR* mutations in non-small-cell lung cancer (IPASS)
III	Standard	Prognostic	No	Clinical utility	MINDACT in early breast cancer TAILORx in early breast cancer
III	Standard	Predictive	No	Randomize-all Interaction Biomarker strategy	MARVEL in non-small-cell lung cancer P53 in advanced breast cancer ERCC1 in non-small-cell lung cancer
II	Experimental	Predictive	Yes	Targeted Bayesian	Herceptin in advanced breast cancer BATTLE in non-small-cell lung cancer I-SPY 2 in advanced breast cancer
III	Experimental	Predictive	Yes	Targeted	PETACC-8 in advanced colorectal cancer TOGA in advanced gastric cancer
II	Experimental	Predictive	No	Adaptive parallel Tandem two-step TTP ratio	Dovitinib in HER2-negative advanced breast cancer Saracatinib in pancreatic cancer Molecular profiling in various tumor types
III	Experimental	Predictive	No	Enrichment Prospective subset	IPASS in non-small-cell lung cancer SATURN in non-small-cell lung cancer

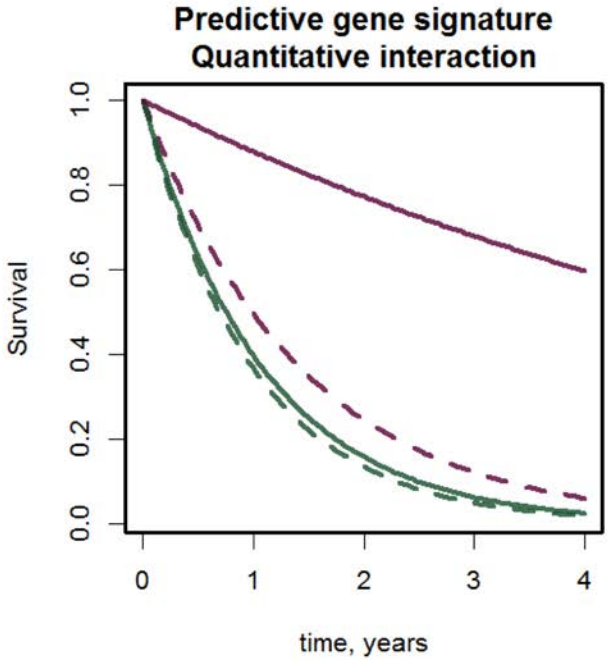
TTP: Time to progression.

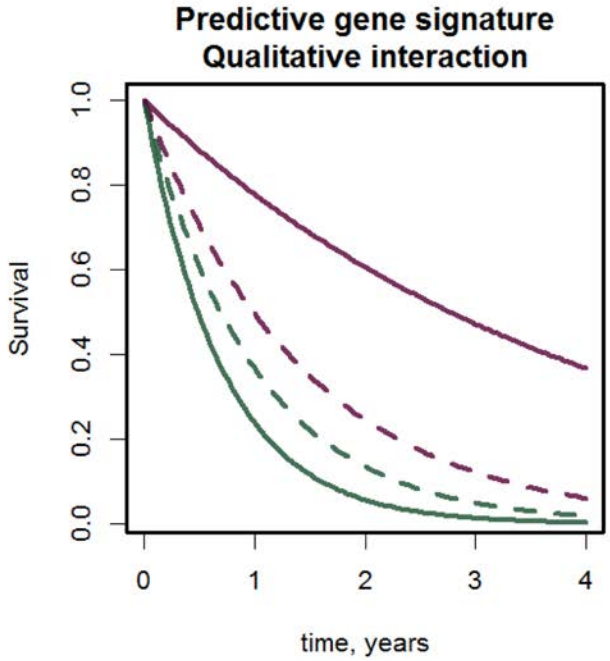
Buyse, Michiels et al, Expert Rev Mol Diag 2011; Buyse, Michiels Curr Op Oncol 2013

Prognostic vs predictive







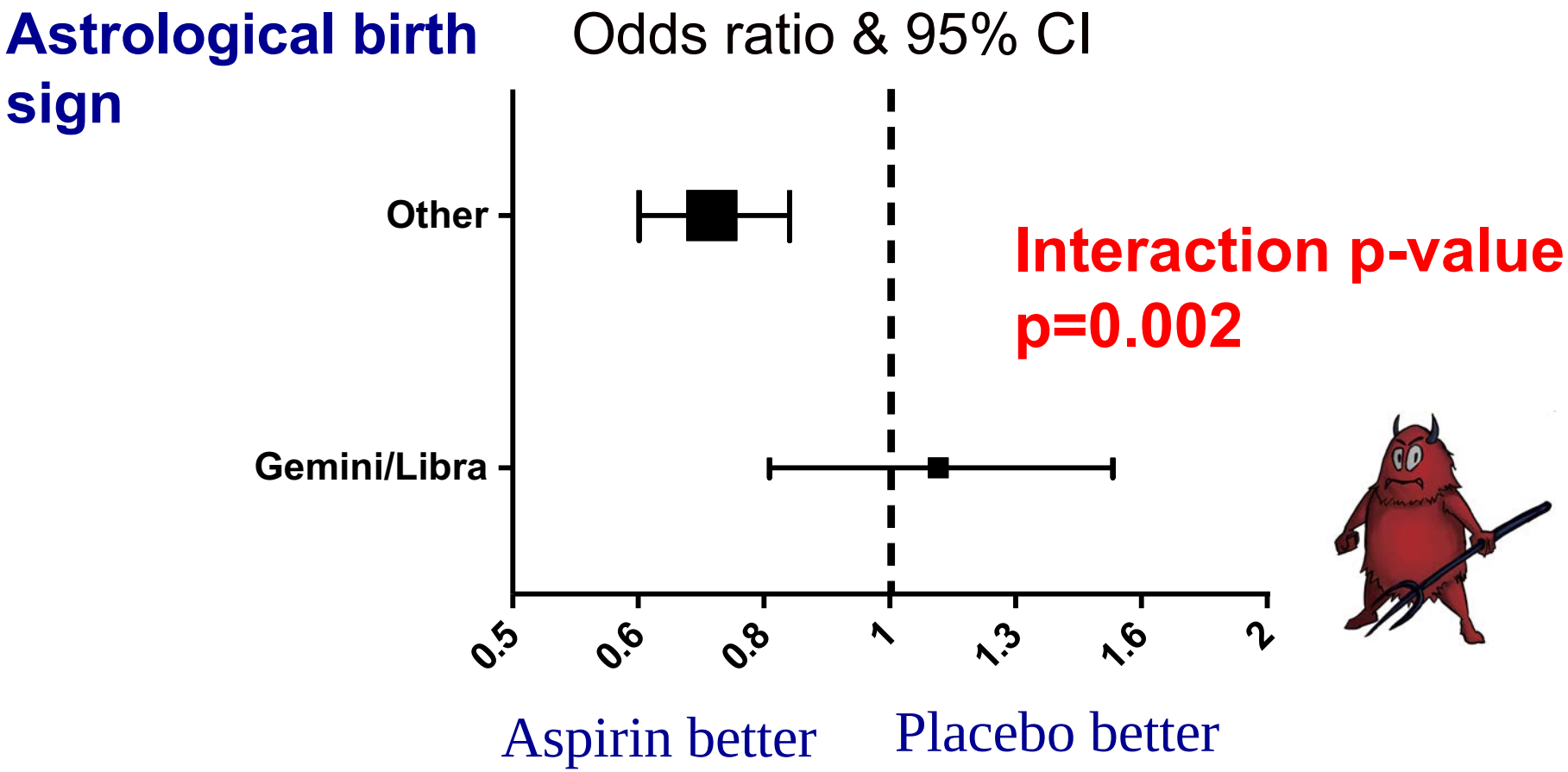


Example of survival curves in experimental (Exp) versus control (Ctrl) arms for patients with a high gene signature score (High score) versus patients with a low gene signature score (Low score) in the case of a prognostic gene signature (top left) or a predictive gene signature, with either quantitative (bottom left) or qualitative (bottom right) interaction.

Michiels Ann Onc 2016

PREDICTIVE EFFECT: INTERACTION TEST

ISIS-2: aspirin vs control - effects on vascular death in 17,187 patients with acute myocardial infarction (Peto et al, Lancet 1988)

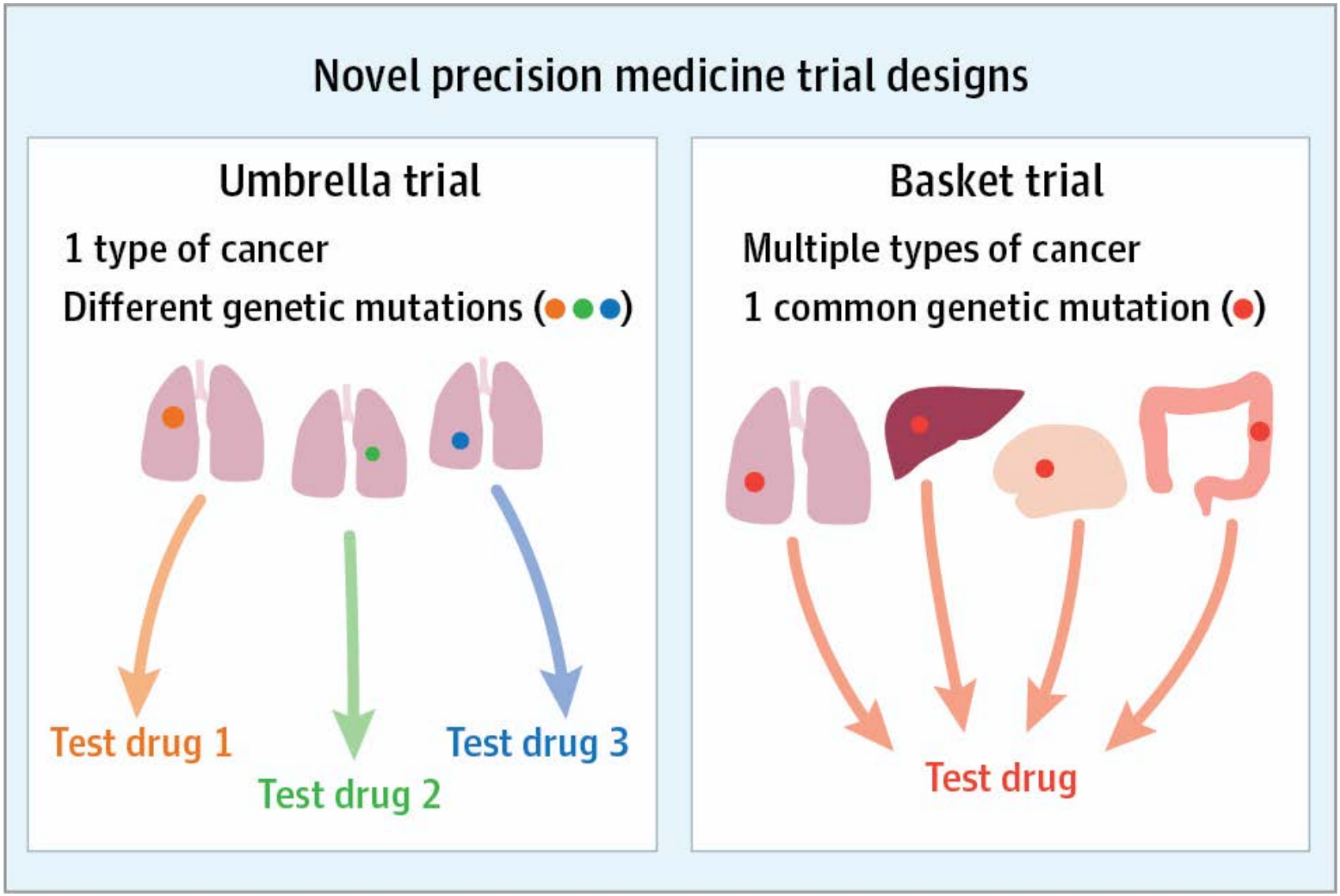


INSTITUT NATIONAL DU CANCER

Predictive biomarkers for targeted therapies' prescription

Biomarker	Cancer type	Targeted therapies	Patients nb in 2016
***KIT* mutations**	GIST	Imatinib	**1 218**
***HER2* amplification**	Breast and gastric cancers	Trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine	**10 832 (B)** **770 (G)**
***RAS* mutations**	Colorectal cancer	Panitumumab, cetuximab	**21 923**
***EGFR* mutations**	Lung cancer	Gefitinib, erlotinib, afatinib, osimertinib	**28 563**
***ALK* translocations**	Lung cancer	Crizotinib, ceritinib, alectinib	**23 434**
ROS1 translocations	Lung cancer	Crizotinib	**17 680**
***BRAF*V600 mutation**	Melanoma	Vemurafenib, dabrafenib, trametinib, cobimetinib	**5 583**
***BCR-ABL* translocation**	Chronic Myeloid Leukaemia/ Acute Lymphoblastic Leukaemia	Imatinib, nilotinib, dasatinib, ponatinib, bosutinib	**9 570**
17p deletion / *TP53* mutation	Chronic Lymphocytic Leukaemia	Ibrutinib, idelalisib	**2 857** **1 808**
***BRCA* mutation (somatic)**	Ovarian cancer	Olaparib	**1 608**

F. Nowak, French National Cancer Institute

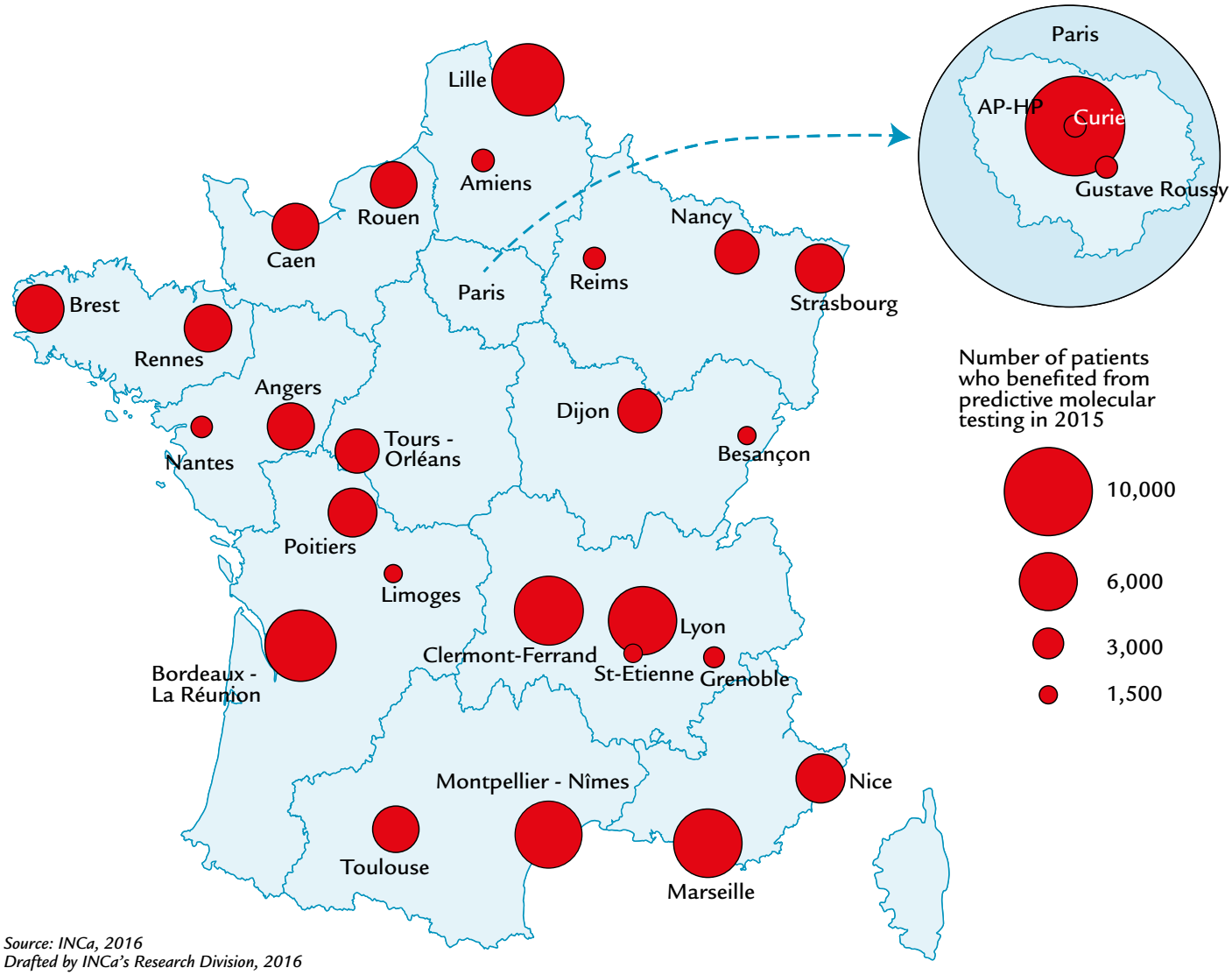


- For definitions, see also The European Society for Medical Oncology (ESMO) Precision Medicine Glossary. Ann Onc 2017

West Jama Oncol 2017

Molecular screening platforms in France funded by National Cancer Institute (INCa)

Predictive molecular testing in France in 2015: Activity of the 28 molecular genetics centres



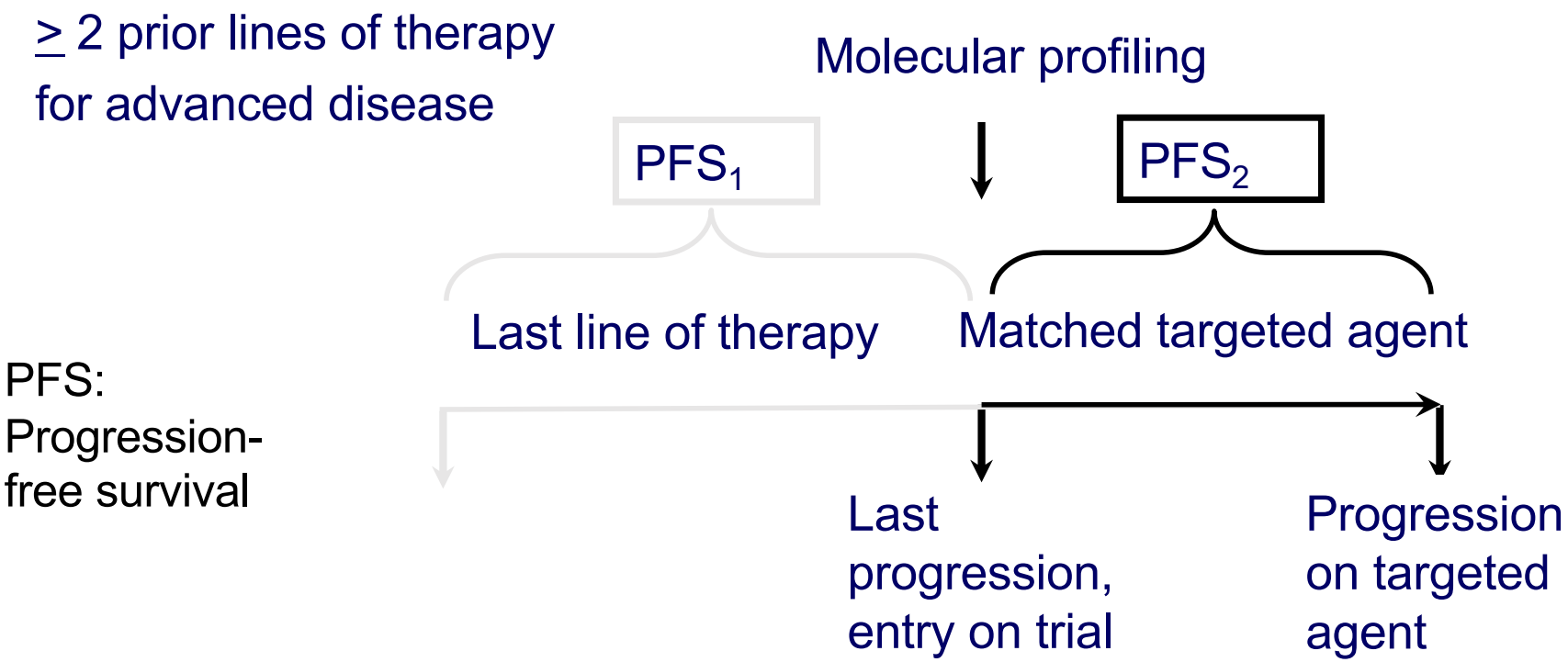
Source: INCa, 2016
Drafted by INCa's Research Division, 2016

Basket trial in France: Acsé

- Crizotinib is registered for the treatment of patients with ALK+ or ROS1+ lung cancer.
- Crizotinib targets are also altered in a wide range of malignancies in adults and children.
- To generate high evidence-based knowledge and to prevent off-label use, the French National Cancer Institute launched the AcSé Program in 2013 in an exploratory multi-basket phase II trial
- About 150 participating centers
- Frequentist / bayesian design

Clinical trial information: NCT02034981

Trial of molecular screening



- The natural history of most advanced tumors suggests that PFS2/PFS1 < 1
- Null hypothesis: ≤15% of the pts have PFS2/PFS1 > 1.3

Von Hoff, JCO 2010; Mick, Contr ClinTrials 2000

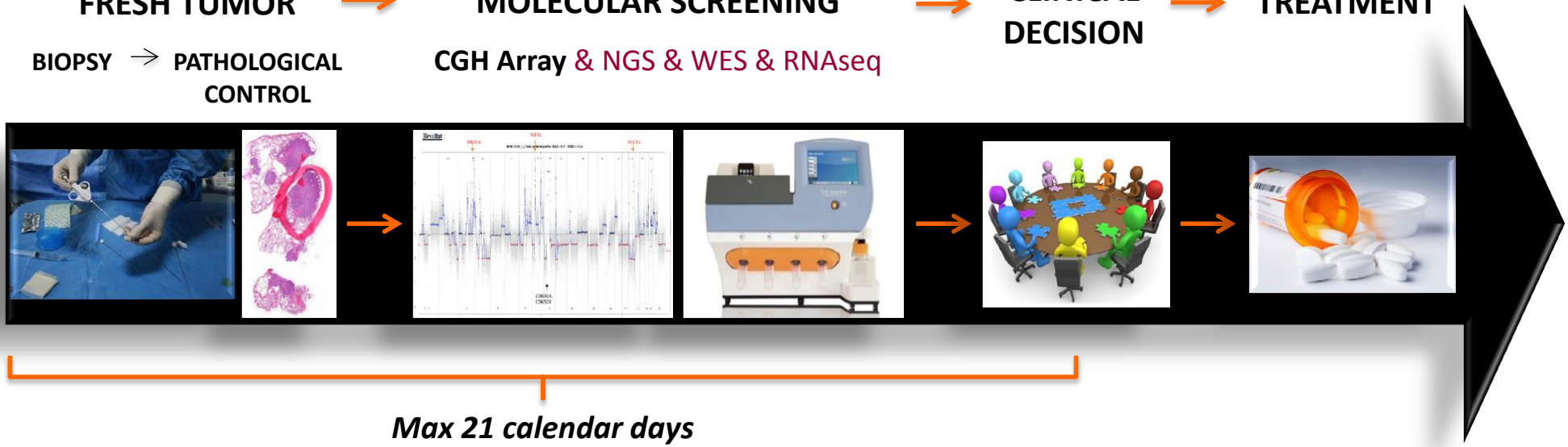
MOSCATO 01 trial:
High through-put analysis in a high volume phase I center

- **Monocentric**
- **Target accrual > 1000 patients**

FRESH TUMOR → **MOLECULAR SCREENING** → **CLINICAL DECISION** → **TREATMENT**

BIOPSY → **PATHOLOGICAL CONTROL**

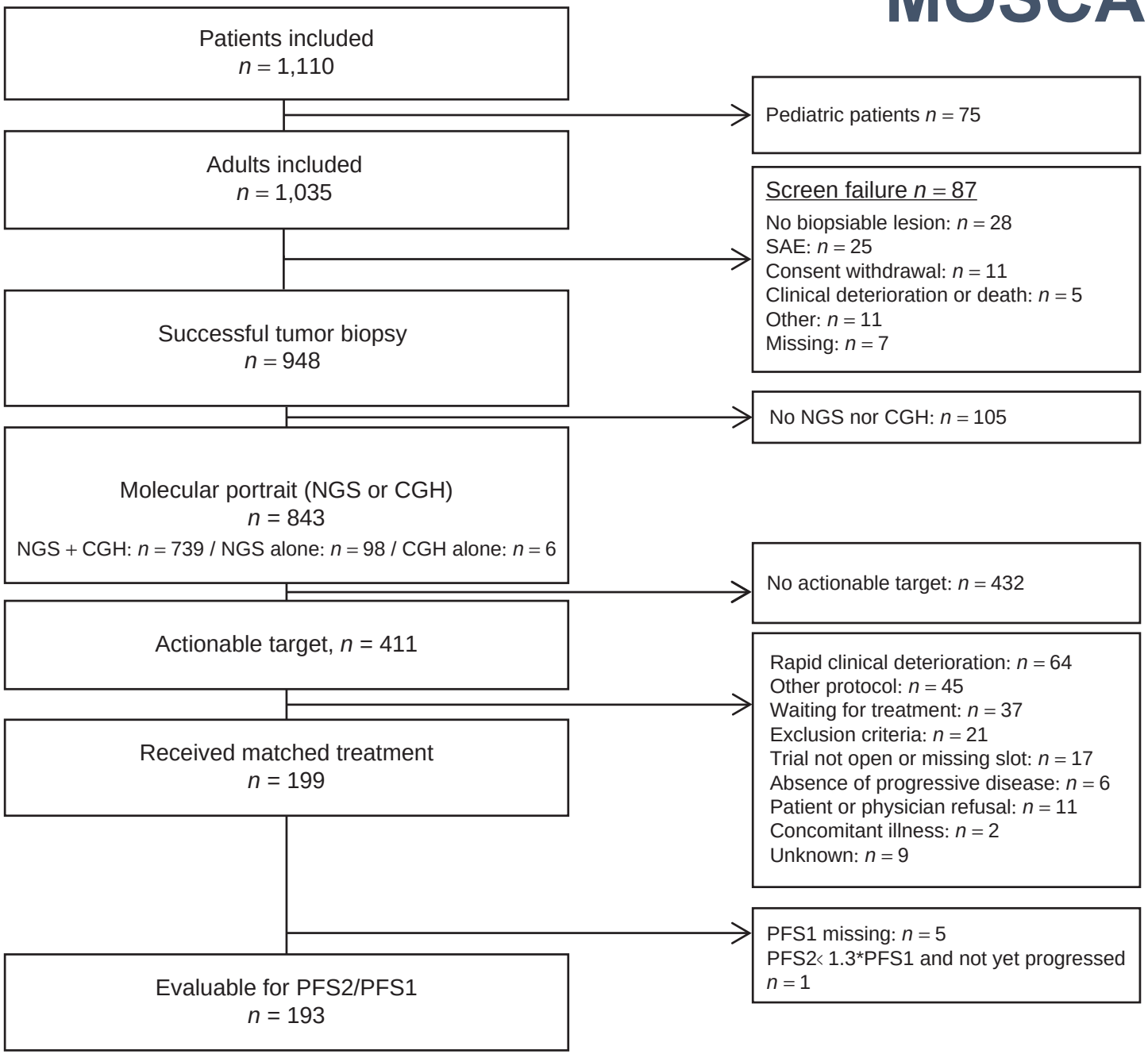
CGH Array & NGS & WES & RNAseq



Max 21 calendar days

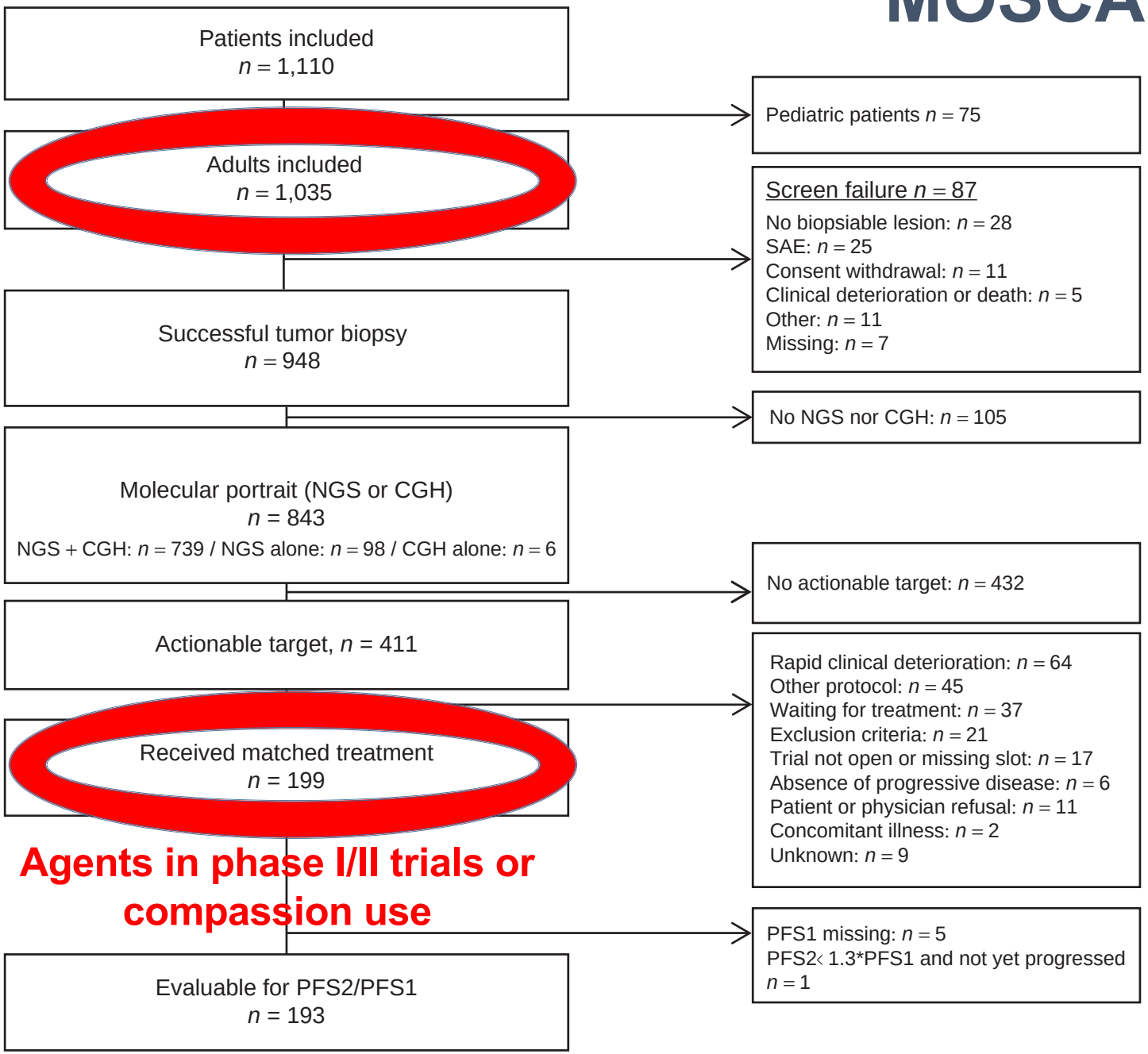
Antoine Hollebecque et al., ASCO 2013; Charles Ferte et al, AACR 2014

MOSCATO 01 trial



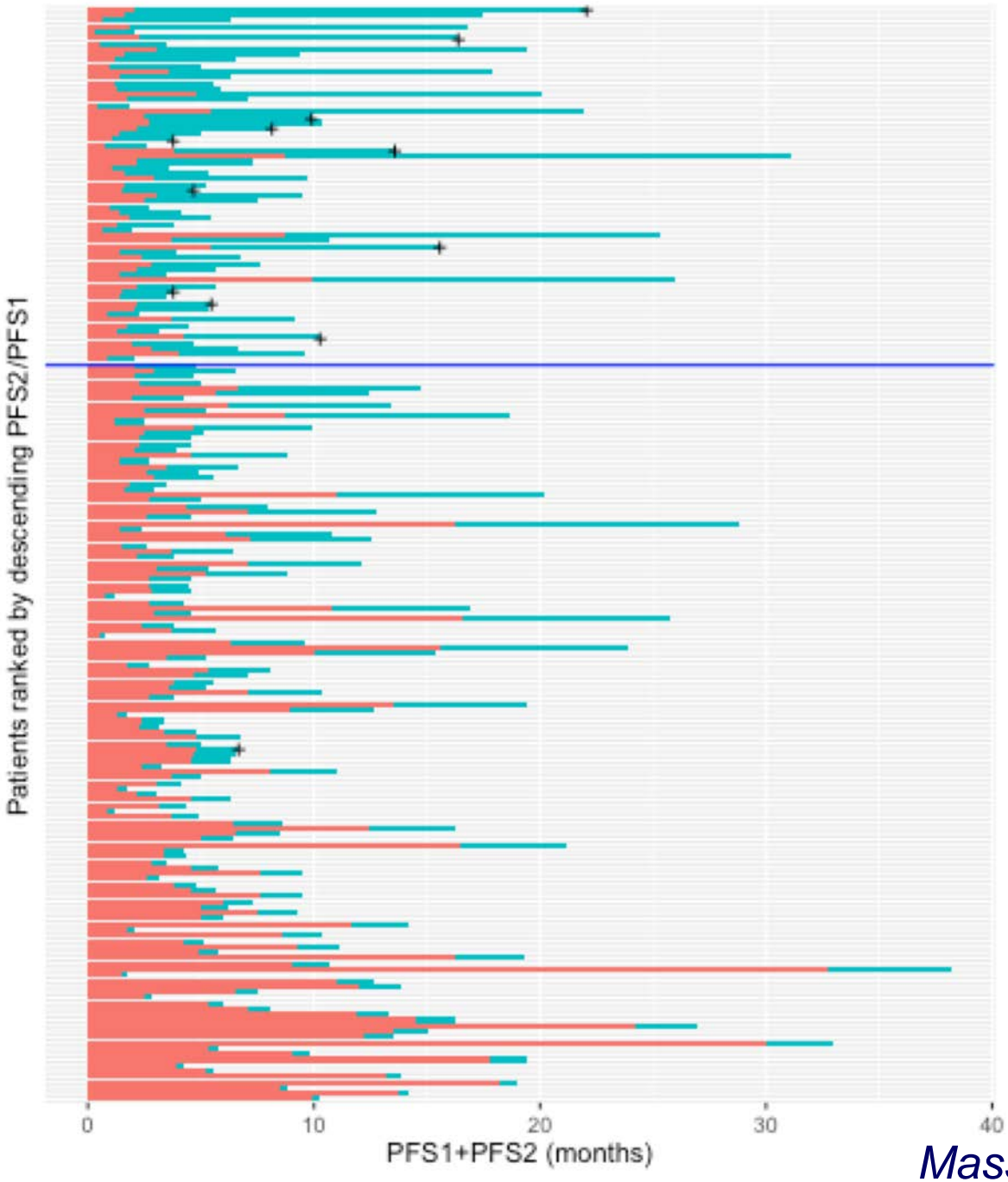
Massard et al, Cancer Discovery 2016

MOSCATO 01 trial



Massard et al, Cancer Discovery 2016

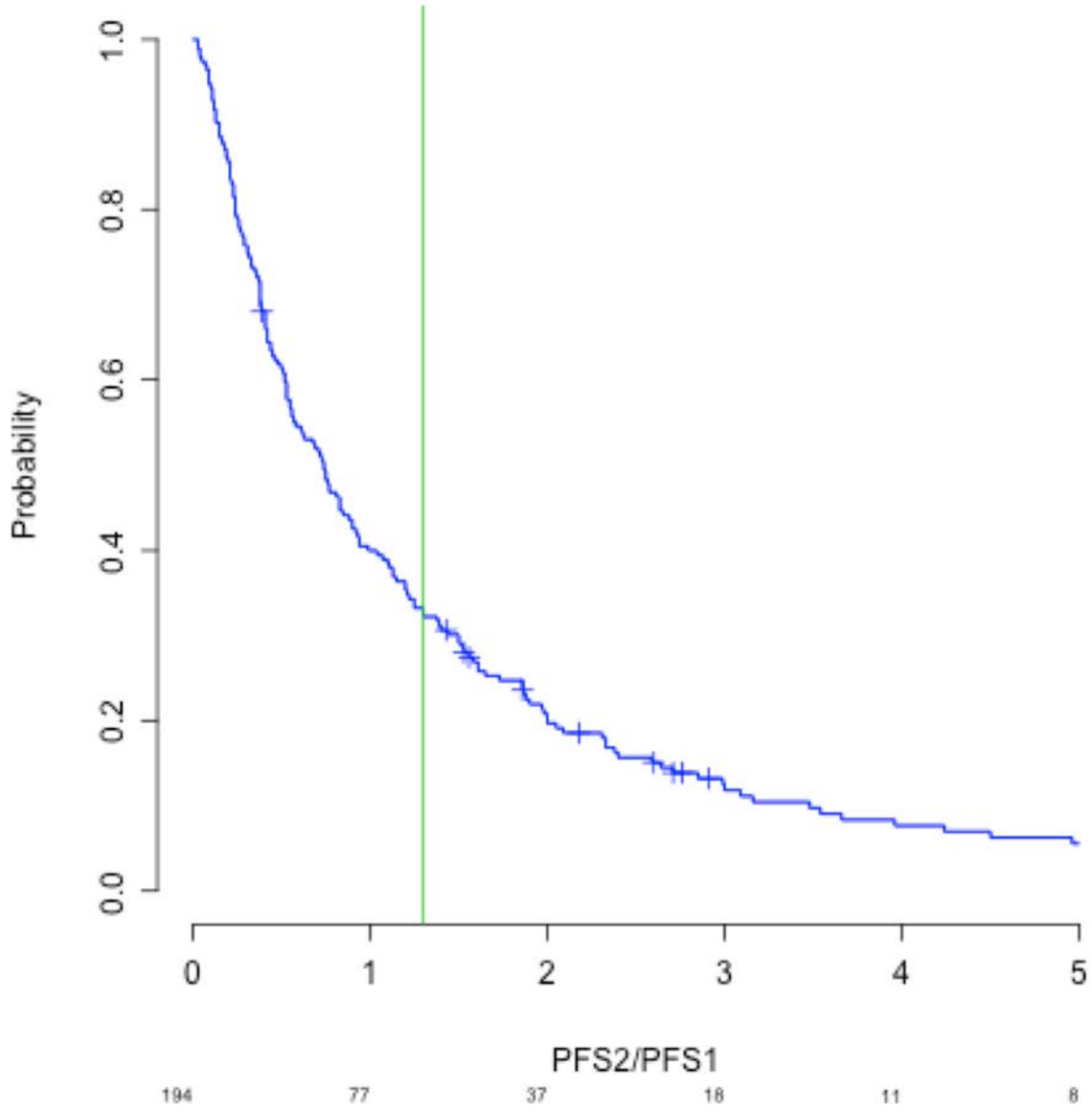
MOSCATO 01 trial



33% of 193 evaluable pts presented a PFS2/PFS1 > 1.3 (95% CI, 26%–39%)

Massard et al, Cancer Discovery 2016

MOSCATO 01 trial



Kaplan-Meier plot of PFS2/PFS1

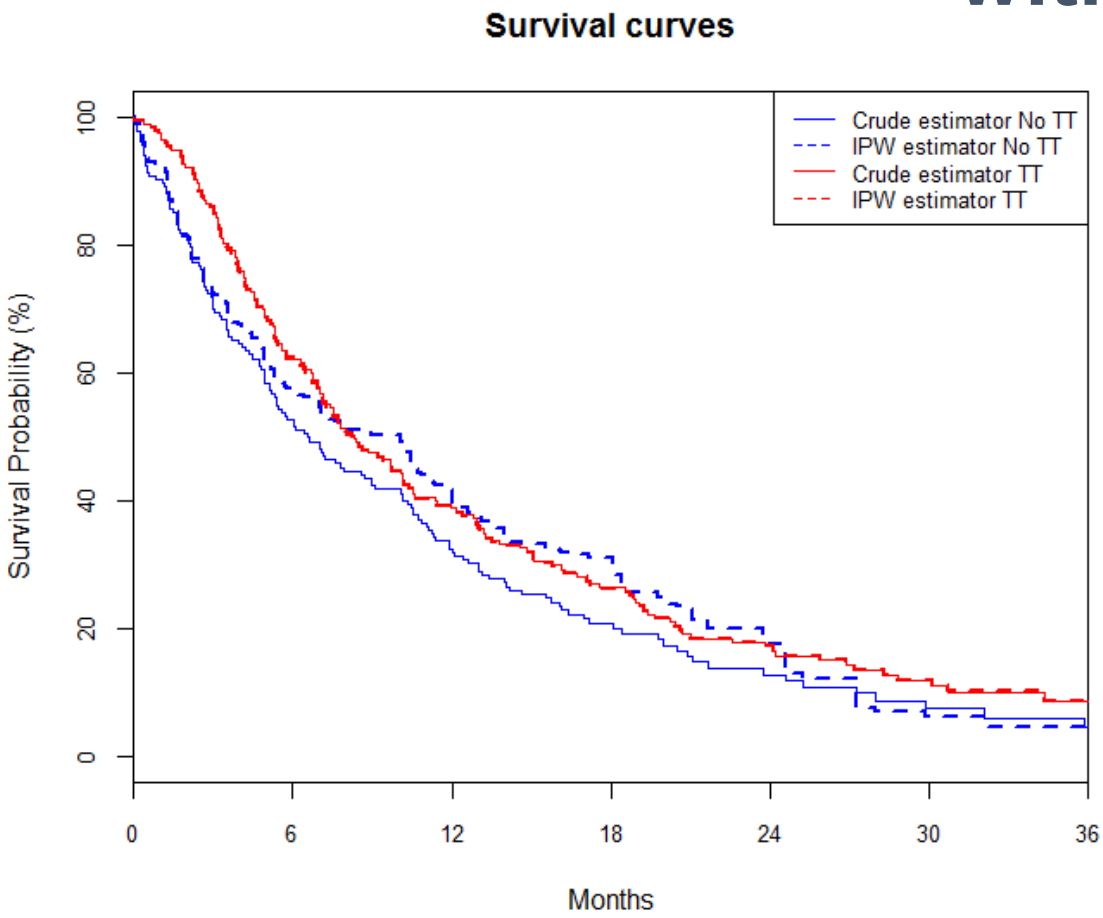
33% of 193 evaluable pts presented a PFS2/PFS1 > 1.3 (95% CI, 26%–39%)

Massard et al, Cancer Discovery 2016

Issues in the MOSCATO 01 molecular screening trial

- In MOSCATO 01, only 199 out of 1035 adult pts received a matched targeted treatment
- Is PFS2/PFS1 a relevant endpoint and what does it mean a null hypothesis of ≤15% of the pts have PFS2/PFS1 > 1.3 ?
- If within-patient correlation of PFS2/1 is moderate in natural history, a higher proportion of pts with PFS2/PFS1 > 1.3 can be expected under the null (Paoletti, Michiels 2017)
- Non-randomized trial, so no evidence that standard treatment would have yielded inferior results …

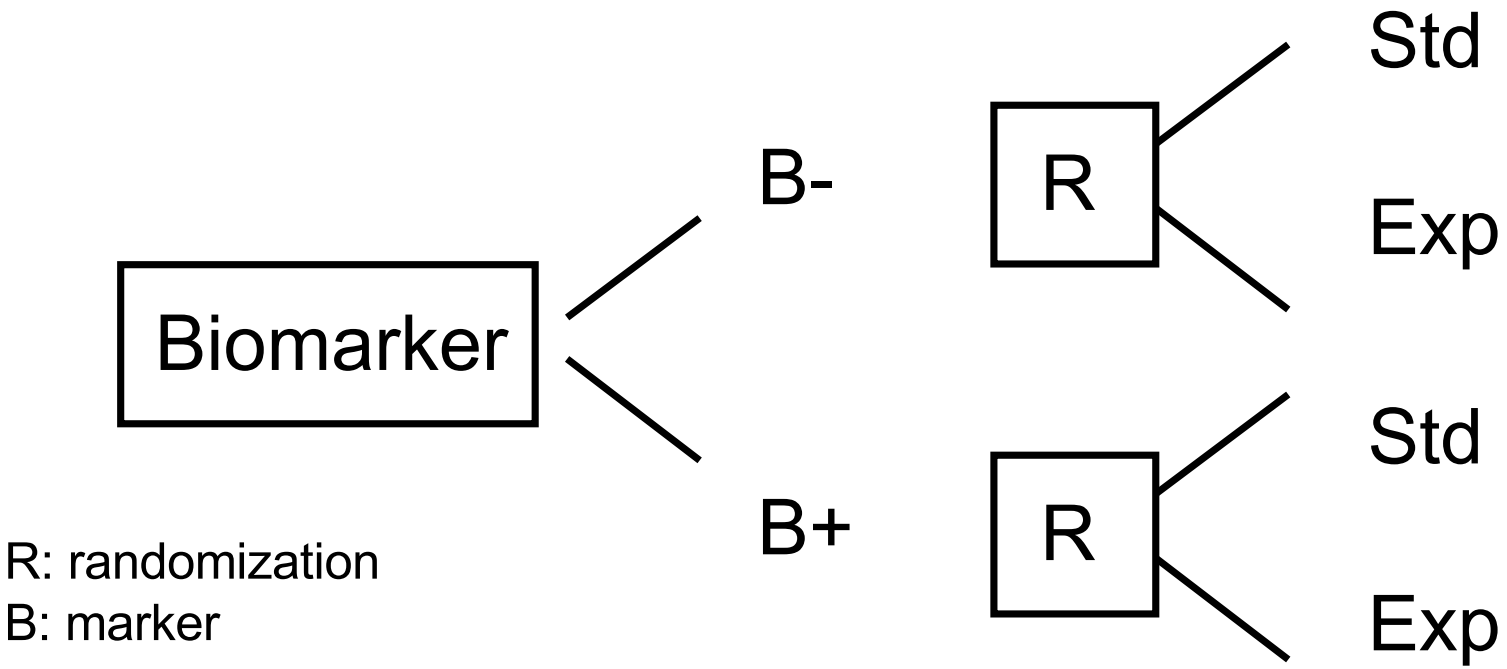
Overall survival results in MOSCATO 01of any targeted treatment (TT) in patients with actionable targets



The inverse probability weighting (IPW) method with a propensity score was used to estimate a causal effect in a Cox model:
HR=0.9 [0.7,1.1], p=0.4

El Dakdouki et al AACR Annual Conference 2018; Cancer Res 2018;78(13 Suppl):Abstract nr 2953.

The many advantages of randomization…



R: randomization
B: marker

- Protects against selection bias and makes groups comparable for benefit/risk
- Allows to evaluate predictive or treatment-modifying effect (vs prognostic)

Statistical framework for discovering predictive biomarkers

Proportional hazard model

$$h(t; T_i, \boldsymbol{X_i}) = h_0(t) \exp\{\alpha T_i + \boldsymbol{\beta}^\intercal \boldsymbol{X_i} + \boldsymbol{\gamma}^\intercal T_i \boldsymbol{X_i}\}$$

with

- $h_0(t)$ the baseline hazard function at times $t > 0$
- T_i the treatment arm
- $\boldsymbol{X_i}$ the p-dimensional vector of biomarkers

and with $\boldsymbol{\gamma}^\intercal T_i \boldsymbol{X_i}$ accounting for the treatment-by-biomarkers interaction

Statistical issues

$$h(t; T_i, \boldsymbol{X_i}) = h_0(t) \exp\{\alpha T_i + \boldsymbol{\beta}^\intercal \boldsymbol{X_i} + \boldsymbol{\gamma}^\intercal T_i \boldsymbol{X_i}\}$$

Aim: selection of the relevant interactions $T_i \boldsymbol{X_i}$

Issue: The model with *all* the main effects $\boldsymbol{\beta}^\intercal \boldsymbol{X_i}$ is not identifiable or at least very DoF-consuming

→ How to select the relevant interactions while properly accounting for the main effects?

(A)LASSO

Full LASSO.

$$l_p(\alpha, \boldsymbol{\beta}, \boldsymbol{\gamma}) = l(\alpha, \boldsymbol{\beta}, \boldsymbol{\gamma}; \boldsymbol{T}, \boldsymbol{X}) - \lambda(\mathbf{1}^\top|\boldsymbol{\beta}| + \mathbf{1}^\top|\boldsymbol{\gamma}|)$$

Adaptive LASSO.

$$l_p(\alpha, \boldsymbol{\beta}, \boldsymbol{\gamma}) = l(\alpha, \boldsymbol{\beta}, \boldsymbol{\gamma}; \boldsymbol{T}, \boldsymbol{X}) - \lambda\left(\boldsymbol{w}_{\boldsymbol{\beta}}^\top|\boldsymbol{\beta}| + \boldsymbol{w}_{\boldsymbol{\gamma}}^\top|\boldsymbol{\gamma}|\right)$$

- **Pros.** Simple. Sparse models, easy interpretation. Solid results in our simulation study

- **Cons.** No hierarchy constraint for interaction

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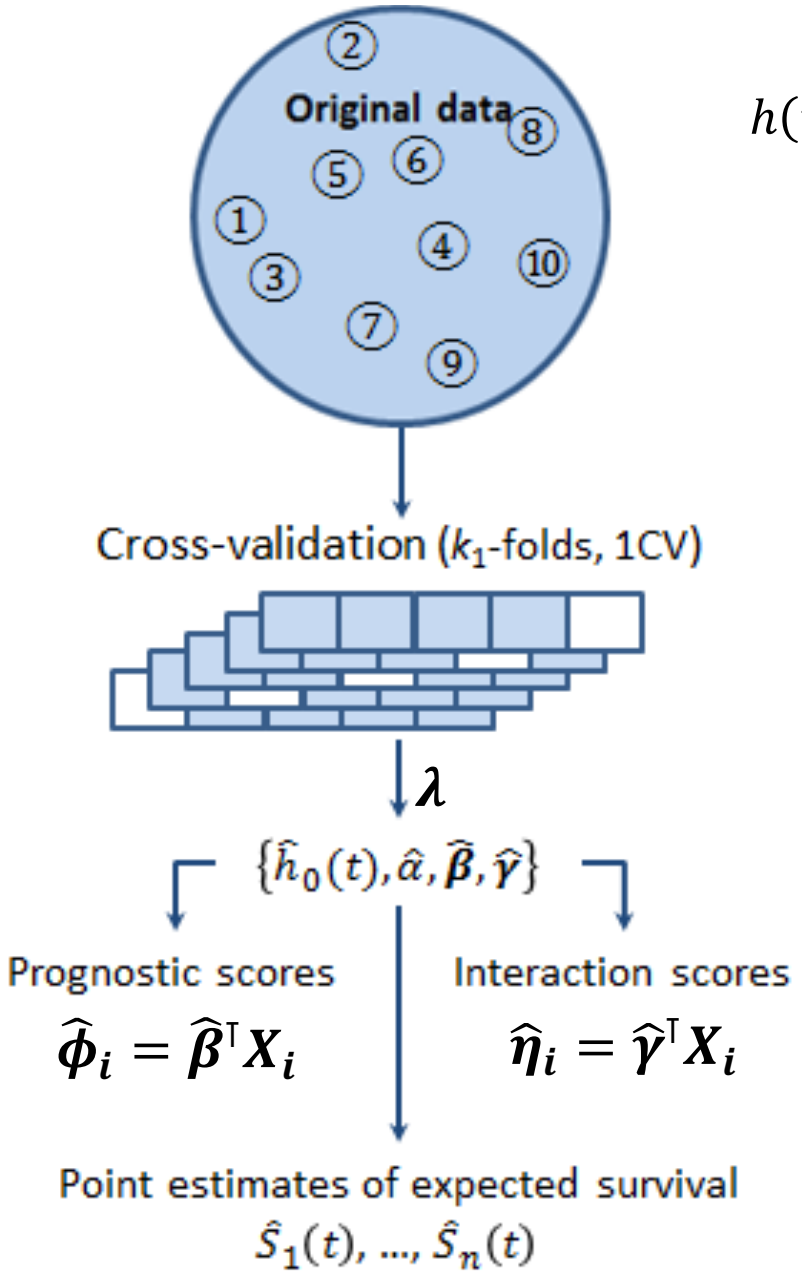
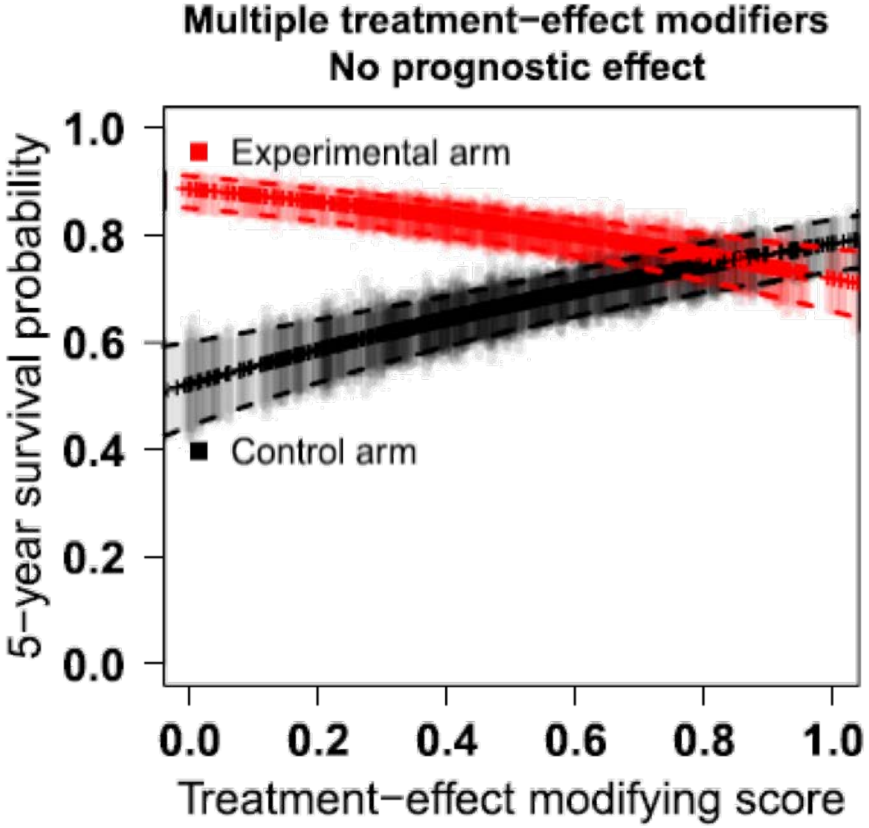
Estimation of expected survival after penalisation



$$h(t; T_i, \boldsymbol{X_i}) = h_0(t) \exp\{\alpha T_i + \boldsymbol{\beta}^\intercal \boldsymbol{X_i} + \boldsymbol{\gamma}^\intercal T_i \boldsymbol{X_i}\}$$

$$l_p(\boldsymbol{\beta}) = l(\boldsymbol{\beta}; \boldsymbol{X}) - p_\lambda(\boldsymbol{\beta})$$



$$\hat{\boldsymbol{\eta}}_i = \hat{\boldsymbol{\gamma}}^\intercal \boldsymbol{X}_i$$

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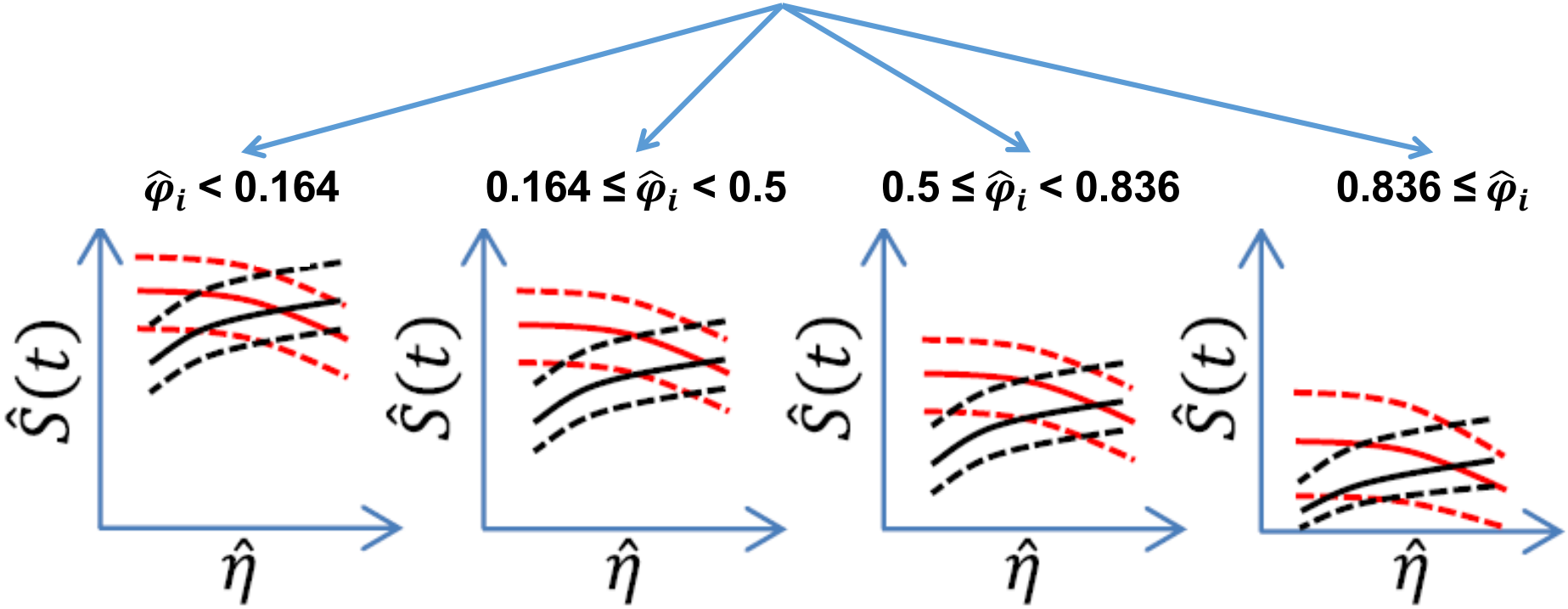
Accounting for prognostic biomarkers

$$h(t; T_i, \boldsymbol{X_i}) = h_0(t)\exp\{\alpha T_i + \boldsymbol{\beta}^{\intercal}\boldsymbol{X_i} + \boldsymbol{\gamma}^{\intercal}T_i\boldsymbol{X_i}\}$$

Prognostic classes based on $\hat{\varphi}_i = \hat{\boldsymbol{\beta}}^{\intercal}\boldsymbol{X_i}$
using percentiles 16.4%, 33.6%, 33.6%, 16.4% (Cox 1957)



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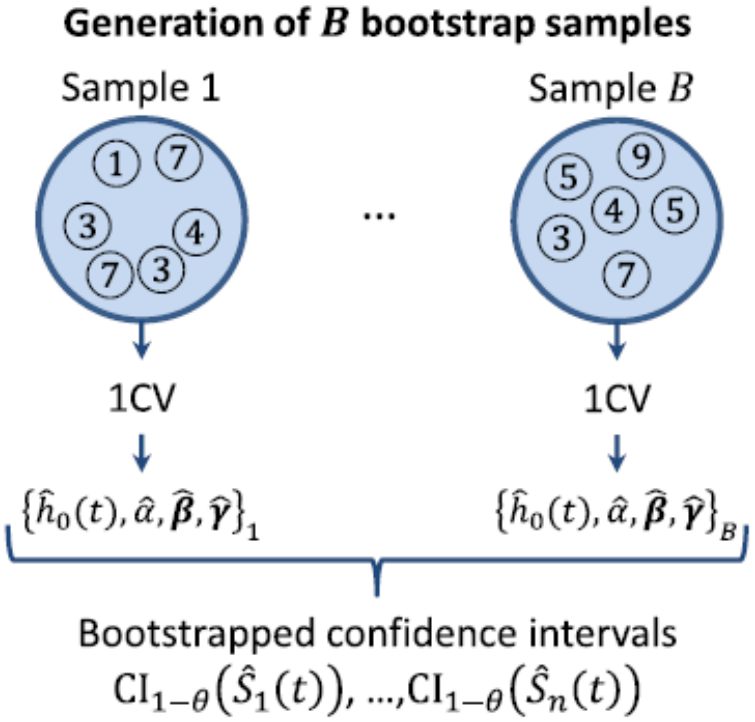
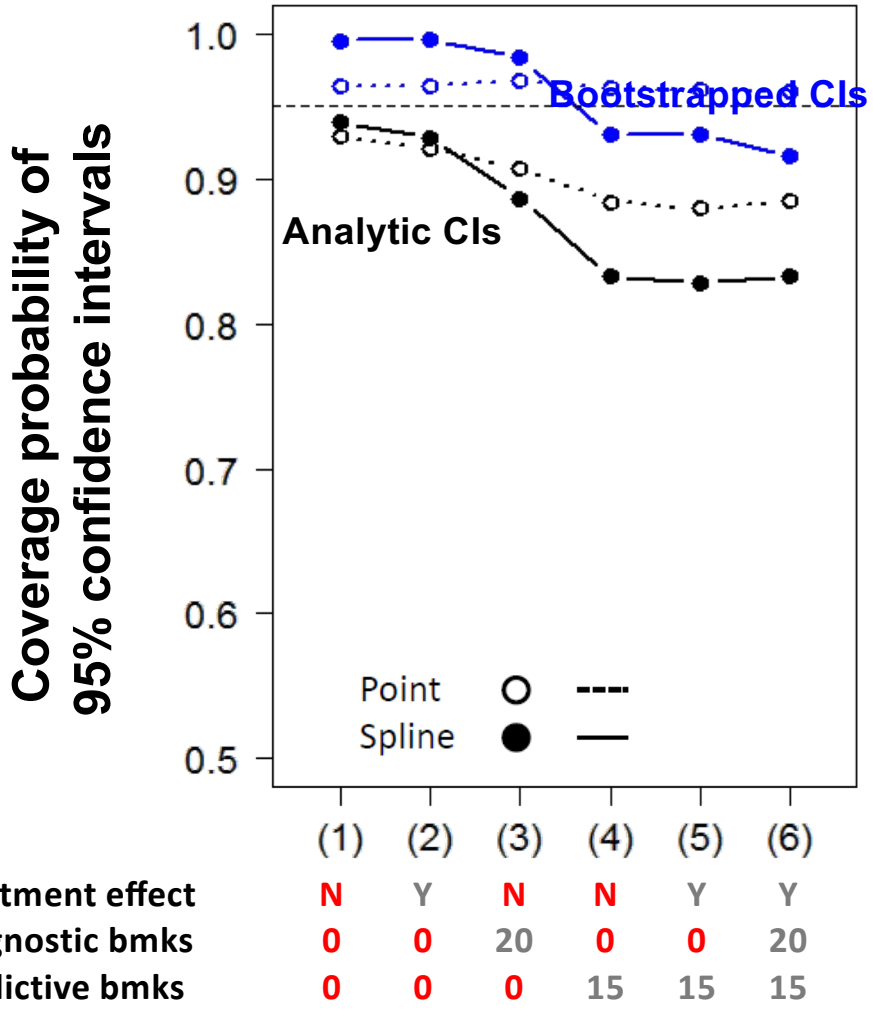
Estimation of the survival probability

Confidence interval estimation:

- Analytic $\mathrm{IC}_{1-\theta}\left(\hat{S}_k(t)\right) = \exp\left(-\hat{H}_k(t) \pm z_{1-\frac{\theta}{2}}\sqrt{\widehat{\mathrm{var}}\left(\hat{H}_k(t)\right)}\right)$
- Smoothed by splines

either in the original data or
in bootstrap samples





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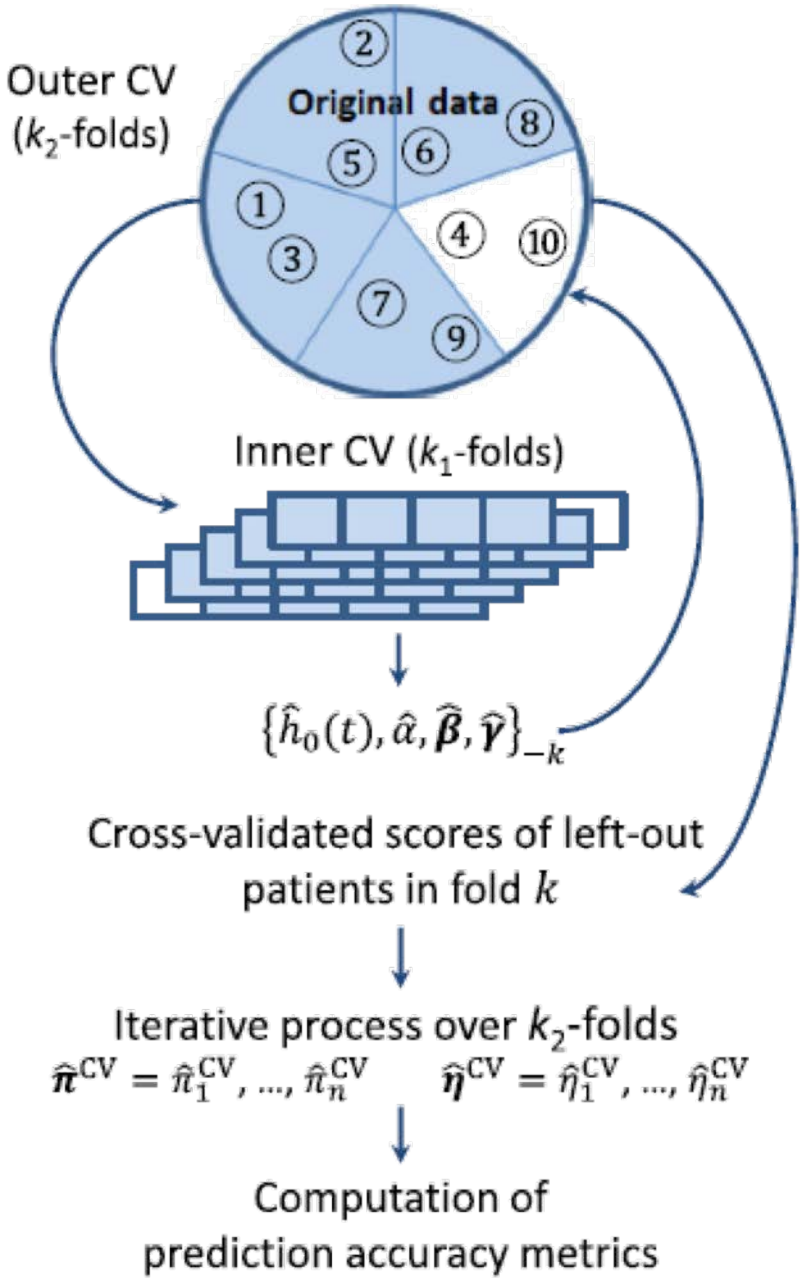
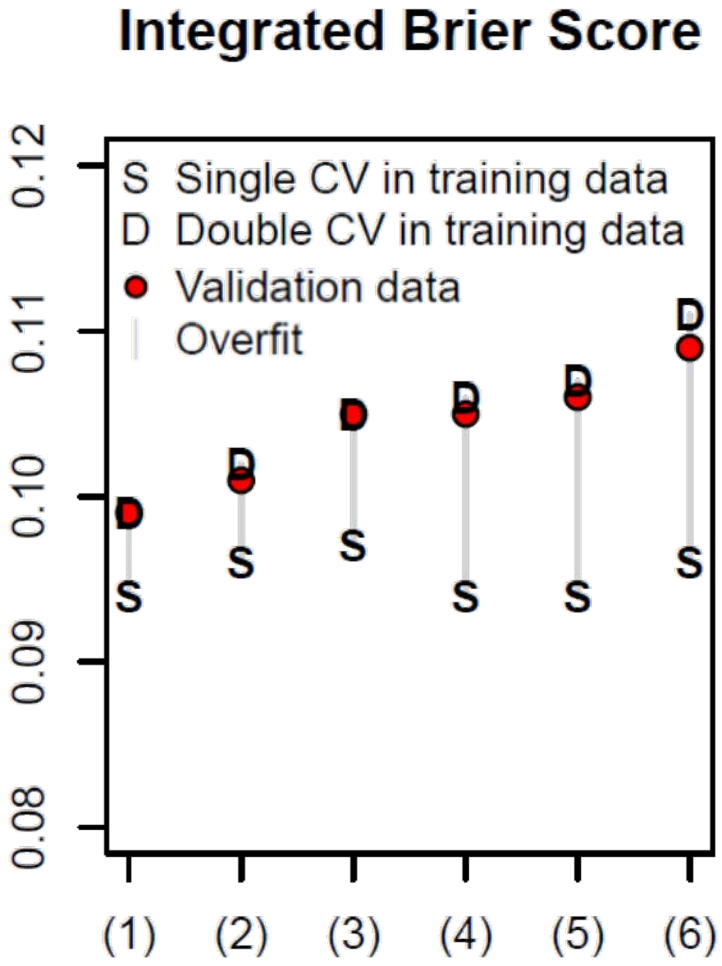
Controlling for overfitting





Treatment effect	**N**	**Y**	**N**	**N**	**Y**	**Y**
Prognostic bmks	**0**	**0**	**20**	**0**	**0**	**20**
Predictive bmks	**0**	**0**	**0**	**15**	**15**	**15**

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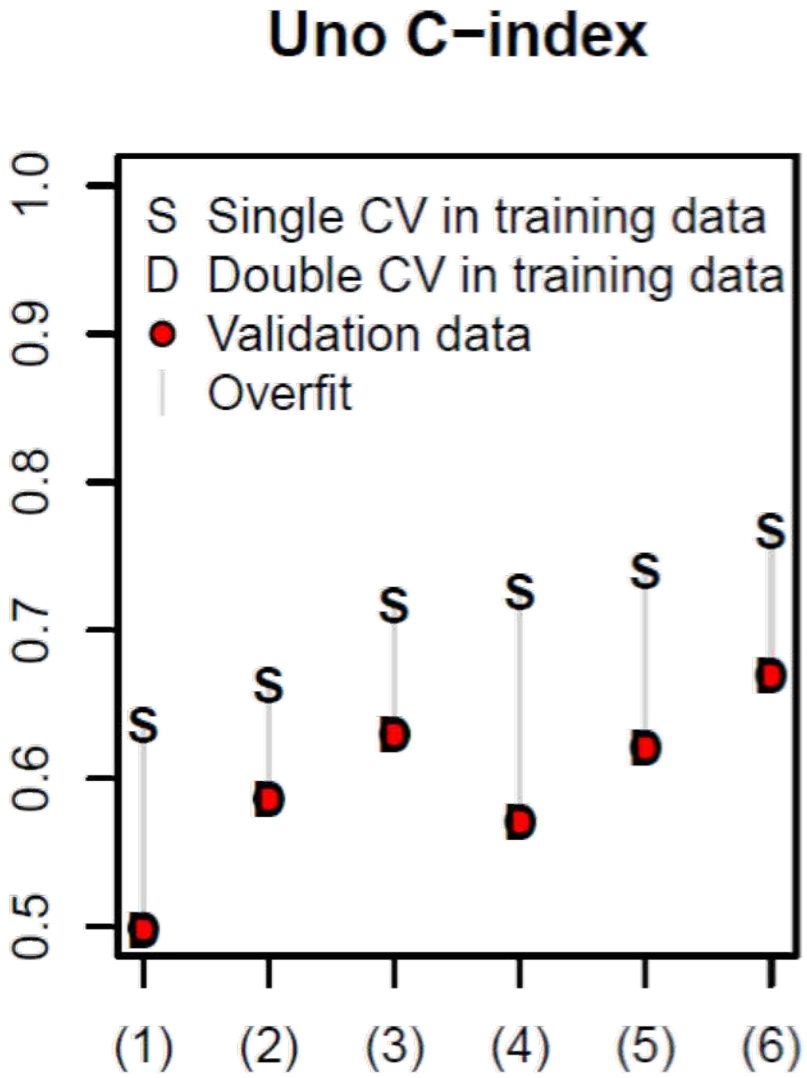
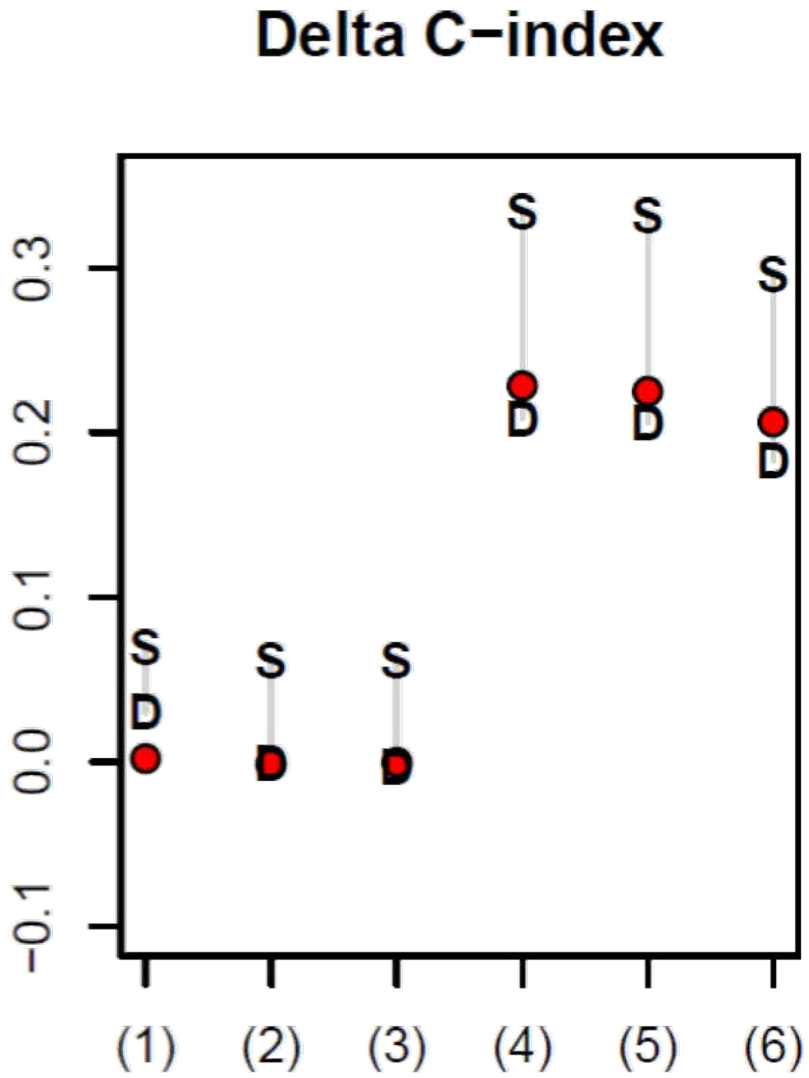
Controlling for overfitting





N	Y	N	N	Y	Y	Treatment effect	N	Y	N	N	Y	Y
0	0	20	0	0	20	Prognostic bmks	0	0	20	0	0	20
0	0	0	15	15	15	Predictive bmks	0	0	0	15	15	15

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Application: Phase III trial in early breast cancer

Pogue-Geile et al (2013)

Retrospective biomarker study in RCT of early breast cancer patients

⇒ Randomized clinical trial (n = 1574 patients, p = 462 genes)

Characteristics	Chemotherapy only	Chemotherapy + adj. trastuzumab
Overall	795	779
Nodal status		
1 – 3 positive	444 (56%)	448 (57%)
4 – 9 positive	238 (30%)	232 (30%)
≥ 10 positive	113 (14%)	99 (13%)
ER status		
Negative	360 (45%)	375 (48%)
Positive	435 (55%)	404 (52%)
Tumor size (cm)		
Mean (SD)	2.9 (1.7)	2.9 (1.8)

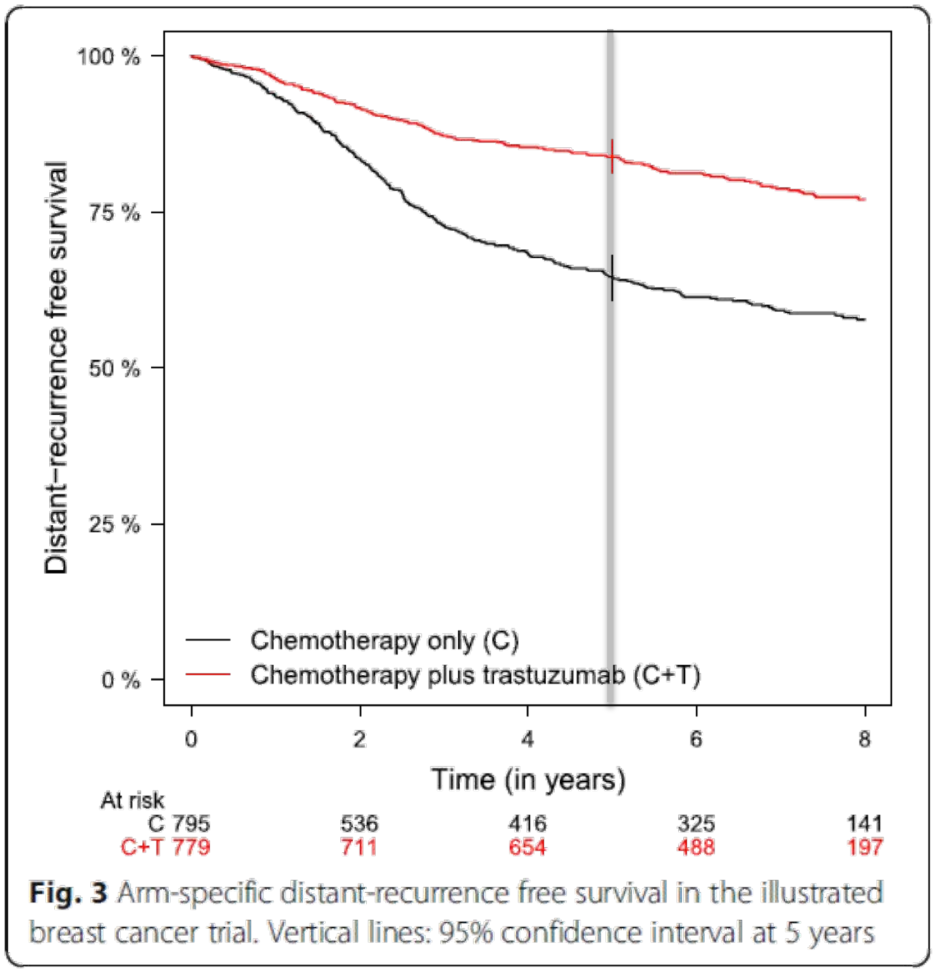

Fig. 3 Arm-specific distant-recurrence free survival in the illustrated breast cancer trial. Vertical lines: 95% confidence interval at 5 years

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Developed signature
with the ALASSO penalty

Prognostic component	
Clinical variables (4)	Treatment, ER status, Tumor size, Nodal status
Genomic variables (p = 98)	ACTB, ADCYAP1, ANGPTL4, ARL8A, BBC3, BDH2, CAPS, CASC3,CCDC74A, CDC6,CDH3, CFLP1, CSNK1A1, *CSNK1D*, CXXC5,DHPS, DNAJC4, DPY19L4, ELAVL4, ELN, ENO1, ERBB4, FABP5,FAM84B, FBXW11,FKSG30, FLJ22659, FLJ22795, FLJ35390, FRAG1,FRMD4A, GHR, GPRIN1, GSN, HIST1H2AA,HIST2H2BE, IDUA, IGJ,IGKV2.24, ILF2,KCNE4, KIAA1920, KIF2C, KRT81, L3MBTL2,LCE3E, LOC400590, MAD2L2, MAP3K13,MBOAT2, **MED13L**, METTL3, MSI2, MTCH2, MVP, NAT1, NAT10, NDC80, NECAB3,NXPH3, OGFR, PCK2,PGM5, PHGDH,PITPNC1, PRPF40A, PTTG1, RBM14, RELB, RHBDD1, RND3, RPL34, RPS2, SFRP1,SLC25A28, SLC25A31,SLC25A5, SLC30A10,SLC6A19, SMCP, *SOX4,SPDEF*, SPP1, ST6GALNAC4, STEAP3, STK11IP,SULT1A2,TBXAS1, TCEB2, TFRC,TMSB10, TRABD, TUBB2C, UBE2W, UGDH, XYLT1, ZNF592, ZNF609
Treatment-effect modifying component	
Genomic variables (p = 24)	ATAD3A, C16orf14, C1orf93, *CCL21*, *CD9,CIAPIN1*, CLIC1, DKFZP434A0131, FAM148A,FNDC4, FURIN, KRTAP2.4, **MED13L**, MIA, MMD, ORMDL3, RPLP0,SIAH2, SLC39A14, SSBP2, THOP1, THRAP1,TMEM45B, UNC119
Prediction measures	
C-statistic (C)	0.80 (1CV), 0.67 (2CV)
ΔC-statistic (ΔC)	0.23 (1CV), 0.02 (2CV)

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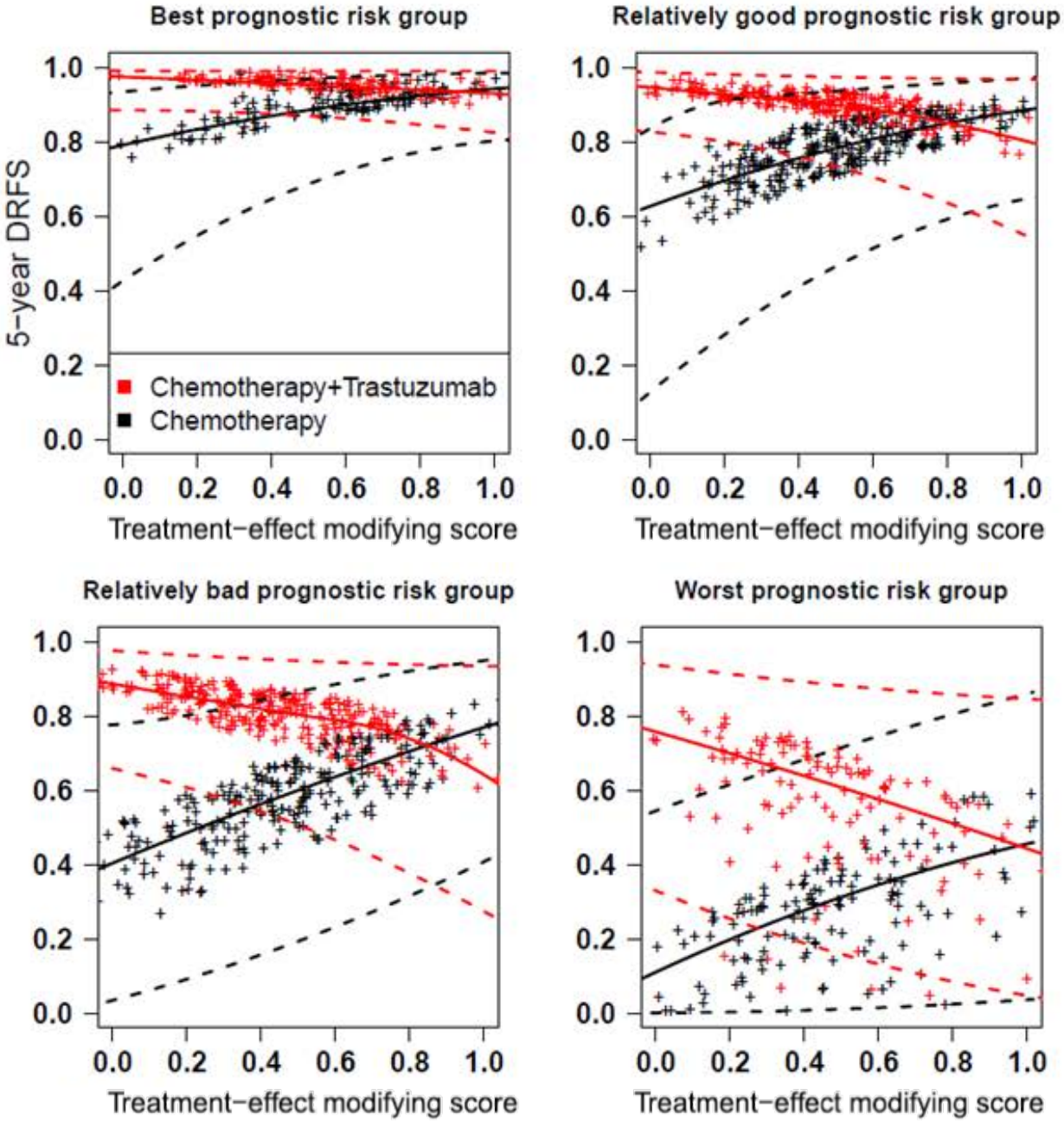
Graphical illustration



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R package biospear

Bioinformatics, 2017, 1–2
doi: 10.1093/bioinformatics/btx560
Advance Access Publication Date: 12 September 2017
Applications Note

OXFORD

Genome analysis

biospear: an R package for biomarker selection in penalized Cox regression

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[1]Gustave Roussy, Université Paris-Saclay, Service de biostatistique et d'épidémiologie, Villejuif, F-94805, France and [2]Université Paris-Saclay, Univ. Paris-Sud, UVSQ, CESP, INSERM, Villejuif, F-94805, France

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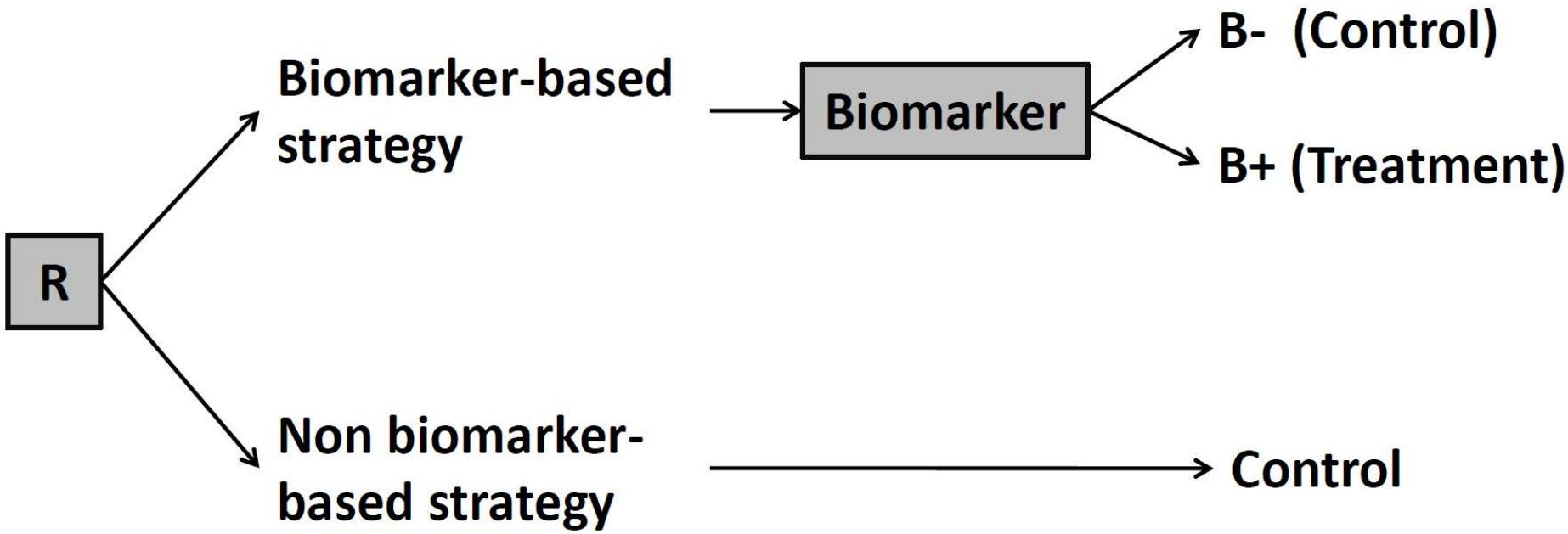
Associate Editor: John Hancock

Received on June 7, 2017; revised on August 11, 2017; editorial decision on September 2, 2017; accepted on September 5, 2017

Abstract

Summary: The `R` package `biospear` allows selecting the biomarkers with the strongest impact on survival and on the treatment effect in high-dimensional Cox models, and estimating expected survival probabilities. Most of the implemented approaches are based on penalized regression techniques.
Availability and implementation: The package is available on the CRAN. (https://CRAN.R-project.org/package=biospear)
Contact: stefan.michiels@gustaveroussy.fr
Supplementary information: Supplementary data are available at *Bioinformatics* online.

Biomarker-based strategy design



Buyse, Michiels et al, Expert Rev Mol Diag 2011

Early breast cancer prevention: polygenic risk

JAMA Oncology | Original Investigation

Use of Single-Nucleotide Polymorphisms and Mammographic Density Plus Classic Risk Factors for Breast Cancer Risk Prediction

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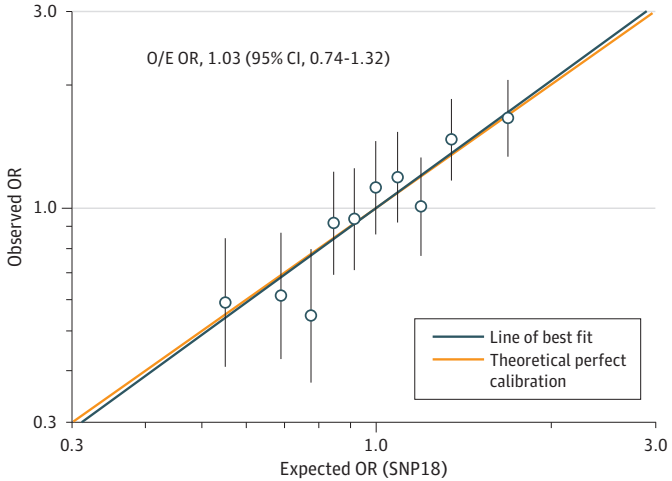
Figure. Unadjusted Observed vs Expected Odds Ratios From SNP18 by Decile



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EPIDEMIOLOGY

Breast cancer risk prediction using a clinical risk model and polygenic risk score

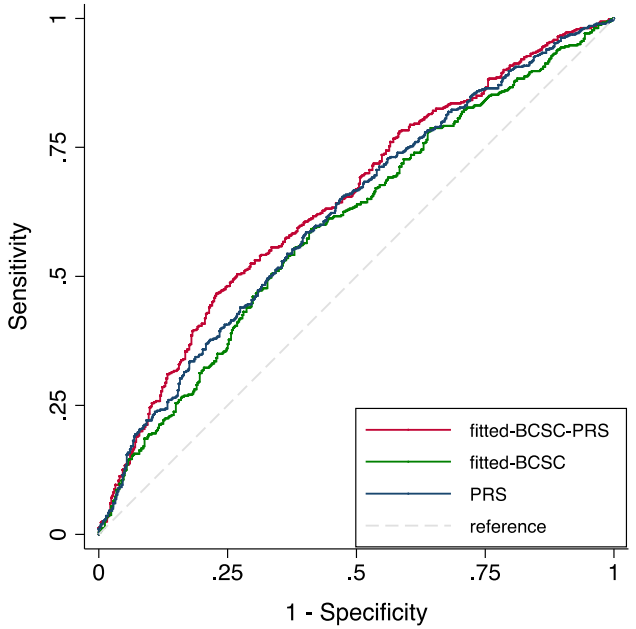
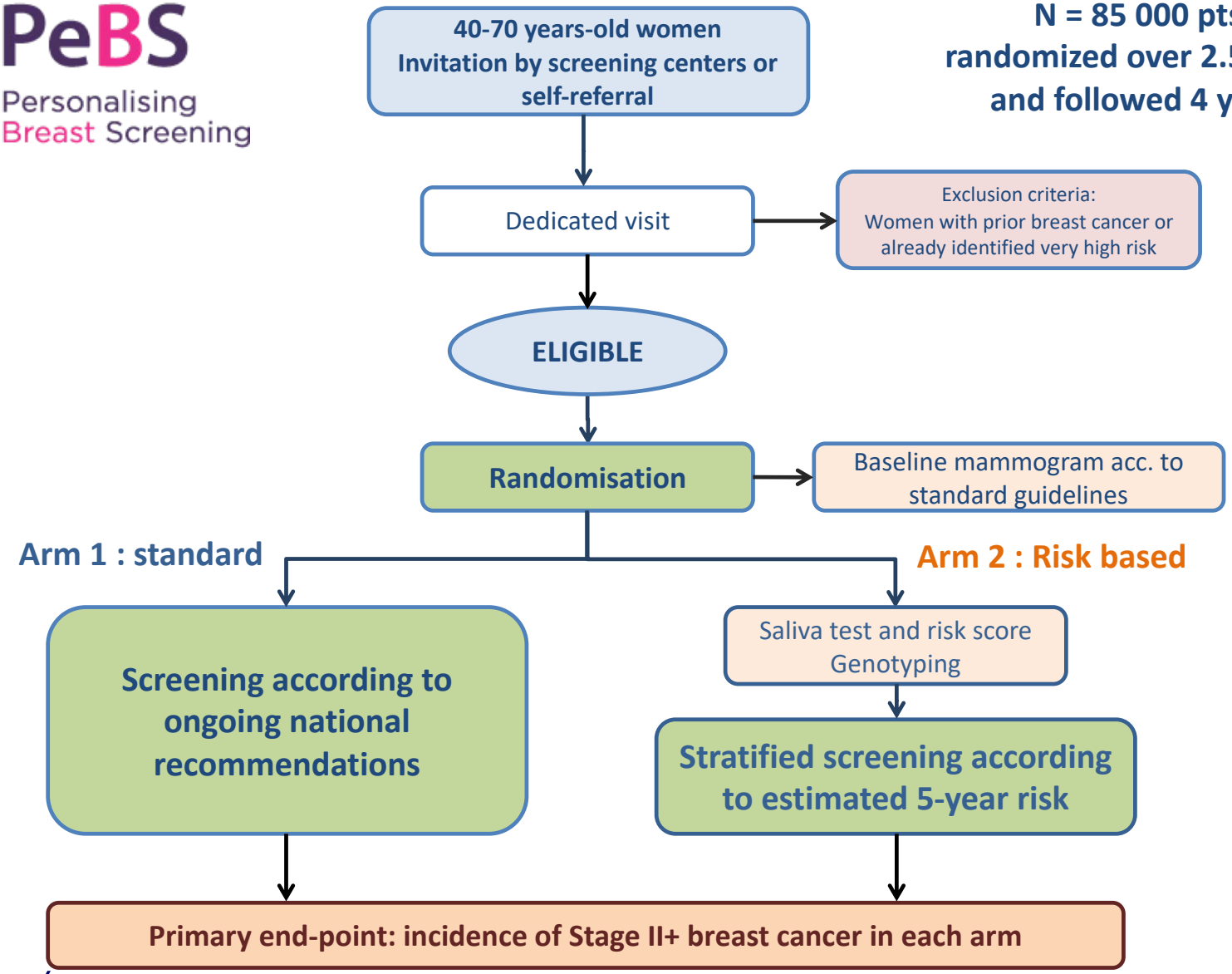


Fig. 1 The receiver operating characteristic curves for the polygenic risk score (PRS), fitted-BCSC model (fitted-BCSC), and the fitted-BCSC model plus polygenic risk score (fitted-BCSC-PRS) are shown

H2020 funded clinical trial on a polygenic risk based breast cancer screening strategy

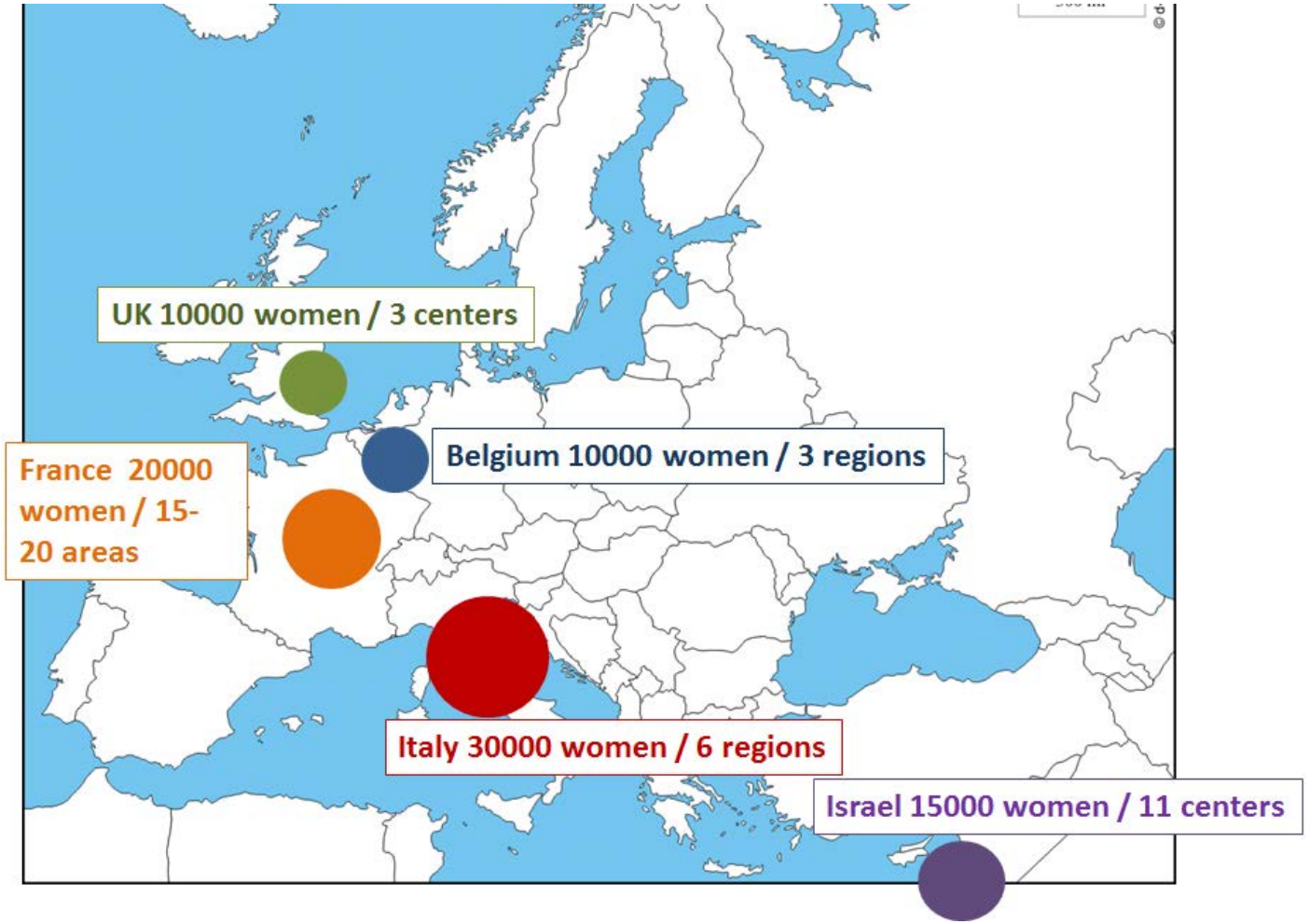
MyPeBS
Personalising Breast Screening



http://mypebs.eu/

MyPeBS
Personalising
Breast Screening

Planned recruitment starting end 2018



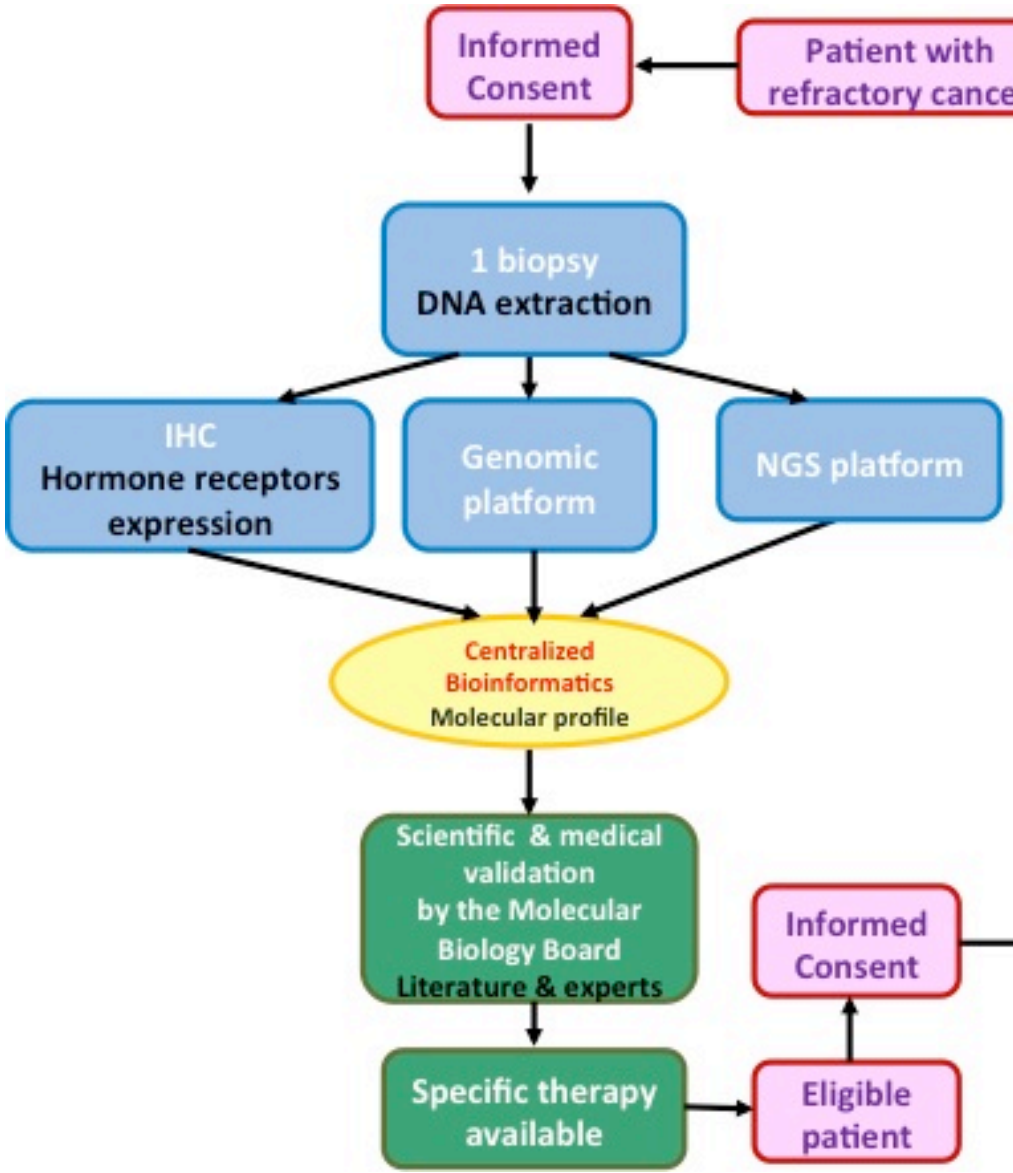
http://mypebs.eu/

Evidence-based criteria for a prognostic gene signature in the path from the lab to the clinic

N°	Concept	Elaboration
1	Proof of concept	Do signature levels differ substantially between patients with and without outcome?
2	Analytical validity	Signature's ability to accurately and reliably measure the genotype of interest between and within-laboratories
3	Clinical validity	Does the signature predict risk of outcome in multiple external cohorts or nested case-control/case-cohort studies?
4	Incremental value	Does the signature add enough information to established clinico-pathological prognostic markers or provide a more reproducible measurement of one of them?
5	Clinical impact	Does the signature change predicted risk sufficiently to change recommended therapy?
6	Clinical utility	Does use of the signature improve clinical outcome, especially when prospectively used for treatment decisions in a randomized controlled trial?
7	Cost-effectiveness	Does use of the signature improve clinical outcome sufficiently to justify the additional costs of testing and treatment?

Michiels Ann Onc 2016

Another strategy trial: SHIVA



11 MTAs = molecular targeted agents

Paoletti, Michiels 2017; Le Tourneau Lancet Oncol 2015

Heterogeneity of treatment effects

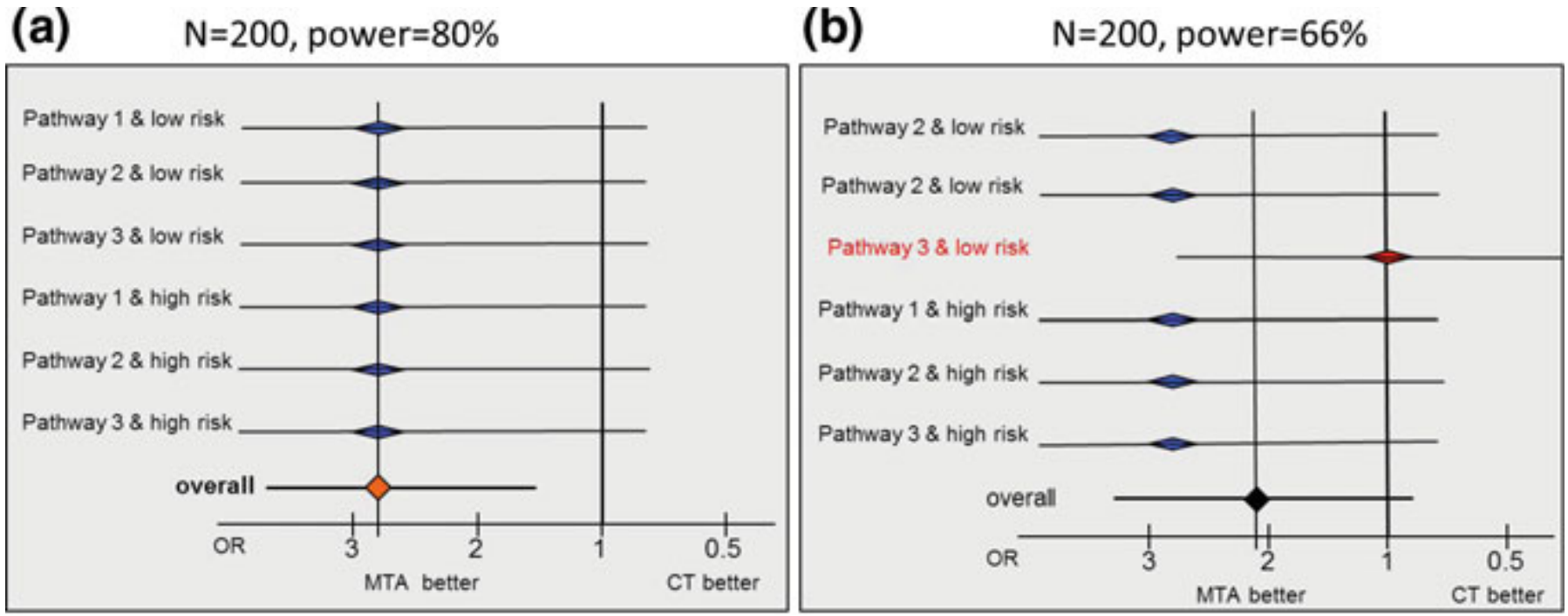


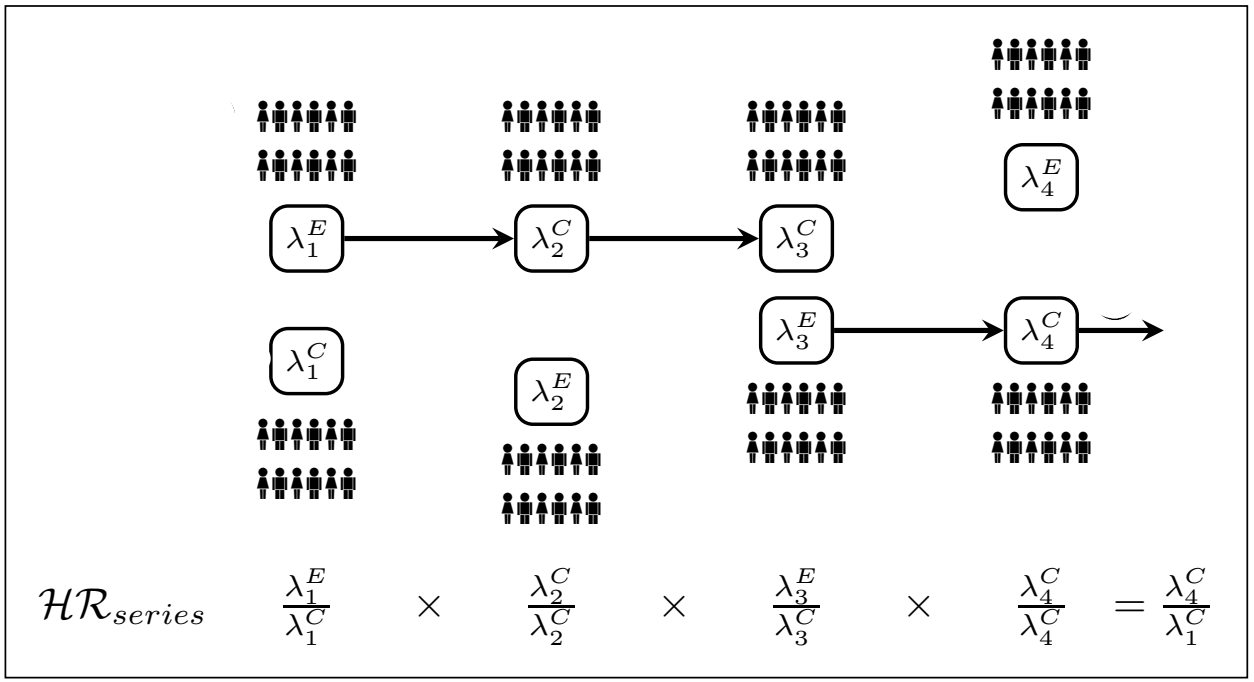
Fig. 3 Impact of heterogeneity in the treatment effect related to the algorithm assuming balanced prevalence for the six different strata and the same follow-up for all patients censored at the cut-off date. High and low risk denote the risk group; Pathway 1, 2, 3 correspond to the grouping of the different targets; MTA stands for molecularly targeted agent; CT stands for control treatment; *N* is the total sample size; OR stands for odds ratio; Point estimates and 95% confidence intervals (horizontal lines) are provided. *Panel A* Homogeneous benefit of the targeted treatment selected based on molecular alterations in all strata (OR = 2.67); *Panel B* benefit of the targeted treatment selected based on molecular alterations in all but one stratum

Paoletti, Michiels 2017

Relaxed signifance levels for randomized trials in rare diseases?

Long-term horizon (15y)

Illustration of one repetition of a series of four consecutive two-arm RCTs



① The hazard rate λ_1^C of the control treatment of the first trial characterizes the severity of the underlying disease as perceived at the beginning of the research horizon.

Bayar A et al, Stat Med 2016; Le Deley et al Clin Trials 2015

Relaxed signifance levels for randomized trials in rare diseases?

Long-term horizon (15y)

- Historical distribution of treatment effects
- Performing a series of small randomized trials with relaxed α-levels leads, on average, to **larger survival benefits over a long horizon compared with larger trials with a 2.5% one-sided α-level for a moderate increase in risk**
- The recommendation is only valid when considering a series of trials run over a relatively long research horizon and when the supply of new treatments is large

- Performing multi-arm multi-stage trials with relaxed α-level can further increase the expected survival benefit on the long run (unpublished work)

Bayar A et al, Stat Med 2016; Le Deley et al Clin Trials 2015

Some References

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Acknowledgments

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