VII CONVEGNO NAZIONALE DELLA
RETE ONCOLOGICA SIFaCT

# Oltre il modello mutazionale e l'oncologia di precisione: la medicina personalizzata

ONCOFARMA

Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Milano 23-24 Giugno 2023

**Focus on: Il presente della medicina di precisione e dell'immunoncologia:**

# I Risultati dei Trial Clinicamente Rilevanti

Gennaro Daniele, MD PhD

# Conflicts of Interest

- Honoraria/Speaking/training fee: GSK; Gilead
- PI of Sponsored Trials by: Genetech/Hoffman-La-Roche; AstraZeneca; Pfizer; Bayer; Exelixis; Sotio biotech; Kinnate; Beigene; Takeda; SEAGEN; BMS;
- I am a member of Ministry of Health's consultation table on Clinical Trials
- Opinions expresed herein are my own.

# The Issue: What is precision Oncology model?

# Comparison of Targeted to Untargeted Design

Simon R, Development and Validation of Biomarker Classifiers for Treatment Selection, JSPI

| Treatment Hazard Ratio for **Marker Positive Patients** | Number of Events for Targeted Design | Number of Events for Traditional Design | | |
|---|---|---|---|---|
| | | Percent of Patients Marker Positive | | |
| | | 50% | 33% | 20% |
| 0.5 | 74 | 316 | 720 | 2040 |
| 0.67 | 200 | 820 | 1878 | 5200 |

"For many treatments *(Generally)*, the variation in **prognosis** among patients exceeds the size of the treatment effect"

R.Simon, S. Matsui, M.Buyse

# Una semplificazione…

Se un trial mostra risultati clinicamente rilevanti, il farmaco/intervento viene incorporato direttamente nella pratica clinica

Ma bisognerà pur fare una selezione…(esempi di rilevanza clinica)

# 1. Un nuovo Inizio

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

# Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

**Study Design:**

- Open-label, multicenter, two-part phase 1 trial
  - Crizotinib: oral ATP-competitive selective inhibitor of ALK and MET tyrosine kinases (inhibits tyrosine phosphorylation of activated ALK)
    - Maximum tolerated dose of 250mg po BID, one cycle was 28 days
- Patients were assessed for adverse events and response to therapy

Kwak EL, et al. NEJM 2010; 363 (18): 1693-1703.

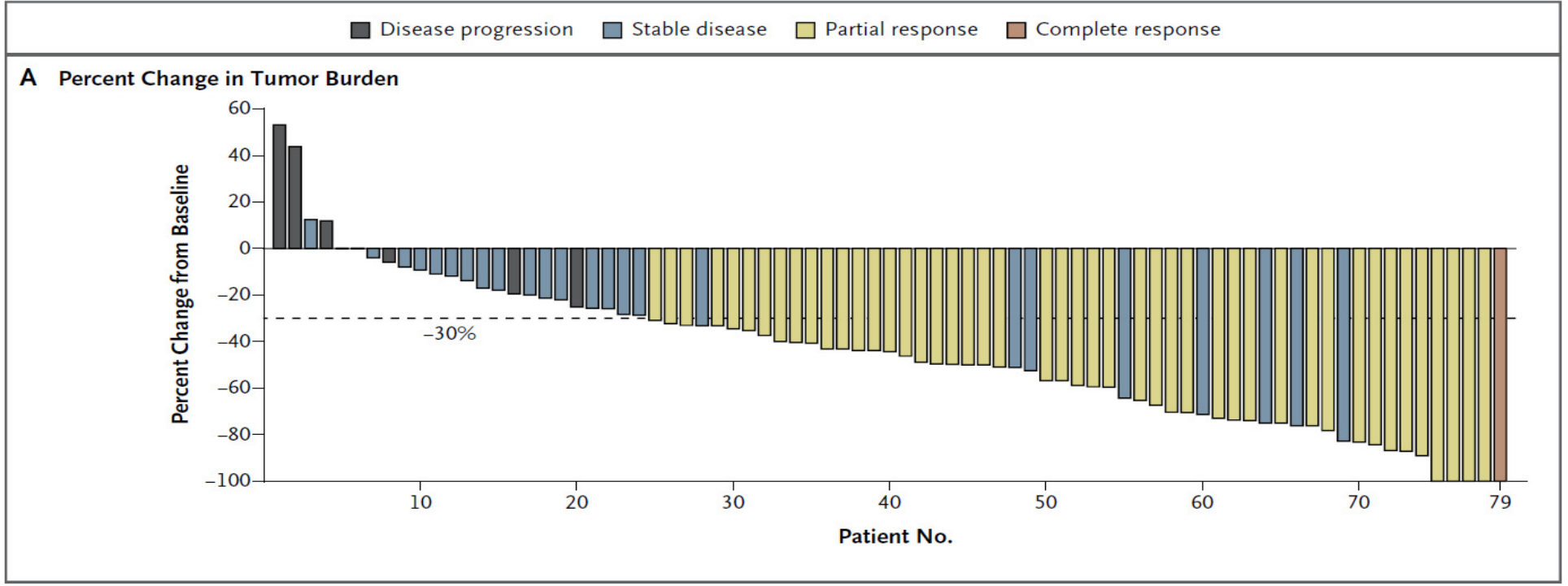
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

# Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

- 2 patients with NSCLC with FISH positive for ALK rearrangement who were treated with crizotinib during dose escalation had dramatic improvement which prompted a large-scale prospective screening for NSCLC w ALK rearrangement
  - 1500 patients were screened from 2008-2010; 82 patients had ALK rearrangement
    - 94% of patients had received at least one previous tx
    - 5 patients received crizotinib as first line

Kwak EL, et al. NEJM 2010; 363 (18): 1693-1703.




ORR: 57% [95% CI 46-68] at a mean treatment duration of 6.4 months

46/82 (56%) of patients had confirmed PR

1/82 patients had CR

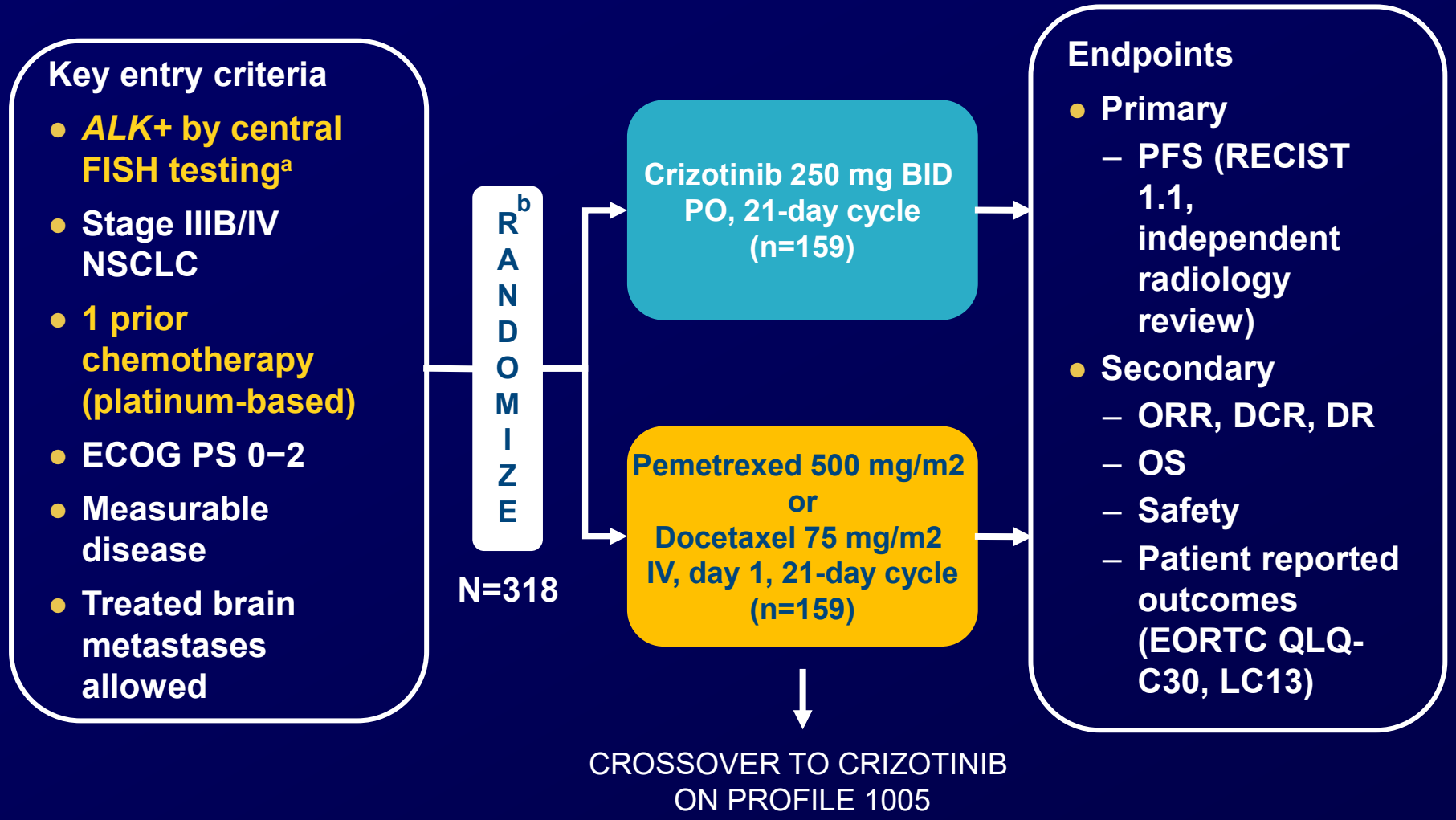
27/82 (33%) of patients had stable disease

Estimated probability of 6-month PFS was 72%

8/2011 FDA granted accelerated approval to crizotinib

Kwak EL, et al. NEJM 2010; 363 (18): 1693-1703.

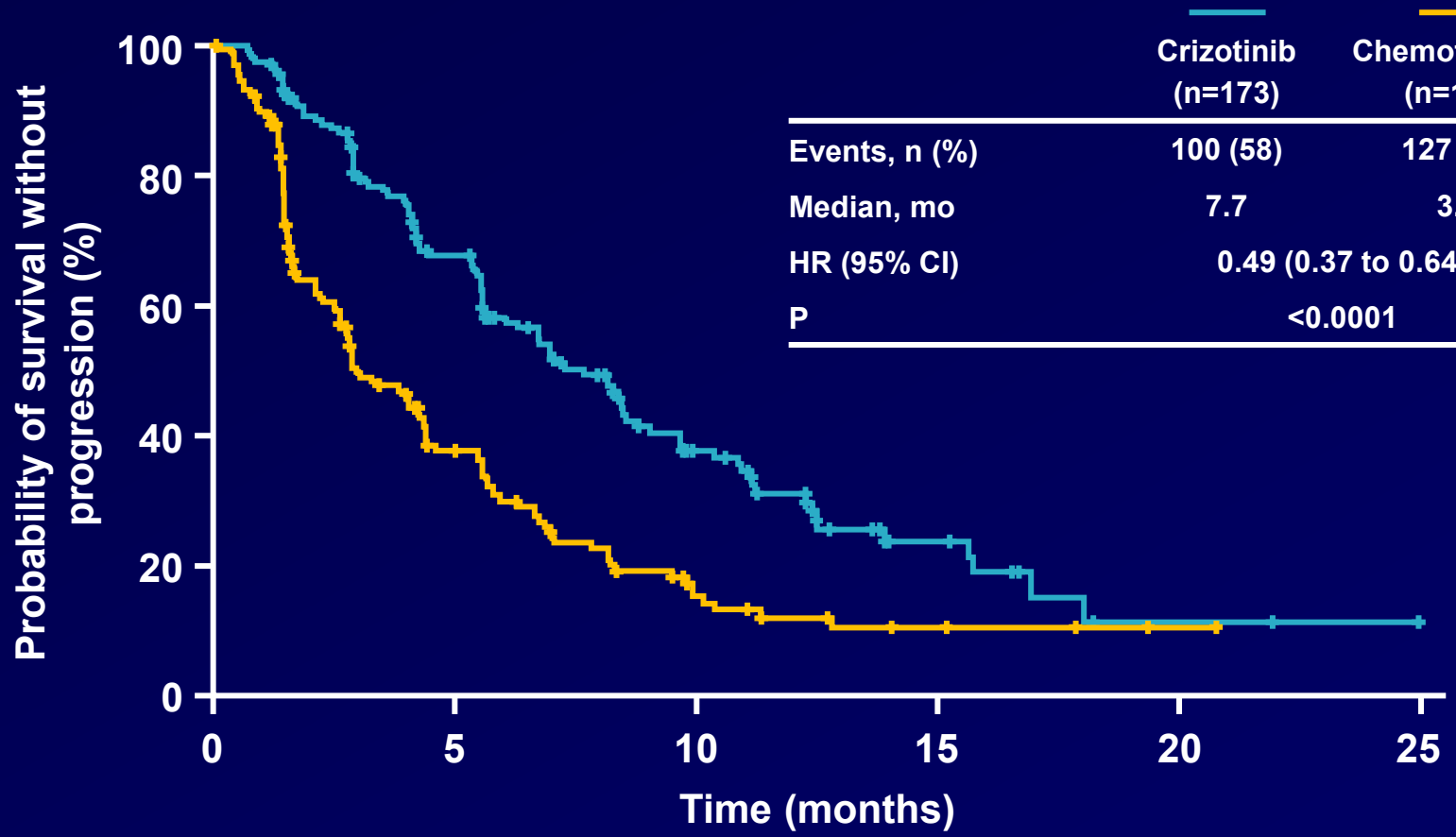
# PROFILE 1007:Study Design




[a]*ALK* status determined using standard *ALK* break-apart FISH assay
[b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Presented at ESMO 2012

# Primary Endpoint: PFS by Independent Radiologic Review (ITT Population)




| | Crizotinib (n=173) | Chemotherapy (n=174) |
|---|---|---|
| Events, n (%) | 100 (58) | 127 (73) |
| Median, mo | 7.7 | 3.0 |
| HR (95% CI) | 0.49 (0.37 to 0.64) | |
| P | <0.0001 | |

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Crizotinib | 173 | 93 | 38 | 11 | 2 | 0 |
| Chemotherapy | 174 | 49 | 15 | 4 | 1 | 0 |

Presented at ESMO 2012

# La rilevanza WOW (IO+Precision)!!

# Mismatch Repair Deficient Colon Cancer

Approximately 10-15% of colon cancers are mismatch repair deficient (dMMR)

1/3 of dMMR colorectal cancers are associated with Lynch Syndrome

Recurrence rates of 20-40% for **stage III dMMR** tumors **despite** standard-of-care chemotherapy

- High-risk disease (T4 or N2) is highly associated with poor survival



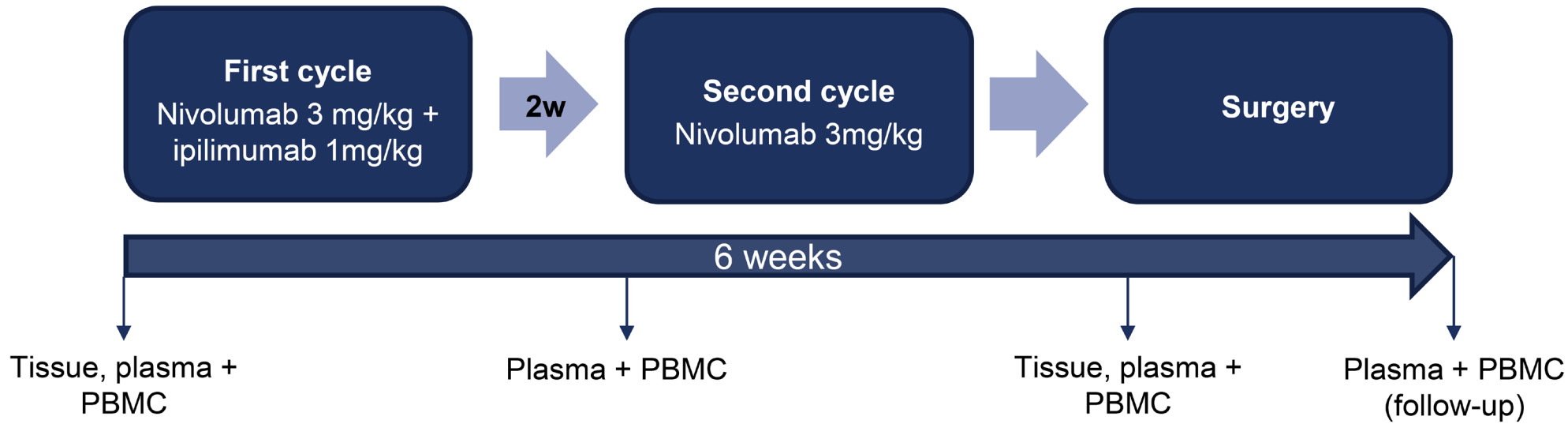
Myriam Chalabi, MD PhD



Eikenboom et. al, Clin Gastroenterol Hepatol 2022; Cohen et al, JCO 2021; Andre et. al JCO 2015; Sinicrope et. al, JCO 2013

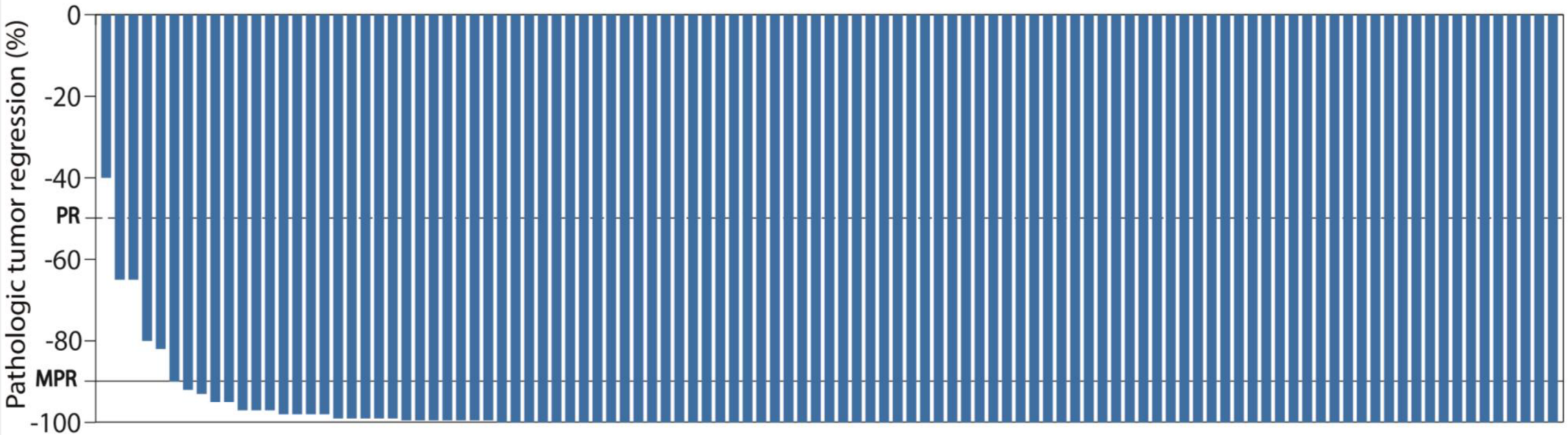
# NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study




*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

# Major pathologic response in 95% of patients; 67% pCR






Myriam Chalabi, MD PhD

# Una oasi (?) nel deserto!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

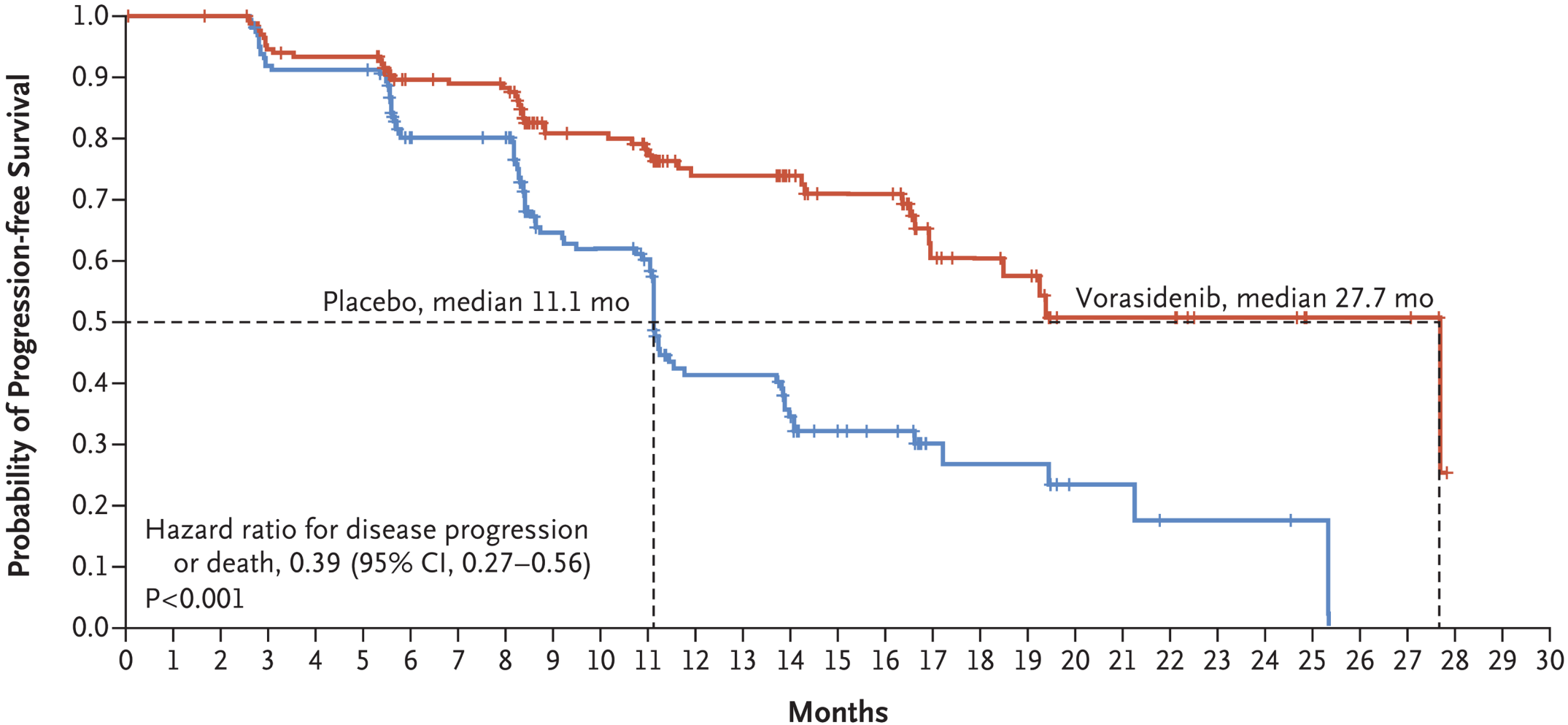
# Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy

# The Indigo Trial

- Phase 3 randomised trial (1:1)
- Double blind/Placebo controlled
- Patients 12y.o. or older with
- Grade 2 glioma (WHO 2016)
- IDH1/IDH2 mutated (Oncomine Dx assessed centrally)
- Primary endpoint: Progression Free Survival
- EXP-RX: Vorasidenib 40mg (qd) q28
- CTRL-RX: placebo (Crossover whther PD at BICR)

**A Progression-free Survival**




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vorasidenib | 168 | 166 | 166 | 157 | 154 | 154 | 133 | 131 | 129 | 93 | 91 | 81 | 63 | 63 | 52 | 45 | 45 | 25 | 22 | 20 | 11 | 11 | 11 | 7 | 7 | 4 | 4 | 4 | 0 |
| Placebo | 163 | 162 | 161 | 146 | 145 | 145 | 117 | 116 | 114 | 73 | 70 | 65 | 38 | 38 | 29 | 21 | 19 | 9 | 8 | 8 | 4 | 4 | 2 | 2 | 2 | 1 | 0 | | |

# Quali sono gli spunti di riflessione nel 2023?

“For many treatments, the variation in prognosis among patients exceeds the size of the treatment effect”

R.Simon, S. Matsui, M.Buyse

- Il paradigma della medicina di precisione non può prescinde dalla «qualità» dei farmaci

- Quale metodologia per produrre dati «rilevanti»

# In un mondo ideale…

- Il successo della strategia di precisione dipende dalla sommatoria di 2 fattori cruciali (indipendenti):
  - Valore prognostico del biomarker  (importanza del target per il tumore)
  - Valore del farmaco nella popolazione selezionata  (attività farmacologica)

# Nel mondo reale…

- Il valore del biomarker è misurato sulla base del suo ruolo di «target» per l'inibizione farmacologica (valore predittivo).
- Ci si è concentrati molto spesso sul valore predittivo ignorando quello prognostico

## ESCAT: ESMO Scale of Clinical Actionability for molecular Targets

| | ESCAT evidence tier | | Required level of evidence | Clinical implication |
|---|---|---|---|---|
| Ready for routine use | I<br>Alteration-drug match is associated with improved outcome in clinical trials | I-A | Prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point | Access to the treatment should be considered standard of care |
| | | I-B | Prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 | |
| | | I-C | Clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types | |
| Investigational | II<br>Alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown | II-A | Retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients | Treatment to be considered "preferable" in the context of evidence collection either as a prospective registry or as a prospective clinical trial |
| | | II-B | Prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points | |
| Hypothetical target | III<br>Alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration | III-A | Clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types | Clinical trials to be discussed with patients |
| | | III-B | An alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data | |
| | IV<br>Pre-clinical evidence of actionability | IV-A | Evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models | Treatment should "only be considered" in the context of early clinical trials. Lack of clinical data should be stressed to patients |
| | | IV-B | Actionability predicted *in silico* | |
| Combination development | V<br>Alteration-drug match is associated with objective response, but without clinically meaningful benefit | | Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome | Clinical trials assessing drug combination strategies could be considered |
| Lack of Evidence | X<br>Lack of evidence for actionability | | No evidence that the genomic alteration is therapeutically actionable | The finding should not be taken into account for clinical decision |

To enquire or ask questions about the ESMO Scale for Clinical Actionability of molecular Targets, please send an email to education@esmo.org

# Nel mondo reale…

- Il valore del biomarker è misurato sulla base del suo ruolo di «target» per l'inibizione farmacologica (valore predittivo).
- Ci si è concentrati molto spesso sul valore predittivo ignorando quello prognostico

# PFS, OS & RR in Precision Oncology Trials and

| Trial | NTC number | PFS | OS | ORR | Attrition |
|---|---|---|---|---|---|
| CREATE | NCT01524926 | 9,00 | NA | 50,00 | 34% |
| PANGEA | NCT02213289 | 8,20 | 15,70 | 74,07 | 49% |
| Battle | NCT00409968 | 1,90 | 8,80 | 3,69 | 72% |
| I-PREDICT | NCT02534675 | 3,67 | 11,80 | 23,29 | 6% |
| NCI-MATCH (subprotocol H) | NCT02465060 | 11.4 | 28.6 | 37,93 | 1% |
| Tapur (breat-TMBh) | NCT02693535 | 2,65 | 7,65 | 21,00 | |
| ROAR | NCT02034110 | 9,00 | 14,00 | 51,20 | 7% |
| NCI-MATCH (subprotocol Q) | NCT02465060 | 3,10 | 8,40 | 5,56 | 1% |
| Drug Rediscovery protocol | NCT02925234 | 3,00 | 10,00 | 15,35 | 33% |
| NCI-MATCH Subprotocol EAY131-Y | NCT02465060 | 5,5 | 14,5 | 28,00 | |
| plasmaMATCH | NCT03182634 | 5,20 | NA | 13,10 | 12% |
| CUSTOM | NCT01306045 | 2,30 | 6,50 | 25,58 | 7% |
| NCI-MATCH (subprotocol Z1D) | NCT02465060 | 6.3 | 17.3 | 35,71 | 1% |
| National Lung Matrix Trial | NCT02664935 | 3,00 | NA | 10,00 | 5% |

# Nel mondo reale…

- Il valore del biomarker è misurato sulla base del suo ruolo di «target» per l'inibizione farmacologica (valore predittivo).
- Ci si è concentrati molto spesso sul valore predittivo ignorando quello prognostico
- Questo non ci consente di valutare correttamente il valore di un farmaco in una popolazione target e crea dei:
  - Dati scontati

Article

# Genomics to select treatment for patients with metastatic breast cancer

https://doi.org/10.1038/s41586-022-05068-3

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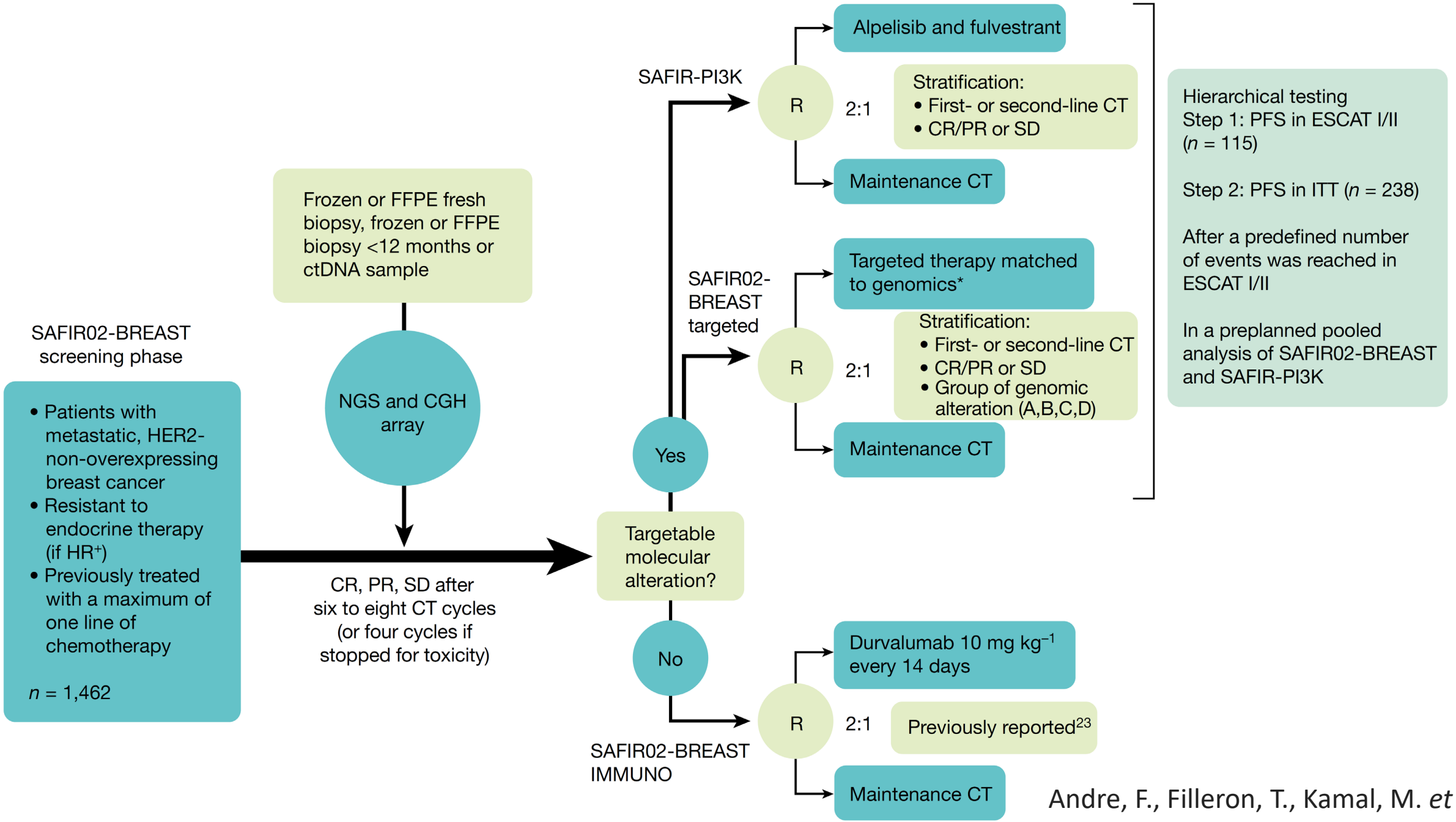
Check for updates

Fabrice Andre[1,2,3,4,34] ✉, Thomas Filleron[5,34], Maud Kamal[6,34], Fernanda Mosele[2], Monica Arnedos[1], Florence Dalenc[7], Marie-Paule Sablin[6,8], Mario Campone[9], Hervé Bonnefoi[10], Claudia Lefeuvre-Plesse[11], William Jacot[12], Florence Coussy[13], Jean-Marc Ferrero[14], George Emile[15], Marie-Ange Mouret-Reynier[16], Jean-Christophe Thery[17], Nicolas Isambert[18], Alice Mege[19], Philippe Barthelemy[20], Benoit You[21], Nawale Hajjaji[22], Ludovic Lacroix[23], Etienne Rouleau[23], Alicia Tran-Dien[2,3,24], Sandrine Boyault[25], Valery Attignon[25], Pierre Gestraud[26], Nicolas Servant[26], Christophe Le Tourneau[6], Linda Larbi Cherif[6], Isabelle Soubeyran[27], Filippo Montemurro[28], Alain Morel[29], Amelie Lusque[5], Marta Jimenez[30], Alexandra Jacquet[30], Anthony Gonçalves[31,35], Thomas Bachelot[32,35] & Ivan Bieche[33,35]

Andre, F., Filleron, T., Kamal, M. *et al*. *Nature* **610**, 343–348 (2022).

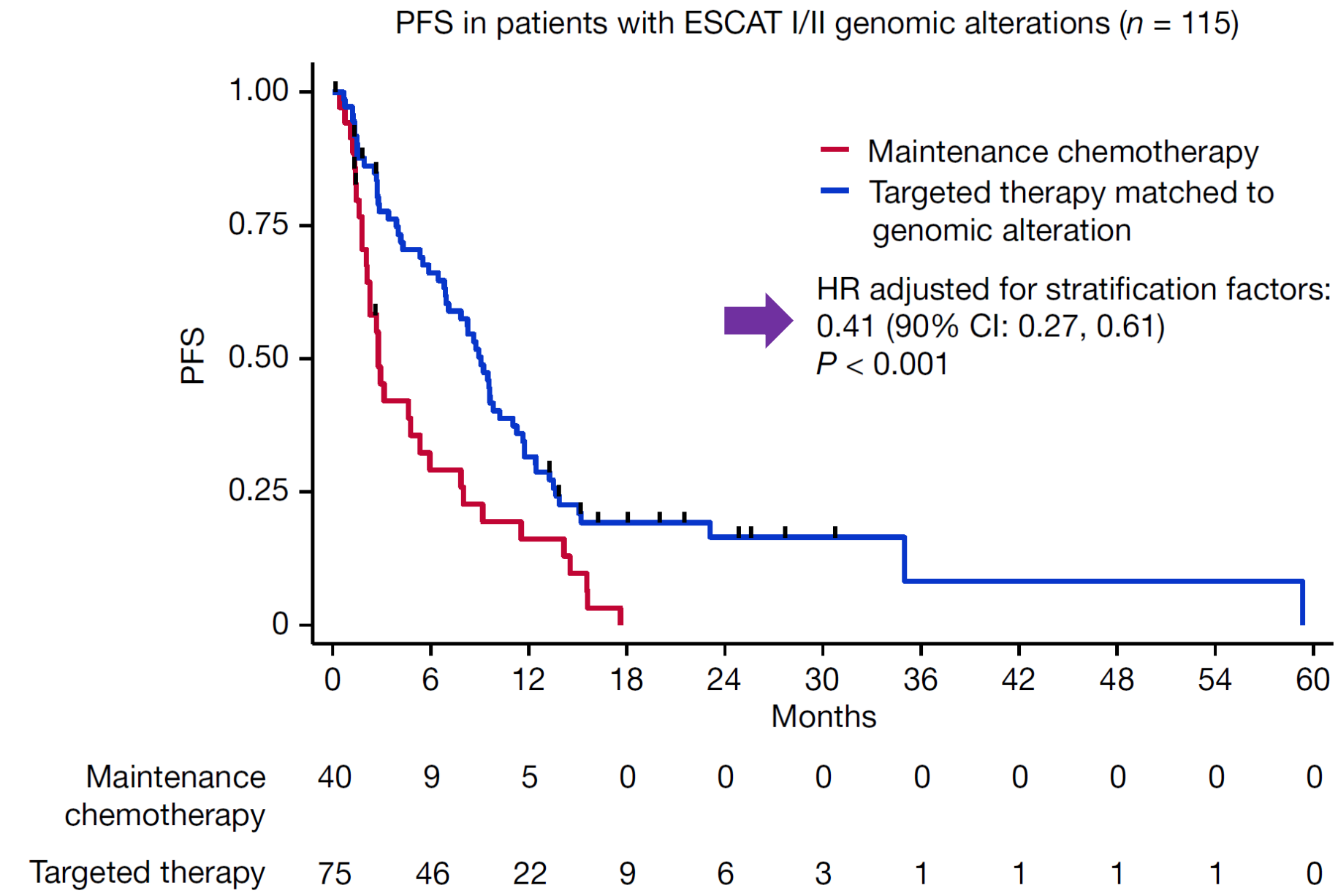



*olaparib, capivasertib, vistusertib, AZD8931, vandetanib, bicalutamide, AZD4547, selumetinib

Andre, F., Filleron, T., Kamal, M. *et al*. *Nature* **610**, 343–348 (2022).

| Matched genomic alteration/targeted therapy decision by MTB | | | | | |
|---|---|---|---|---|---|
| IGF1R amplification (*n*=3), TSC1/2 mutation (*n*=3), STK11 deletion (*n*=1), RPTOR amplification (*n*=1) and AZD2014 | 7 (4%) | 1 (1%) | – | NA | NA | – |
| AKT1 mutation and AZD5363 | 12 (8%) | 4 (5%) | | 12 (16%) | 4 (10%) | |
| PTEN mutation and/or deletion and AZD5363 | 8 (5%) | 2 (2%) | | 4 (5%) | 1 (3%) | |
| PIK3CA (*n*=36), PIK3R1 (*n*=2); mutations/PIK3CB (*n*=1), AKT1 (*n*=1), AKT3 (*n*=1), PDPK1 (*n*=1); amplifications and AZD5363 | 30 (19%) | 12 (15%) | | NA | NA | |
| FGFR1 (*n*=19), FGFR2 (*n*=1), FGF4 (*n*=4), FGFR3 (*n*=1); amplifications/ FGFR2 (*n*=1), FGFR4 (*n*=1); mutations and AZD4547 | 17 (11%) | 10 (12%) | | NA | NA | |
| ERBB2 mutation and AZD8931 | 1 (0.5%) | 2 (2%) | | 1 (1%) | 2 (5%) | |
| EGFR mutation/amplification (*n*=3) or ERBB3 mutation (*n*=2) and AZD8931 | 2 (1%) | 3 (4%) | | NA | NA | |
| FRS2 amplification (*n*=10), NF1 mutation (*n*=7), KRAS mutation (*n*=4), BRAF amplification (*n*=1), BRAF mutation (*n*=1) and selumetinib | 17 (11%) | 6 (7%) | | NA | NA | |
| VEGFA amplification (*n*=3), RET mutation (*n*=1), EGFR amplification (*n*=1), KDR mutation (*n*=1) and vandetanib | 3 (2%) | 3 (4%) | | NA | NA | |
| AR amplification and bicalutamide | 0 | 1 (1%) | | NA | NA | |
| BRCA1 mutation and olaparib | 11 (7%) | 10 (12%) | | 11 (15%) | 10 (25%) | |
| BRCA2 mutation and olaparib | 26 (16%) | 10 (12%) | | 26 (35%) | 10 (25%) | |
| PALB2 mutation and olaparib | 1 (0.5%) | 2 (2%) | | 1 (1%) | 2 (5%) | |
| ATR/ATM mutation/deletion and olaparib | 2 (1%) | 4 (5%) | | NA | NA | |
| PIK3CA mutation and alpelisib | 20 (13%) | 11 (14%) | | 20 (27%) | 11 (27%) | |

André, F., Filleron, T., Kamal, M. *et al*. *Nature* **610**, 343–348 (2022).

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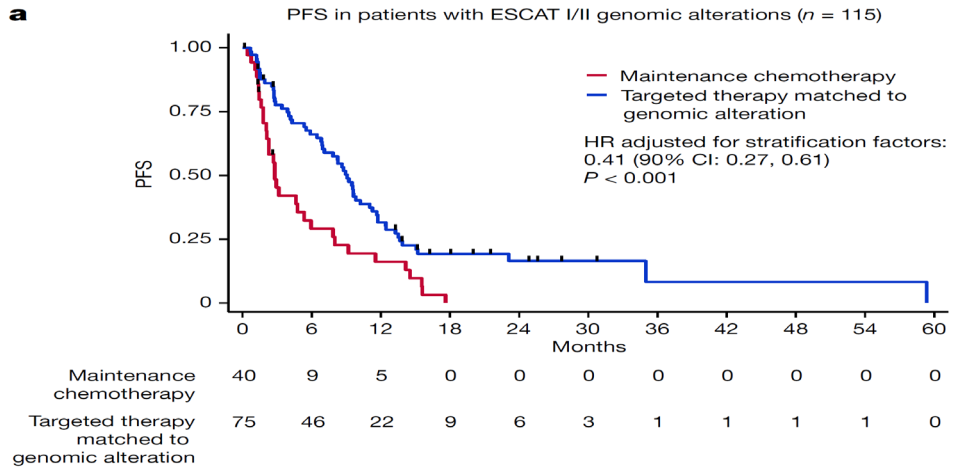
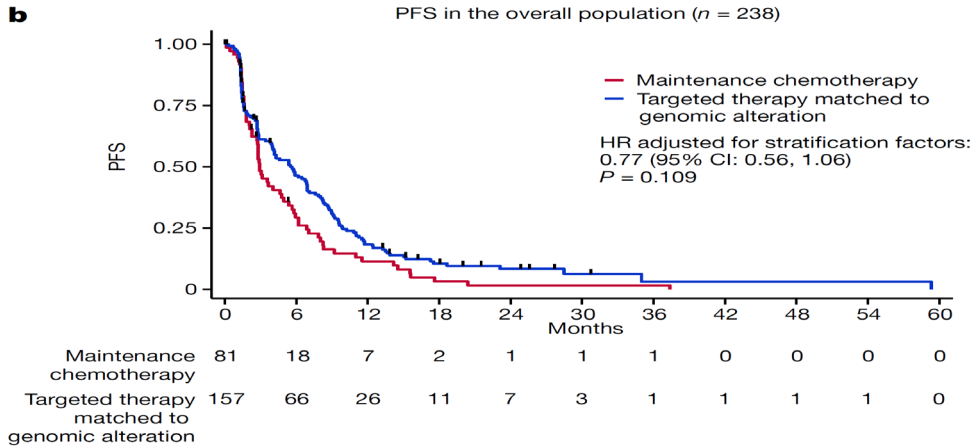
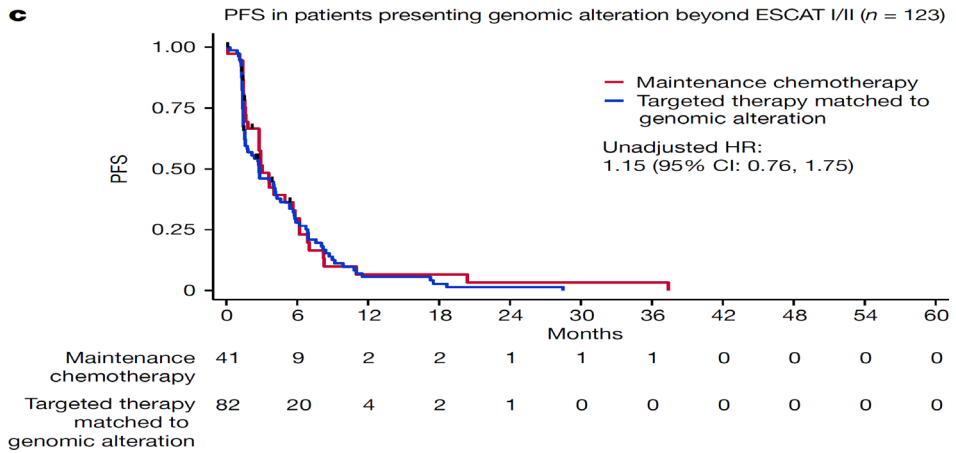


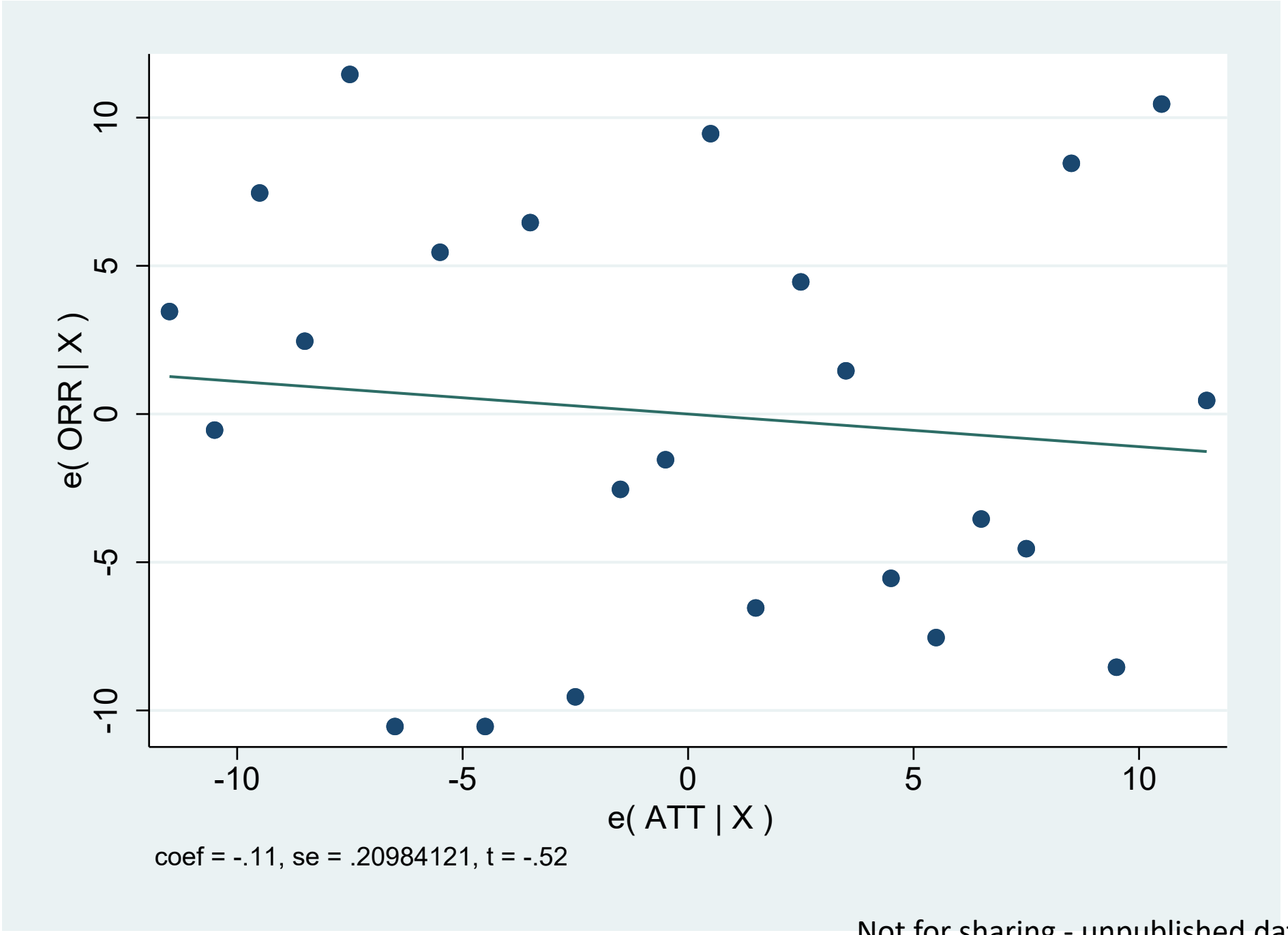




- Il vantaggio si ottiene esclusivamente nelle mutazioni ESCAT I/II
- E' molto debole e (non statisticamente significativo nella popolazione generale, test gerarchico)
- Nullo (dato forte) nella popolazione con mutazione ESCAT III-
- **Questo dato può essere considerato più una validazione dell'ESCAT come fattore predittivo nelle pazienti mBC HER2- che un'informazione aggiuntiva rispetto a quanto noto!!**

# Nel mondo reale…

- Il valore del biomarker è misurato sulla base del suo ruolo di «target» per l'inibizione farmacologica (valore predittivo).
- Ci si è concentrati molto spesso sul valore predittivo ignorando quello prognostico
- Questo non ci consente di valutare correttamente il valore di un farmaco in una popolazione target e crea dei:
  - Dati scontati
  - Potenziali paradossi



- Il paradigma della medicina di precisione non prescinde dalla «qualità» dei farmaci

- Quale metodologia per produrre dati «rilevanti»

## Why will there never be a randomized trial for NTRK-rearranged tumors?

The optimal assessment of the risk-to-benefit ratio of a new treatment, particularly in oncology, has always been based on the results of prospective randomized trials, ideally carried out in a double-blind manner with a large sample size and overall survival as the primary endpoint. This is still the best level of evidence available and has been an indisputable metric for discussing approval and reimbursement with health authorities for decades. This remains true in clinical oncology. However, it is no longer an appropriate standard in personalized medicine, particularly when focusing on rare subtypes. Indeed, molecular screening can categorize common diseases into several ultra-rare pathologies, each grouping a limited number of patients. For example, patients with NTRK-rearranged tumors are textbook cases. They could be identified and receive personalized treatment; but, in some countries, access to treatment is suspended pending the results of randomized trials. However, the demand is insurmountable.

However, (RCT) is no longer approriate for Precision Oncology…
…Rarity of the molecular alteration (ultra-rare tumorus) and the absence of standard-of-care pose risk to EQUIPOISE!!

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Available online 15 April 2023



https://doi.org/10.1016/j.annonc.2023.04.001

# E voi randomizzereste i pazienti NTRK??

# Take home message

Bisogna fare ancora molta ricerca sulla ricerca in oncologia di precisione.