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Biomarker-driven clinical trials

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BeSHG February 2022

Introduction

What is a biomarker ? (National Cancer Institute)

- A biological molecule found in *blood, other body fluids, or tissues*
- that is a sign of a *normal or abnormal process,* or of *a condition or disease*
- Also called *molecular mark*er and *signature molecule*

Introduction

Clinical utility of markers

- PROGNOSTIC

Biomarker associated with disease outcome *independent of any treatment*

- PREDICTIVE

Biomarker that *predicts for response or resistance to a specific treatment*

Prognostic ≠ Predictive

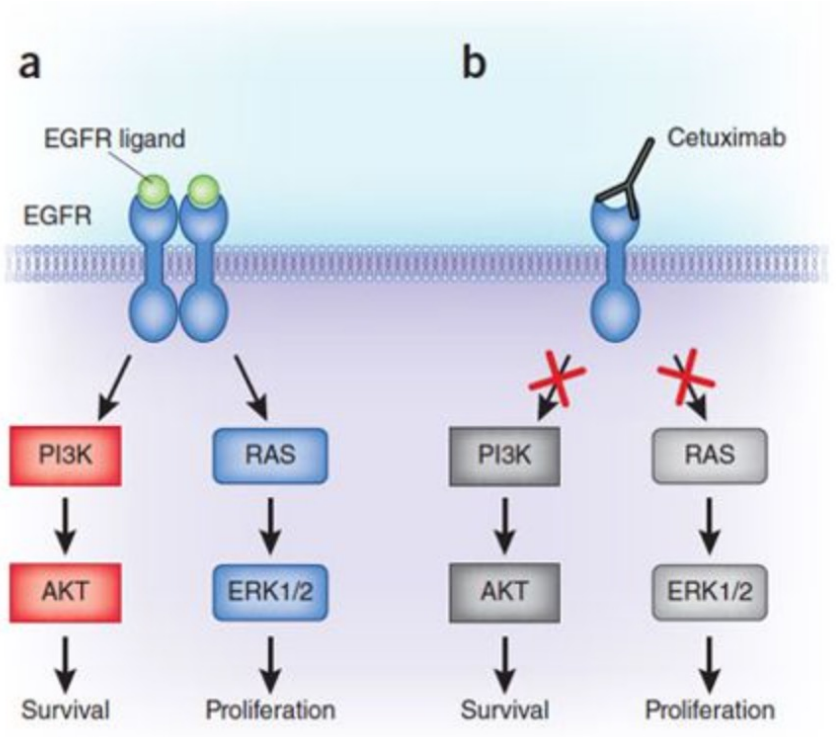
Introduction

CETUXIMAB

= monoclonal antibody against EGFR

- Only approved targeted therapy in head and neck cancer
- Response rate as single agent: 13%

No biomarker predictive of response or resistance!



Nature 2012

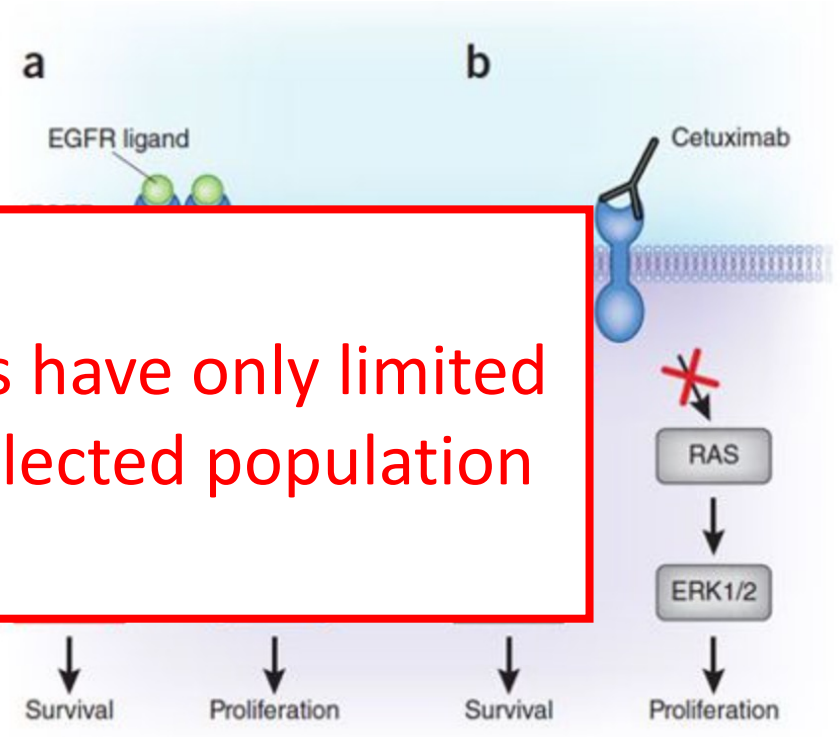
Introduction

CETUXIMAB

= monoclonal antibody against EGFR

- Only appro
  therapy in l
  cancer
- Response r
  agent: 13%

Targeted agents have only limited activity in unselected population



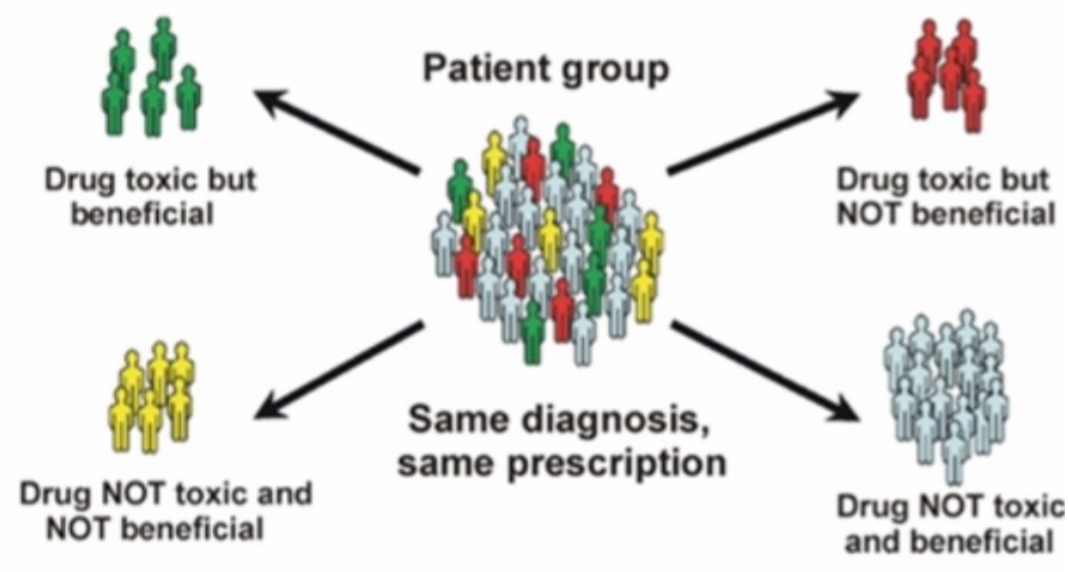
No biomarker predictive of response or resistance!

Nature 2012

Introduction

Can we select the population based on biomarker ?

Biomarker + patient → Targeted drug



PRECISION ONCOLOGY

Give the right drug to the right patient !

Introduction

Biomarker-based treatment in clinical practice

- *HER2* amplified breast cancer treated with HER2 targeting therapies

- *EGFR* mutated lung cancer treated with EGFR tyrosine kinase inhibitors

Introduction

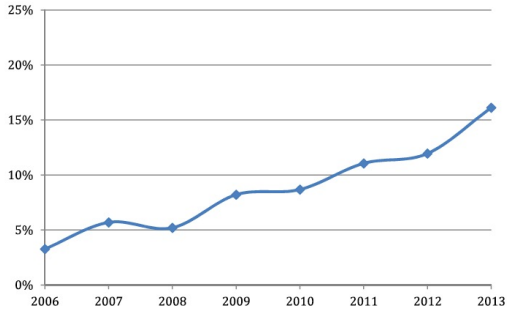
Treatment landscape in oncology is changing !

« One treatment fits all »

« Precision Medicine » based on biomarkers

Proper testing in clinical trials is indispensable to validate claims of efficacy and safety !

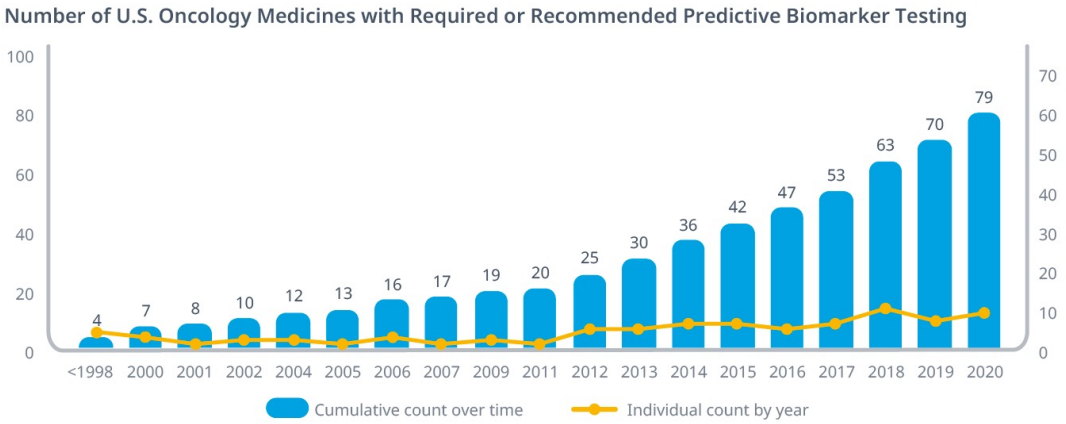
Introduction



Proportion of trials in USA requiring the presence/absence of a genomic alteration increased over 5-fold between 2006 and 2013

Cancer Treat Rev, 2015

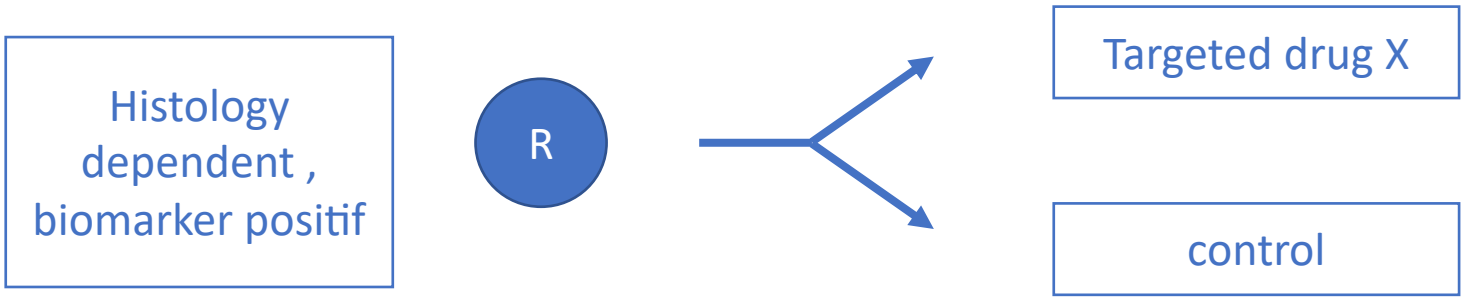
In 2018, over one-third of trials were using biomarkers to stratify patients (IQVIA, Global trends in oncology 2018)



Introduction

Standard approach

Investigating one or two interventions in a single disease enriched for 1 biomarker



Introduction

Trastuzumab (Herceptin): Anti-HER2 Antibody, targets HER2 oncoprotein

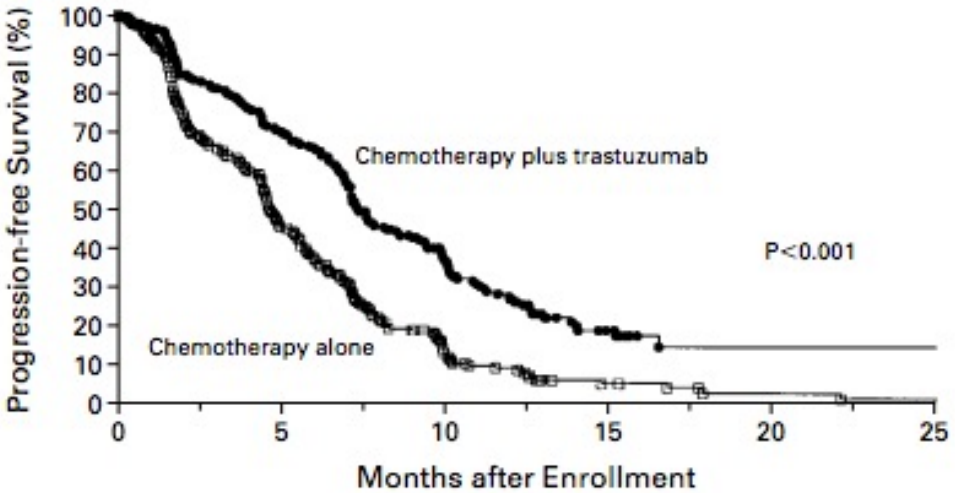
25-30% of breast cancers

Metastatic breast cancer overexpressing HER2

R

Chemotherapy + Trastuzumab

Chemotherapy



NEJM, 2001

Introduction

Challenges

- Slow recruitment (low incidence biomarker)
- Expensive
- Time-consuming

Next-generation clinical trials

- Master protocols
  - Basket trials
  - Umbrella trials
- Screening programs
- Strategy trials

Master protocols

= Framework in wich several (sub)studies that investigate multiple therapies are operated under one « overarching » master protocol

Regroups under the same protocol, sub-studies sharing key designs and operational aspects

Master protocols

Main aims

- Facilitate screening and patient accrual
- Answer more questions more efficiently and in less time
- Operational efficiency

Master protocols

Basket

histology independent

marker-specific cohorts

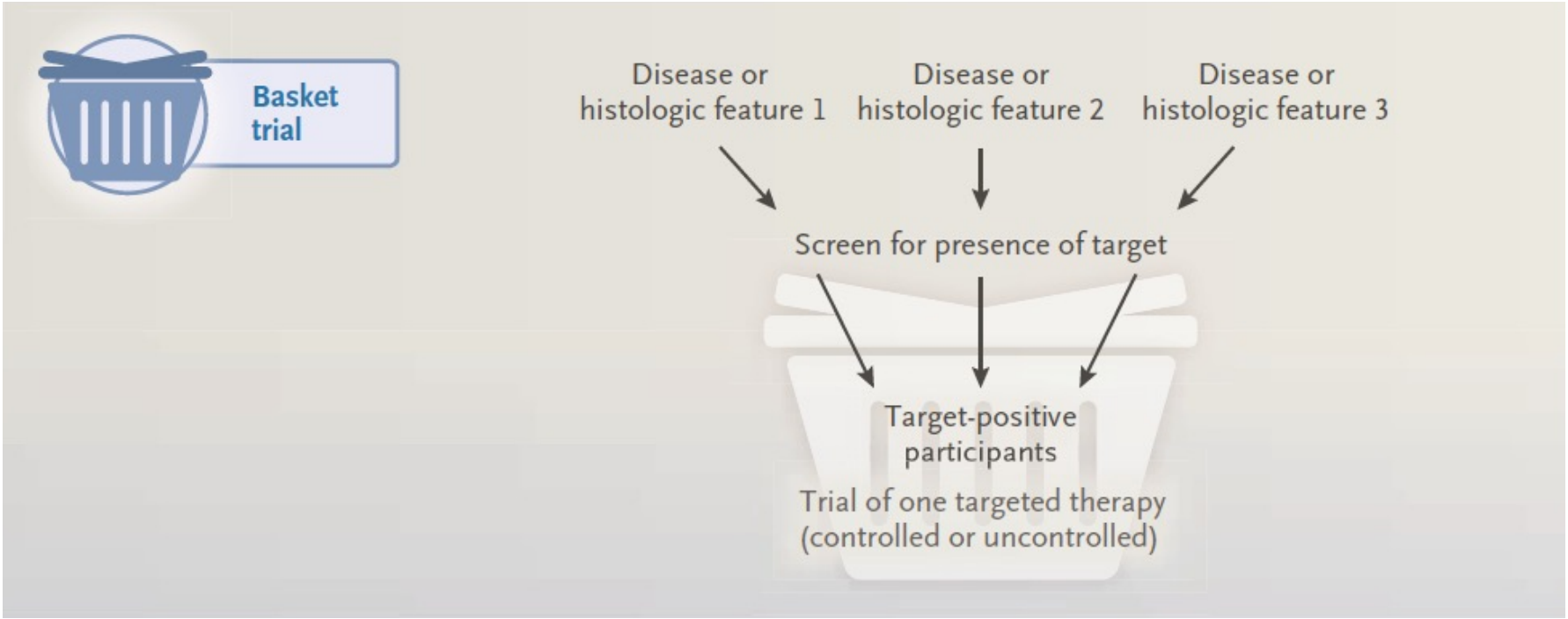
Umbrella

Histology dependent

many marker cohorts

Basket Trials

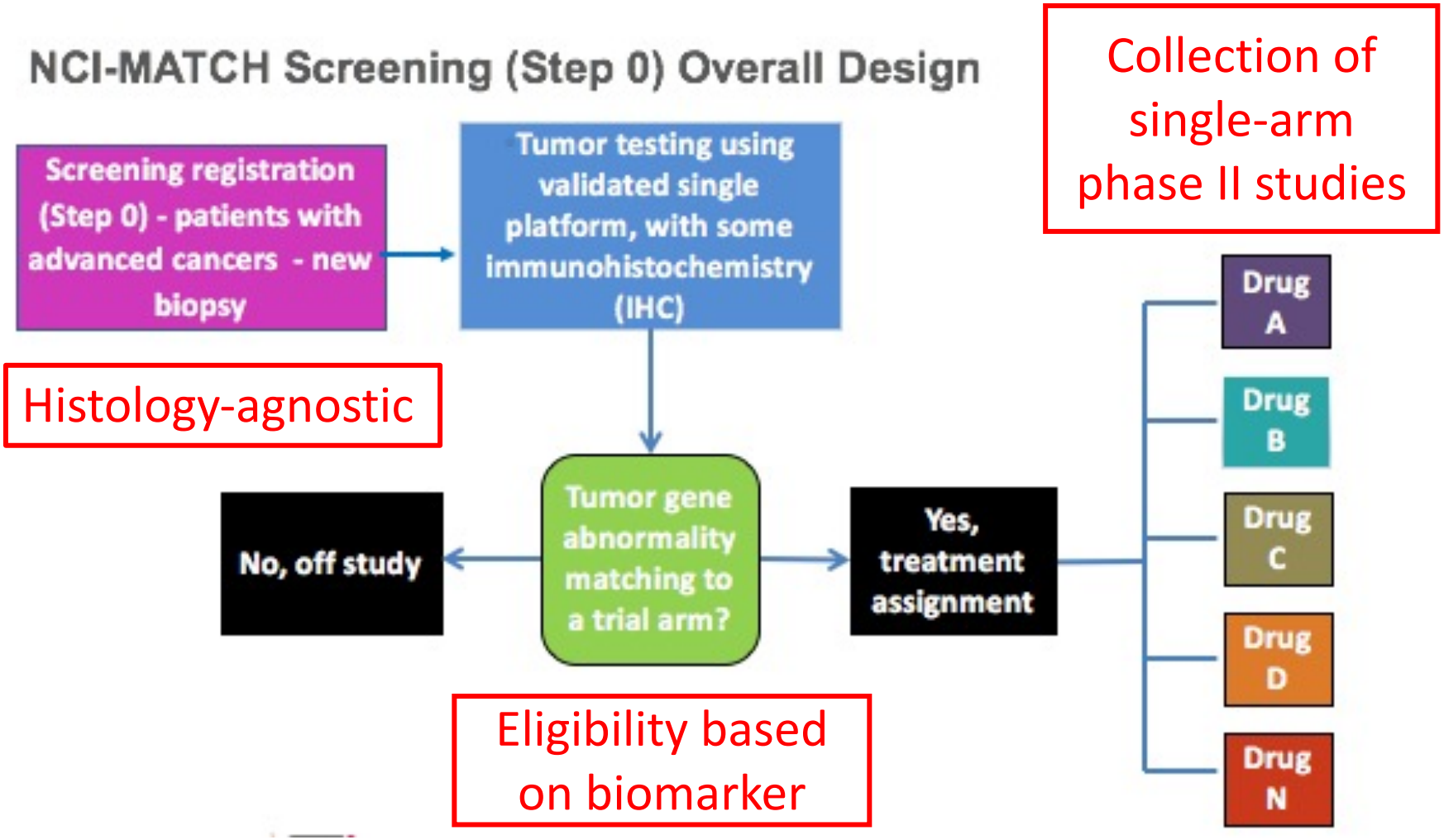
Histology-agnostic



Basket Trials

Study	Tumor	Biomarker testing	Methodology	Endpoint	Results
NCI-MATCH	All, **advanced solid tumors**	New biopsy, **sequencing on 143 genes**	Patients with **molecular alteration** are assigned in **1 of predefined treatment cohorts**	Objective response rate (ORR)	Reported per arm
Mypathway	**Advanced refractory solid** tumor harboring **molecular alteration in HER2, EGFR, BRAF or Hedgehog pathway**	Molecular profiling was **not conducted as part of the trial**	Patients are assigned to **specific treatment cohorts** based on the presence of a relevant molecular alteration	ORR within each tumor-pathway cohort	ORR: 23% within different tumor types
SUMMIT	**Solid tumors** harboring **HER2 and HER3 mutations**	MP was **not conducted as part of the trial**	Pts wit HER2-mutations were enrolled into **disease-specific cohorts** and HER3 mutants into 1 cohort	ORR	HER2-mutant: primary endpoint only met for BC (ORR 32%) and not for lung, colorectal or bladder No responses in HER3 mutant cohort

Basket trial – NCI MATCH



Basket trial – NCI MATCH

Objective

- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, **regardless of the cancer type**

- **signal-finding trial**—treatments that show promise can advance to larger, more definitive trials

Basket trial – NCI MATCH

- Open at US-based sites (nearly 1100 cancer centers)
- Master protocol with multiple phase II treatment arms (nearly 40 treatment arms)

  Eligibility defined by molecular characteristics

- Single agents or combinations with recommended phase II dosage(s) known

  FDA-approved for another indication or investigational

- Treatment arms open and close without affecting others

Basket trial – NCI MATCH

- Succesful laboratory testing for 93% of patients (5560/5962)

- Preplanned acces to drugs within the trial (<-> screening programs)…however **only 12 %** (689/5560) were finally enrolled in the trial...

Basket trial – NCI MATCH

NCI-MATCH 30 Treatment Arms, By Prevalence Rate of Gene Abnormality

Arm	Variant	Prevalence Rate %	Drug	Arm	Variant	Prevalence Rate %	Drug
I	PIK3CA	3.47	Taselisib	Y	AKT	0.77	AZD5363
W	FGFR	2.86	AZD4547	H	BRAF V600 E/K	0.69	Taflinar® Mekinist™
Z1I	BRCA1 or BRCA2	2.79	AZD1775	U	NF2 loss	0.69	Defactinib (VS-6063)
P	PTEN loss	1.93	GSK2636771	C2	MET exon 14	0.61	Xalkori®
Z1A	NRAS	1.90	Binimetinib	C1	MET amplif.	0.51	Xalkori®
S1	NF1	1.77	Mekinist™	T	SMO/PTCH1	0.42	Erivedge®
N	PTEN	1.75	GSK2636771	L	mTOR	0.31	TAK-228
Z1D	dMMR status	1.51	Opdivo®	S2	GNAQ/GNA11	0.16	Mekinist™
Q	HER2 amplif.	1.49	Kadcyla®	E	EGFR T790M	0.11	AZD9291
J	HER2 amplif.	1.49	Herceptin® Perjeta®	V	cKIT	0.11	Sutent®
Z1C	CDK4 or CDK6	1.36	Ibrance®	Z1E	NTRK	0.10	Larotrectinib
M	TSC1 or TSC2	1.11	TAK-228	G	ROS1	0.05	Xalkori®
B	HER2 activating	1.04	Gilotrif®	A	EGFR activating	0.05	Gilotrif®
Z1B	CCND1/2/3	0.84	Ibrance®	F	ALK	0.03	Xalkori®
R	BRAF fusions	0.80	Mekinist™	X	DDR2	0.00	Sprycel®

Basket trial – NCI MATCH

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P	PTEN loss						ri®
Z1A	NRAS						ri®
S1	NF1						dge®
N	PTEN						28
Z1D	dMMR statu						nist™
Q	HER2 ampli						291
J	HER2 amplif.	1.49	Herceptin® Perjeta®	V	cKIT	0.11	Sutent®
Z1C	CDK4 or CDK6	1.36	Ibrance®	Z1E	NTRK	0.10	Larotrectinib
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R	BRAF fusions	0.80	Mekinist™	X	DDR2	0.00	Sprycel®

18% of screened tumors was found to have a genetic mutations that matched the patient to 1 of the 30 treatment arms: low prevalence of targeted variants

Basket trial – NCI MATCH

Less Common Disease Type	% of Total Screened (N=5560)
Ovarian	9.5
Uterine	6.2
Pancreas	6.1
Sarcoma	4.6
Head and Neck	3.9
Neuroendocrine	3.3
Gastroesophageal	3.2
Cholangiocarcinoma	2.8
Liver and Hepatobiliary other than Cholangio.	1.9
Central Nervous System	1.7
Bladder/Urinary Tract	1.6
Cervical	1.6
Small Cell Lung	1.4
Melanoma	1.4
Kidney	1.2
Anal	0.8
Mesothelioma	0.8
Lymphoma	0.7
Myeloma	0
Other	9.7
Less Common Cancers	**62.5%**

Common Disease Type	% of Total Screened (N=5560)
Colorectal	15.3
Breast	12.4
Non-Small cell lung	7.3
Prostate	2.5
Common Cancers	37.5%

Aim was to include 25% of « less common cancers »

Far exceeded !

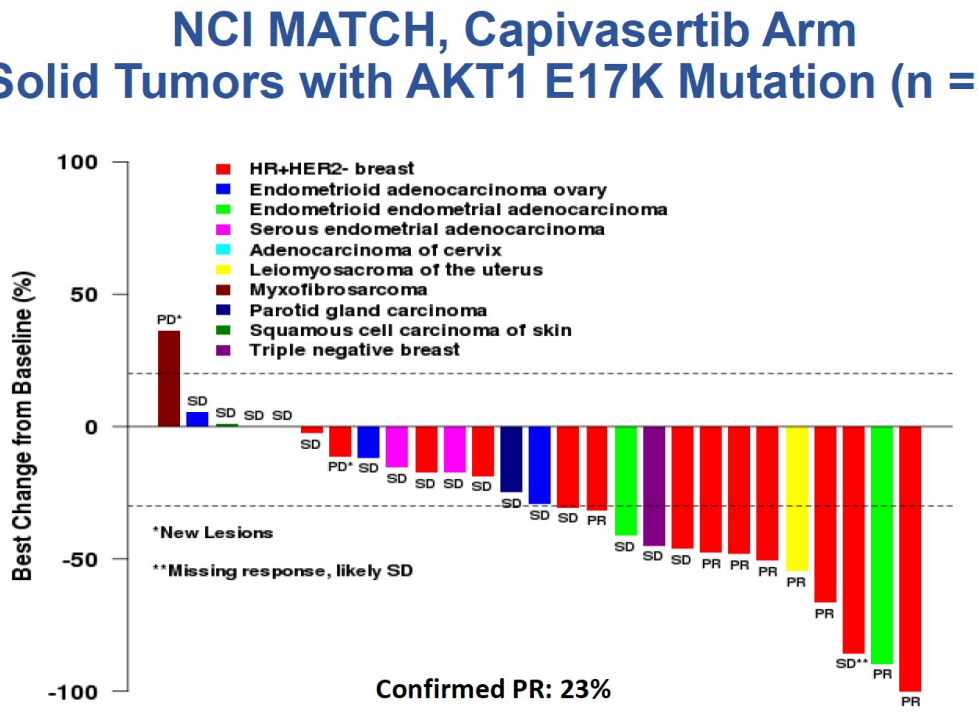
Basket trial – NCI MATCH

NCI MATCH: 11 of 35 Arms With Results
3/11 Positive (27%)

Subprotocol	Drug/molecular	Reported out	Result
Z1D	Nivolumab for MMRd	SITC 2017; manuscript pending	Positive
Y	Capivasertib/AKT mutations	Nov 2018	Positive
H	Trametinib/Dabrafenib/BRAFV600	June 2019	Positive
I	Taselisib/PIK3CA mutations	June 2018 (ASCO)	Neg
Q	Ado-trastuzumab emtansine/ERRB2 amplification	June 2018 (ASCO)	Neg (8% RR)
W	AZD4547/FGFR amplification, mutation, fusion	June 2018 (ASCO)	Neg (8% RR)
N/P	GSK2636771/PTEN mut or loss	October 2018 (ESMO)	Neg
B	Afatinib/ERRB2 activating mutations	April 2019 (AACR)	Neg (2.7%)
Z1-B	Palbociclib/CCND1, 2, or 3 amplifications	April 2019 (AACR)	Neg
Z1-I	AZD1775/BRCA 1 or BRCA2 mutations	April 2019 (AACR)	Neg (3.2%)

Basket trial – NCI MATCH

- Promising signals in some of the reported cohorts

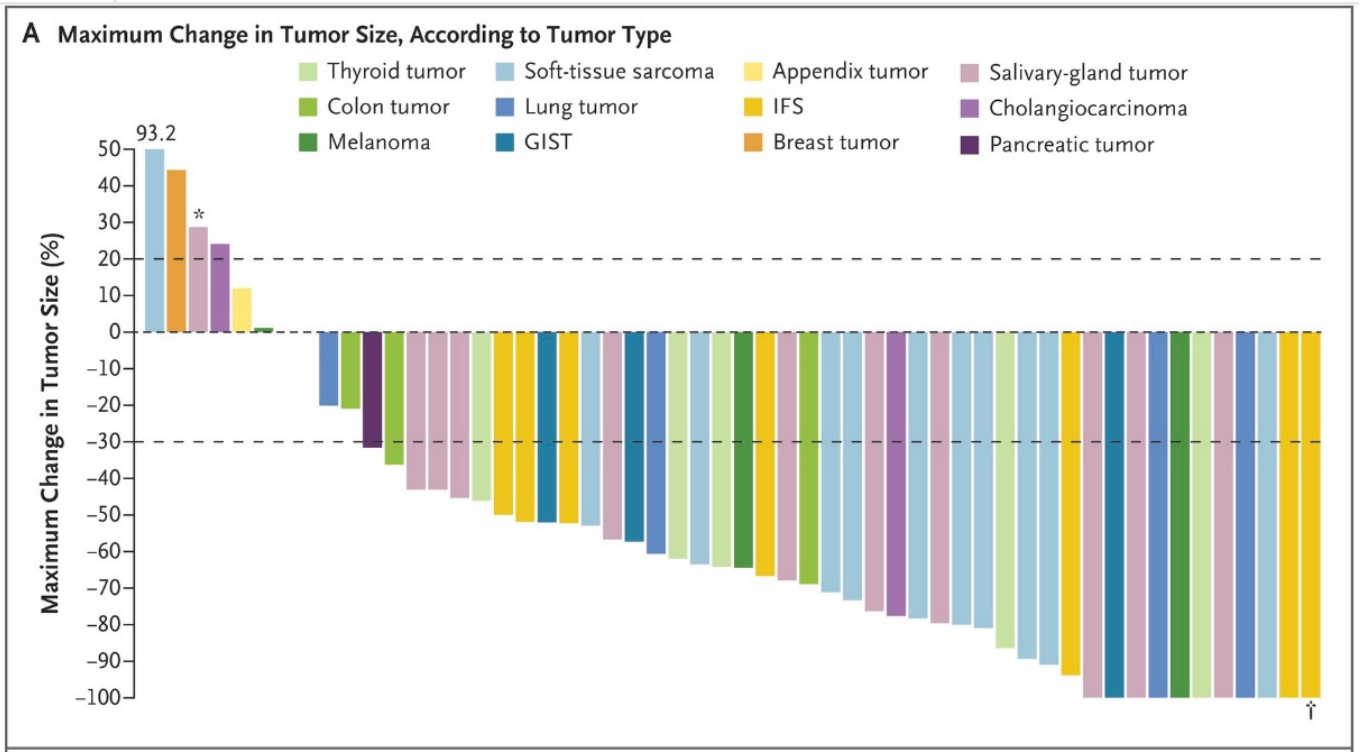


AKT1 E17K mutation: 1.3% (70 of 5,548 patients)

ECOG-ACRIN K Kalinsky et al 2018 EORTC-NCI-AACR Symposium

Basket trial

Larotrectinib in *NTRK*-fusion positive cancers



NEJM 2018

Succesfull tumor agnostic approach

Master protocols

$BRAF^{V600E}$ mutated cancers treated with BRAF inhibitor

70% melanoma, 10% colorectal cancer, and 30-70% papillary thryoid carcinoma

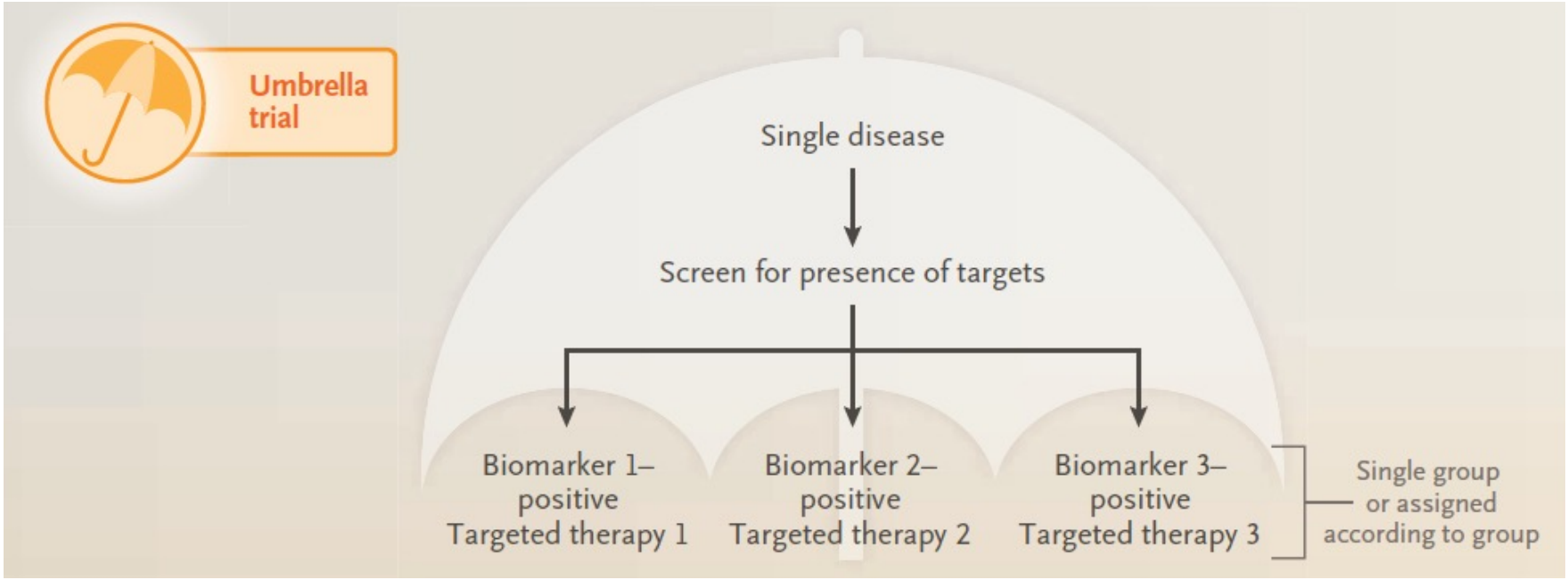
	Melanoma	Colorectal cancer
Response rate	80%	5%

Not always the case…

Tumors having the same oncogenic driver mutations can differ significantly in their responses to targeted cancer drugs.

Umbrella trials

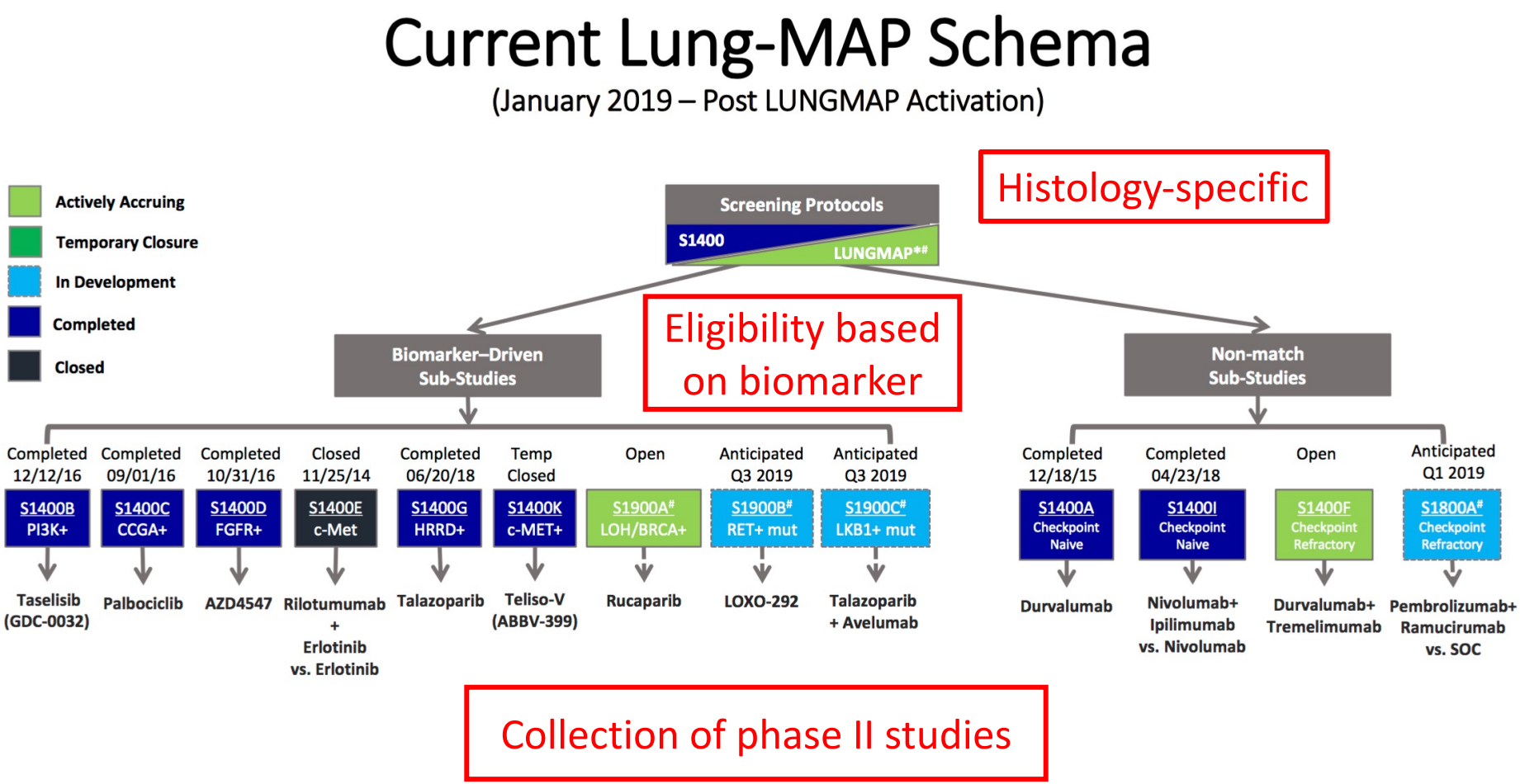
Histology-specific



Umbrella trials

Study	Tumor	Biomarker testing	Methodology	Endpoint	Results
LUNG-MAP master protocol	Advanced **lung** SCC	Archival or new biopsy **FoundationOne NGS assay**	**Multiple arms**: based on the molecular profile, each patient is enrolled in substudy (matched or nonmatch)	Objective response rate (ORR)	Results for 3 biomarker-driven cohorts ORR 4-7%: closed for futility
The National Lung Matrix	Advanced **NSCLC**	Prescreening of tumor biopsy trough the stratified Medicine Program (in // with 1st line): **adaptable 28-gene NGS sequencing platform**	**Multiple arms**, Patients are allocated to the appropriate targeted therapy according to the molecular genotype of their cancer	ORR or PFS	Some interim results per cohorts
FOCUS 4	Advanced **colorectal cancer**	FFPE before commenced of standard chemotherapy **Mutations of some preselected genes + some IHC**	**Multiple arms**; After induction chemotherapy, patients are enrolled in differents cohorts on the basis on the MA	PFS	First results for 1 patient cohort (FOCUSD): Closed for futility

Umbrella Trial – Lung-MAP



Umbrella Trial – Lung-MAP

Objective

- To learn whether targeted cancer therapies that are matched to the genomic makeup of a patients' lung cancer tumors are more effective than the current standard therapies in halting or reversing the progress of the disease and in extending the patient's life.

Umbrella Trial – Lung-MAP

- Open at more than 700 sites in the US and Canada
- Master protocol with multiple phase II-III treatment arms
- “Umbrella” infrastructure allowed redesign with the major change of immunotherapy emergence
- “Umbrella” infrastructure & autonomy of each sub-study facilitates opening-closing of new sub- studies quickly (“Self-Sustaining”)

Umbrella Trial – Lung-MAP

Update june 2018

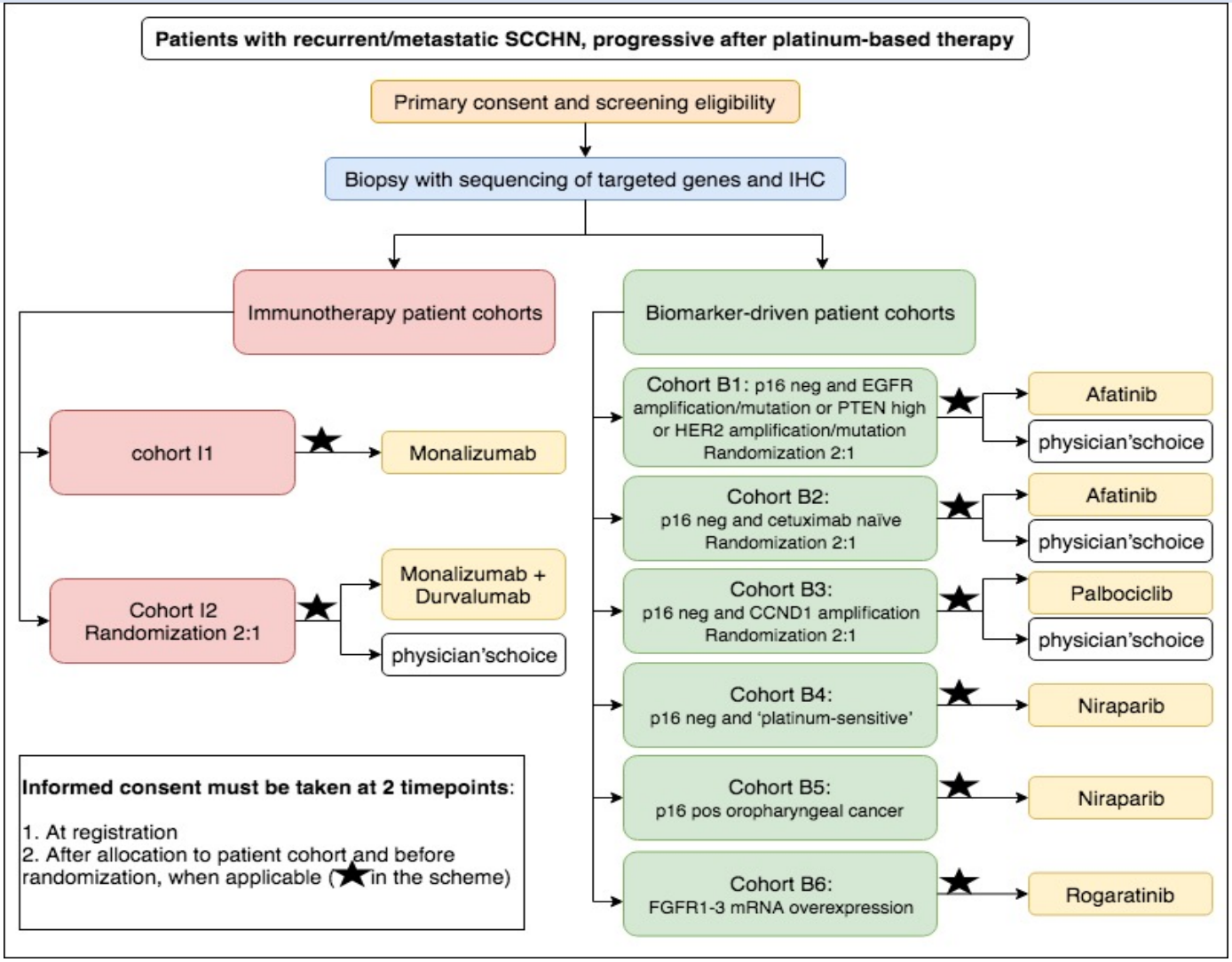
- 1407 pts registered for screening , 1244 have biomarker results, 529 registered for a substudy (43%)

- Results for 3 matched cohorts :

  S1400B (PI3K inhibitor), S1400C (CDK4/6 inhibitor) and S1400D (FGFR inhibitor)

  → Modest ORR 4-7%: closed due to futility at interim analysis

Umbrella Trial – Upstream trial



Galot et al, Annals of Oncology 2018

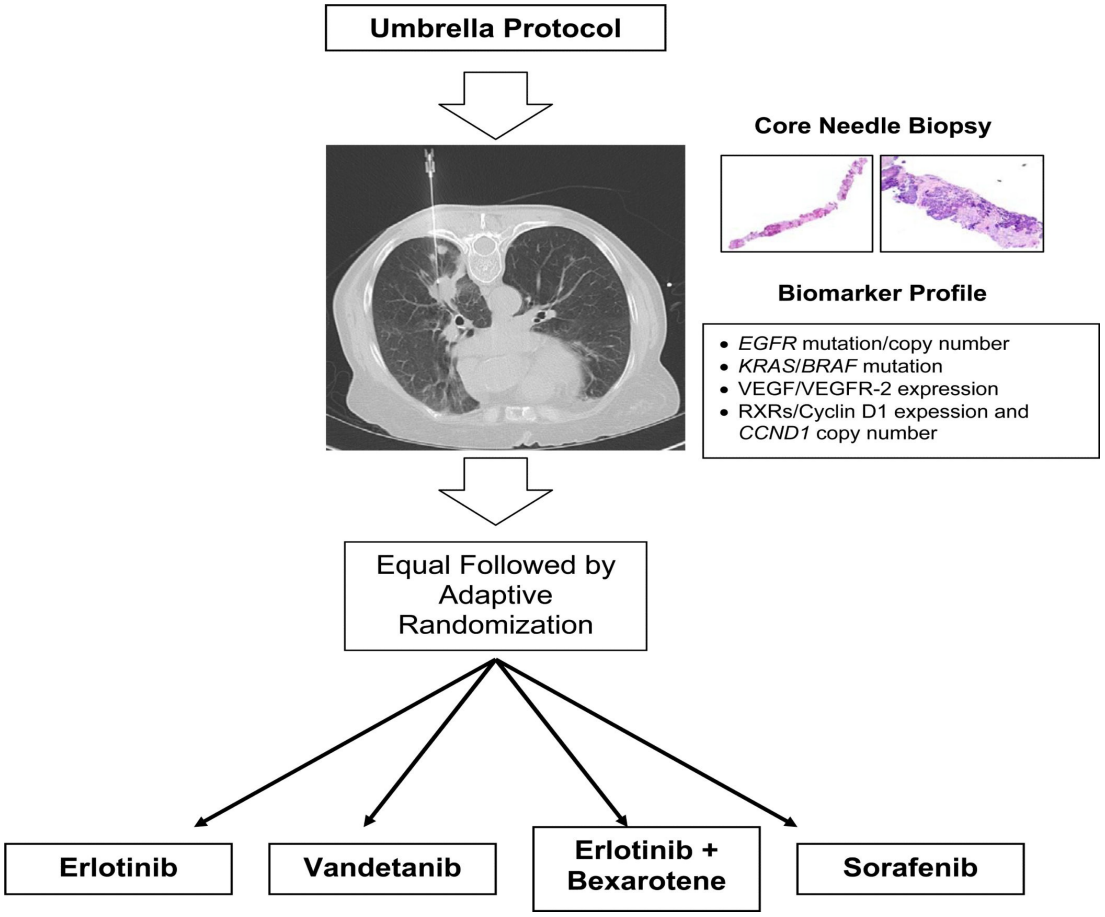
Adaptive randomization

Adaptive randomization assigns more patients to the most promising therapies based on an appraisal of accumulated data

Aim:

Accelerate the identification of targeted therapies performing better within a biomarker-matched subgroup while avoiding unnecessary exposure of patients to therapies that are not beneficial to them.

Adaptive randomization– Battle



Adaptive randomized umbrella trial in advanced NSCL

Pts were asigned in 4 biomarker-positive subgroups and 1 biomarker negative subgroup

Within each subgroup, pts were randomized to 4 different targeted therapies

Screening programs

Molecular screening program to **facilitate the access to precision medicine trials**

Can be

- histology agnostic (IMPACT, MOSCATO 01)
- histology specific (SAFIR 01)

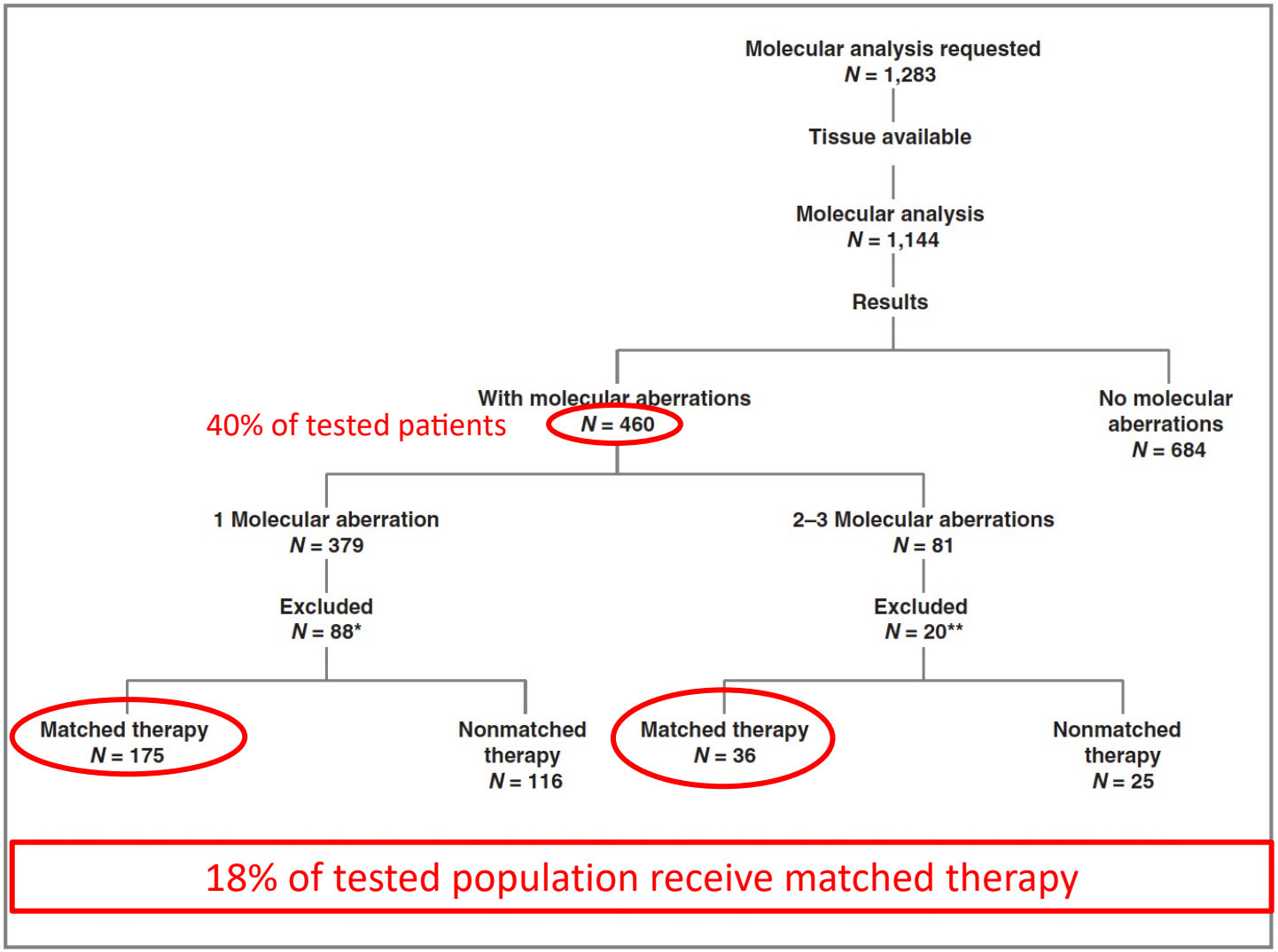
Screening programs - IMPACT

IMPACT trial = Initiative for Molecular Profiling and Advanced Cancer Therapy

- personalized medicine program for patients who were referred to the phase I clinical trials program at MD Anderson Cancer Center

- **Assignement to phase I clinical trials** based on identification of a molecular alteration

Screening programs - IMPACT



CCR, 2012

Screening programs

Number of patients finally treated with matched therapy in different screening programs: **13%-19%**

→ Why a low enrolment rate ?

- Tumor tissue issues
- Decline of performance status
- Rapidly progressing disease
- Absence of targetable event
- Acces to matched clinical trials or drugs

Screening programs - IMPACT

Endpoint:

clinical outcome of pts with MA treated with matched therapy versus pts not treated with matched therapy

	Matched therapy (n=381)	**Non-matched therapy (n=238)**	**HR (95% CI)**	**p**
ORR	43 (11%)	12 (5%)		.0099
SD >/= 6mo + CR + PR	111 (29%)	56 (24%)		.13
FFS (months)	3.4	2.9	0.81 (0.69 to 0.96)	0.015
OS (months)	8.4	7.3	0.84 (0.71 to 0.99)	0.041

JCO, 2017

Only **8%** of the of the whole population finally experienced a clinical benefit (111/1436 pts)

Screening programs

→ Why limited clinical benefit ?

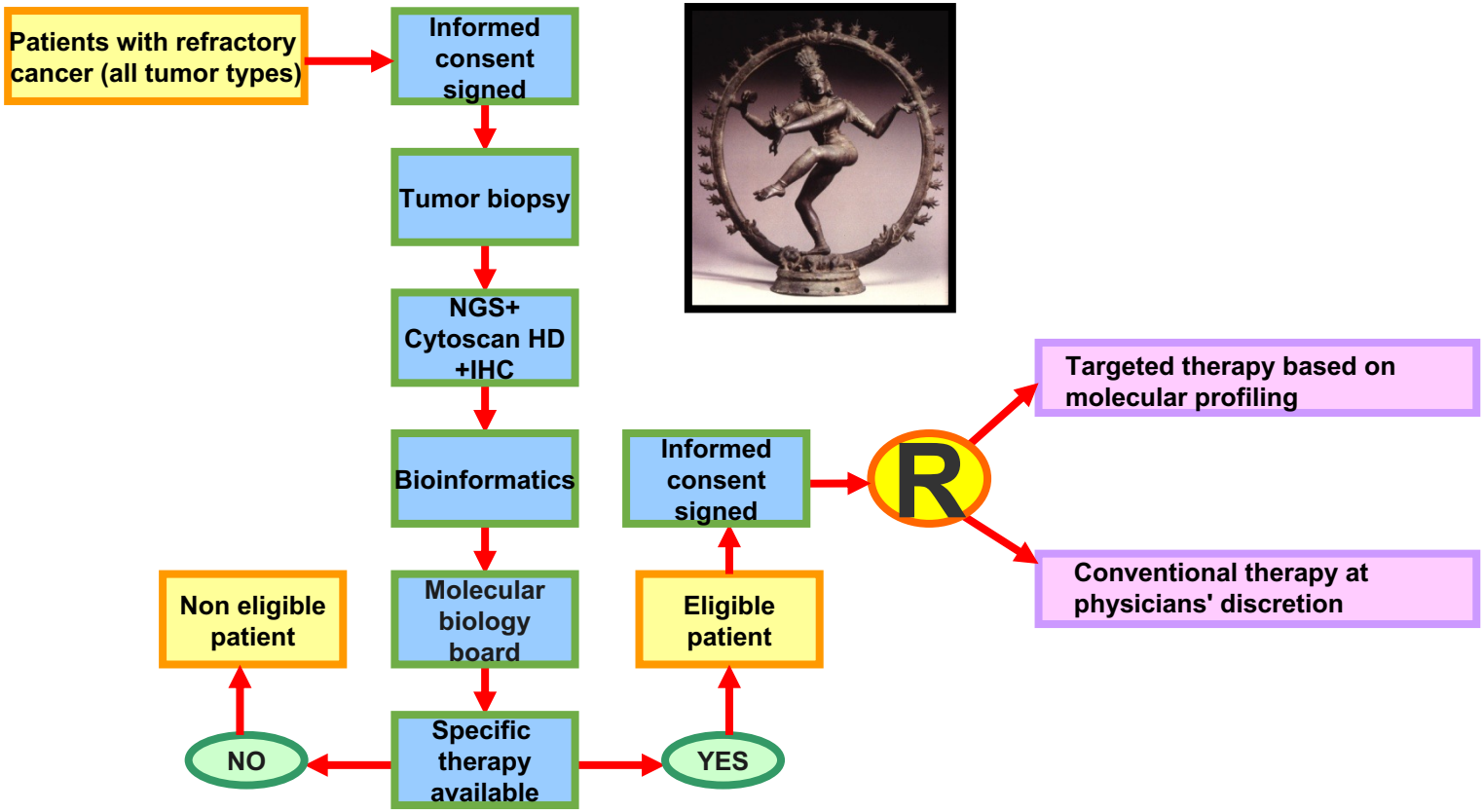
- Non-optimal targeted drugs in phase I trials
- Suboptimal dosages in phase I trials
- Level of evidence concerning the investigated biomarker

Strategy trials

Testing the strategy of precision medicine

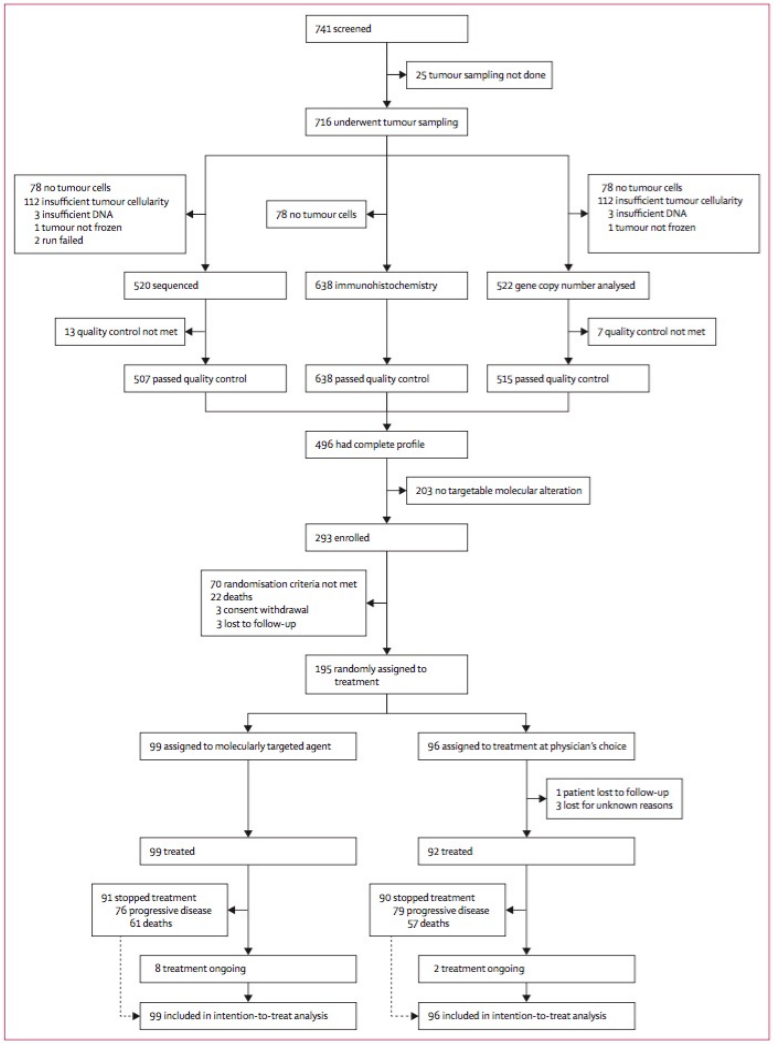
Investigates if selecting the treament based on molecular alterations (independently of the disease, the studied biomarker and the targeted drug) results in superior outcome compared with standard therapy

Strategy trials: SHIVA



Lancet Oncol 2015

Strategy trials: SHIVA



- Oct 2012– July 2014:

Screening of 741 patients (any tumour type)

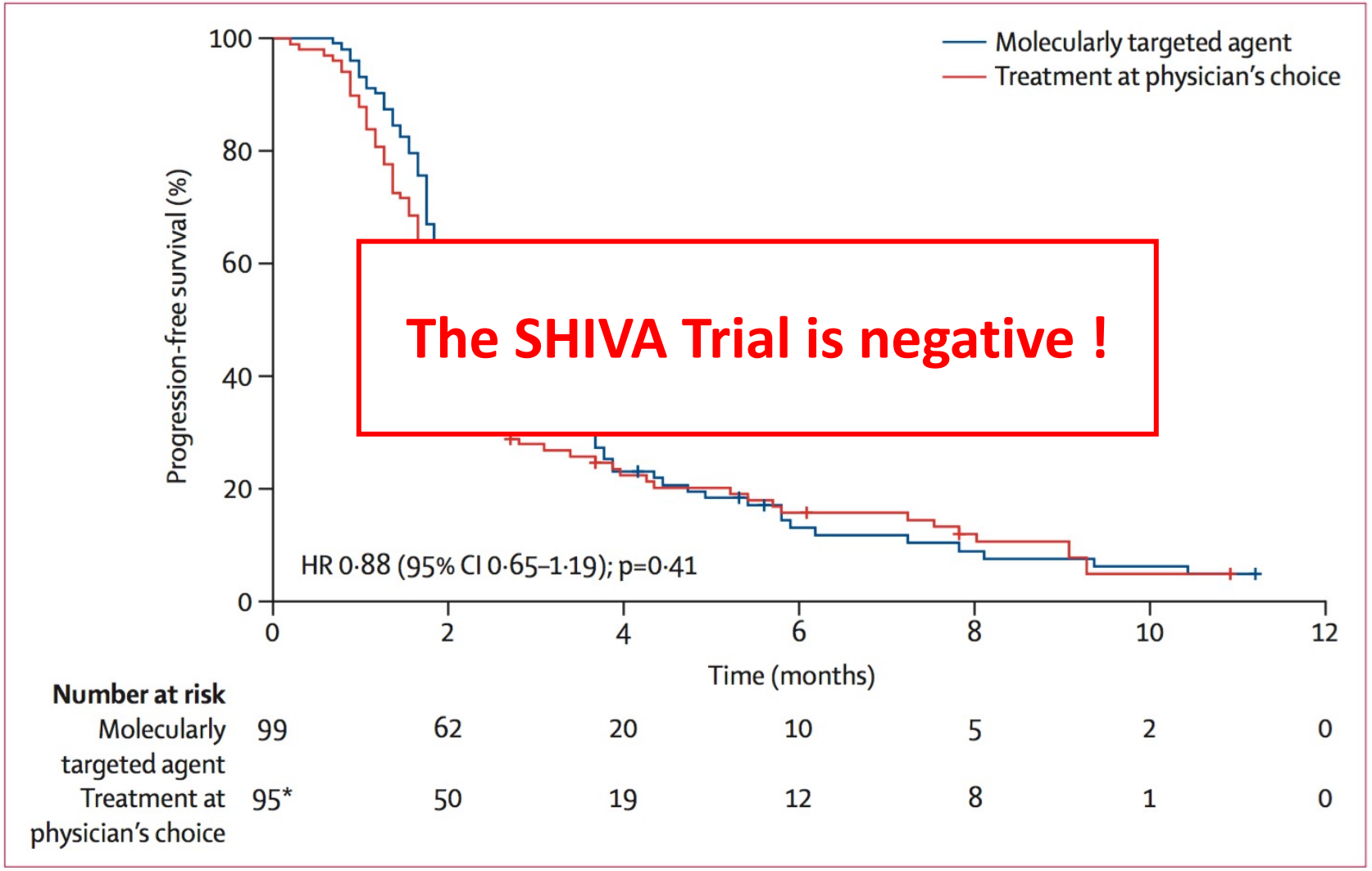
293 (40%) had at least one molecular alteration matching one of the 11 available regimens

195 (26%) randomly assigned, 99 in experimental group and 96 in control group

- Primary endpoint: progression-free survival

Lancet Oncol 2015

Strategy trials: SHIVA



Number at risk							
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

Strategy trials: SHIVA

→ Why ?

- Drugs marketed in France at that time…old molecules (eg everolimus instead of double mTor inhitor)
- Heterogeneous experimental arm with various drugs and various tumor types: can blind the benefit of some drugs in some specific cancers
- Unidimensional treatment algorithm: single molecular alteration to predict efficacy: us multidimensional treatment algorithm including information from several genes ?

Disappointments in Master protocols

- The tissue in which the cancer mutation occurs can determine treatment response (*BRAF*^{v600e} : Melanoma versus colon)

- *KRAS* mutation is classified as « actionable » (MEK inhibitor) but MEK inhibitors have modest activity in this setting.

- *BRCA1/2* mutations confer sensitivity to PARP inhibitors. BRCA1-like tumors are lacking *BRCA1* mutation are sensitive to PARP inhibitors

Dissapointments in Master protocols

- Tumors having the same oncogenic driver mutations can differ significantly in their responses to targeted cancer drugs

- Tumors that lack a specific oncogenic driver mutation may nevertheless display very similar responses to therapy due to similarity in gene expression patterns

Dissapointments in Master protocols

- Tumors having the same oncogenic driver mutations can differ significantly in their responses to t

These explain why biomarker-driven studies based on the genotype of the tumor only, are only moderately successful

- Tum
  mu
  responses to therapy due to similarity in gene expression patterns

Testing beyond genomics

WINTHER: genomic + transcriptomics (DNA + RNA)

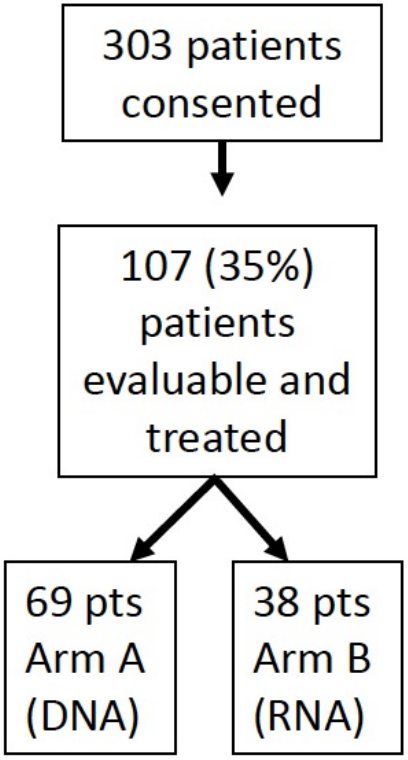


Table 1 | Outcome data including SD ≥6 months and PR/CR as well as PFS2/PFS1 in the WINTHER trial

	Arm A (DNA)[a]	Arm B (RNA)[a]	All patients
SD ≥6 months/PR/CR[b]	16 (23.2%)	12 (31.6%)	28 (26.2%)
Response: CR/PR	9 (13.0%)	3 (7.9%)	12 (11.2%)
SD ≥6 months	7 (10.1%)	9 (23.7%)	16 (15.0%)
PD or SD <6 months[a]	53 (76.8%)	26 (68.4%)	79 (73.8%)
Total	69 (100%)	38 (100%)	107 (100%)
Frequency (*N* (%))[c]			
PFS2/PFS1 of >1.5			
Yes[d]	14 (20.3%)	10 (26.3%)	24 (22.4%)
No	55 (79.7%)	28 (73.7%)	83 (77.6%)
Total	69 (100%)	38 (100%)	107 (100%)

Rodon et al. Nature Medicine 2019

Testing beyond genomics

WINTHER: genomic + transcriptomics (DNA + RNA)

303 patients consented

69 pts Arm A (DNA)

38 pts Arm B (RNA)

Table 1 | Outcome data including SD ≥6 months and PR/CR as well as PFS2/PFS1 in the WINTHER trial

No	55 (79.7%)	28 (73.7%)	83 (77.6%)
Total	69 (100%)	38 (100%)	107 (100%)

Transcriptomic profiling expands precision medicine

Transcriptomics enhanced the number of patients treated with a matched therapy from 23% to 35% of consented patients

Rodon et al. Nature Medicine 2019

Dissapointments in Master protocols

Biomarker-driven clinical trials use monotherapy targeted agents…

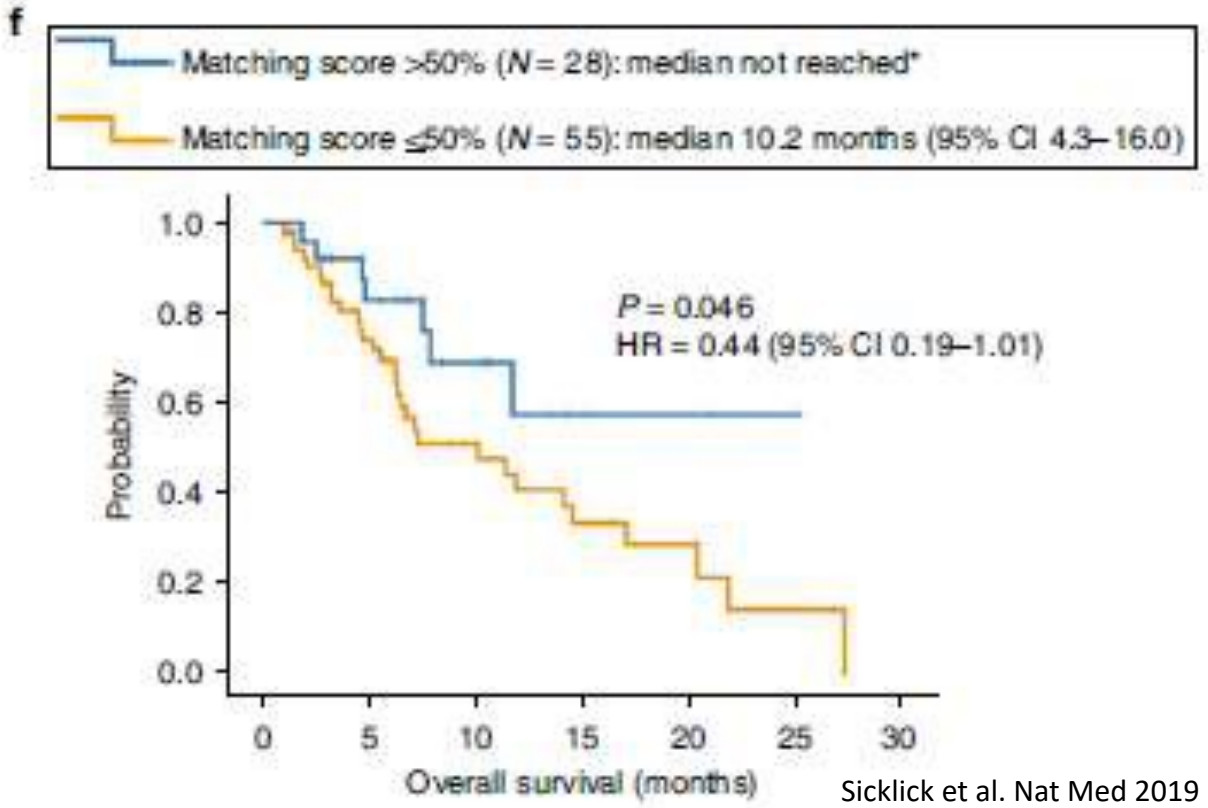
Does not adress tumor heterogenity that can cause treatment resistance

Combination strategies

I-PREDICT: personalized multidrug combinations to target the majority of genomic alterations in each patient's tumor

Matching score

= Total number of molecular alterations matched to the administered drugs divided by the total number of characterized genomic aberrations



Sicklick et al. Nat Med 2019

Combination strategies

I-PREDICT: personalized multidrug combinations to target the majority of genomic alterations in each patient's tumor

Combination treatment can perform better than single agents

Biomarkers beyond a single genomic alteration

Personalization of combination therapies to each individuals' tumor

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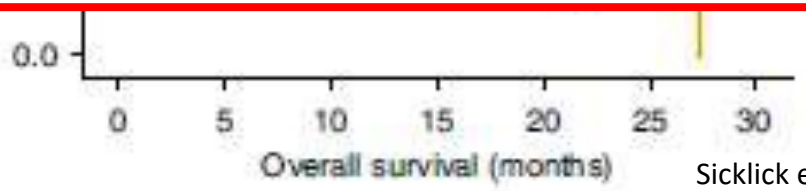

Sicklick et al. Nat Med 2019

Conclusion

Table 1. Advantages and pitfalls of 'biomarker-driven' clinical trial designs

Master protocols	Advantages	Disadvantages
Basket trials Histology agnostic	Can include rare cancer types Can target low incidence actionable/targetable molecular alterations	Assumes that molecular biology can replace histology and that a specific genetic alteration has the same signification across different tumor types
Umbrella trials Histology specific	Targets molecular alterations in one cancer type and avoid heterogeneity due to multiple cancer histologies Enables to get more conclusive results for one tumor type	Feasibility limited for rare cancers
Screening programs	Have the potential to identify an actionable/targetable genetic alteration Can facilitate the access to early development clinical trials	If an actionable/targetable alteration is present, the specific drug is not always available with the risk that a low number of patients finally benefits from this program
Strategy trials	Have the potential to identify an actionable/targetable genetic alteration	Effect of the strategy can be diluted by less effective target-drug pairs

Biomarker beyond genomics + combination therapies to be implemented in the future !

Thank you !