Can adaptive designs help to proceed in clinical trials in lung cancer? 5 reasons contra

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IDDI
ADDING VALUE TO CLINICAL DATA

Adaptive designs

New paradigms…

treatments

patients

design

endpoints

Better treatments…

treatments

patients

Targeted drugs,
immunotherapies, …

design

endpoints

Stratified patients…

treatments

Targeted drugs, immunotherapies, …

patients

Predictive biomarkers (*EGFR*, *KRAS*, *BRAF*, *FGFR*, NGS, …)

design

endpoints

Biomarker-based endpoints…

treatments

Targeted drugs, immunotherapies, …

patients

Predictive biomarkers (*EGFR*, *KRAS*, *BRAF*, *FGFR*, NGS, …)

design

endpoints

PD biomarkers (molecular targets, CTCs, cDNA, functional imaging, …)

Innovative trial designs…

treatments

Targeted drugs, immunotherapies, …

patients

Predictive biomarkers (*EGFR*, *KRAS*, *BRAF*, *FGFR*, NGS, …)

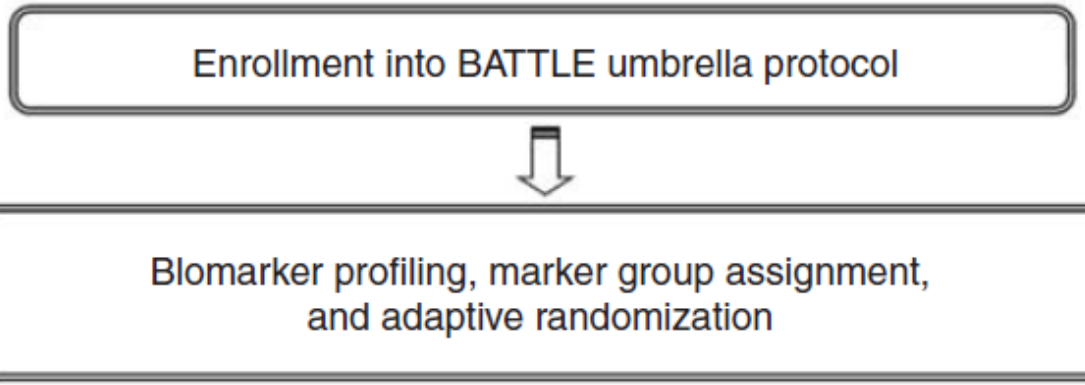
design

Biomarker-driven, Adaptive, Bayesian, Platform, …

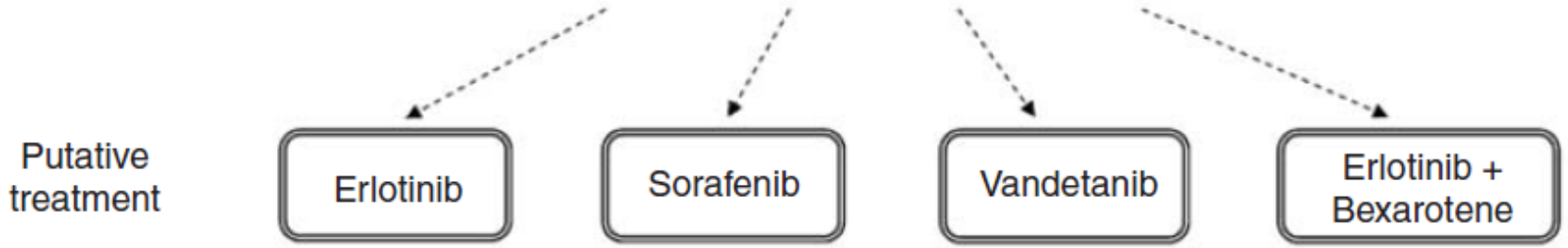
endpoints

PD biomarkers (molecular targets, CTCs, cDNA, functional imaging, …)

Example of a Bayesian Adaptive Design for patients with NSCLC refractory to chemotherapy



Biomarker group					
Biomarker	1	2	3	4	5
EGFR	+	−	−	−	−
K-ras/B-raf	×	+	−	−	−
VEGF/VEGFR	×	×	+	−	−
RXR/Cyclin D1	×	×	×	+	−
Percentage	15%	20%	30%	25%	10%

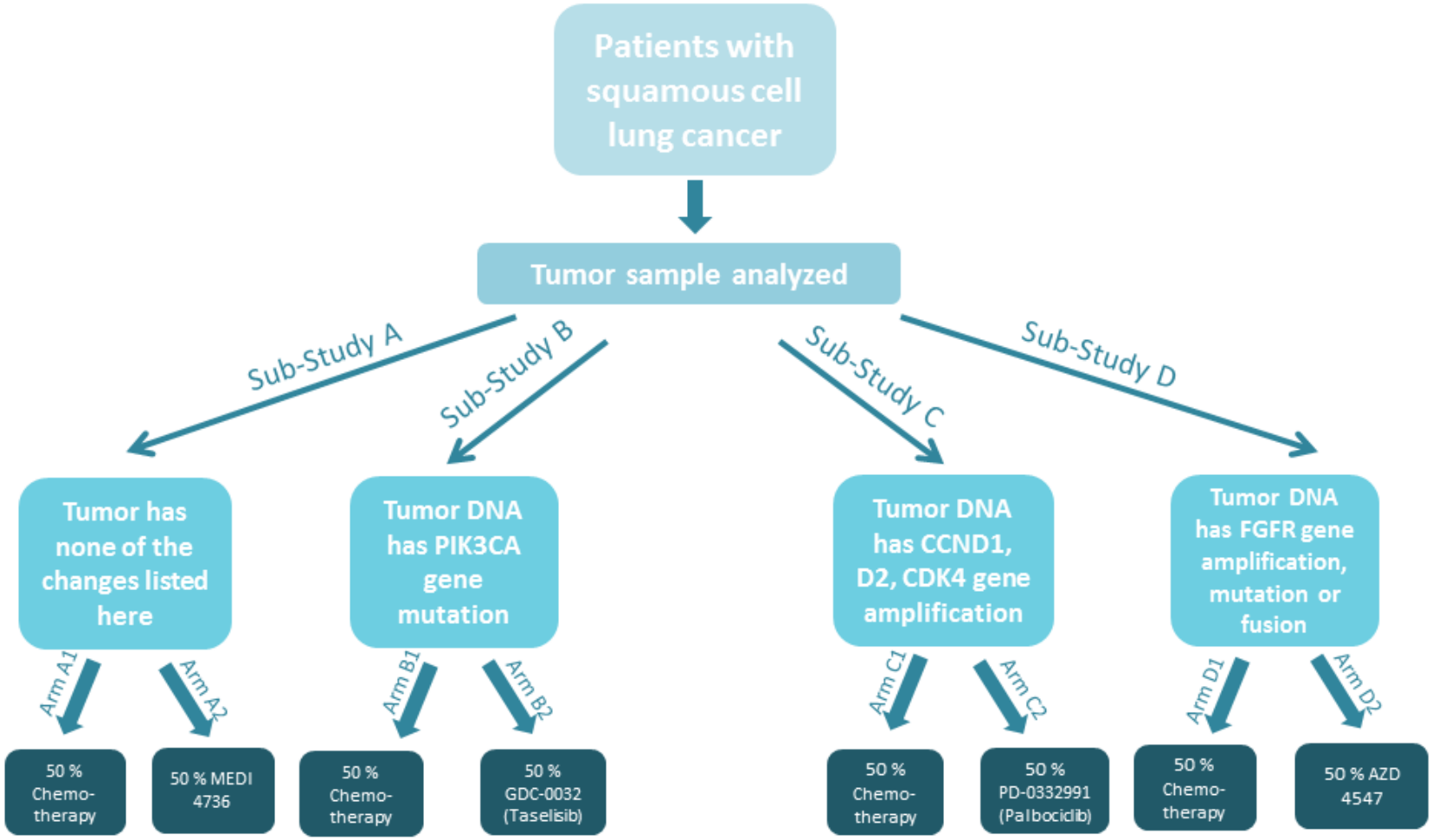


Refs: Zhou et al, Clinical Trials 2008;5:181-93; Lee et al, Clinical Trials 2010; 7:584-596; Kim et al, Cancer Discov 2011;1:44-53.

Example of a stratified, randomized, master protocol trial for 2nd line treatment of patients with squamous cell NSCLC

LUNG-MAP

Lung-MAP Sub-Studies for Treatment



Comparison between BATTLE and LUNG-MAP

Innovative treatments

BATTLE

Targeted agents

(erlotinib, vandetanib,

bexarotene, sorafenib)

LUNG-MAP

Docetaxel

vs. targeted agents

(MEDI4736, palbociclib,

taselisib, AZD4547)

Innovative treatments

BATTLE

Targeted agents

(erlotinib, vandetanib, bexarotene, sorafenib)

(Roche/Genentech, AstraZeneca, Eisai, Bayer)

Docetaxel

vs. targeted agents

(MEDI4736, palbociclib, taselisib, AZD4547)

(AstraZeneca, Pfizer, Roche/Genentech)

Stratified patients

BATTLE

5 biomarker groups based on putative predictive factors

4 sub-studies based on established predictive factors

Biomarker-based endpoints

BATTLE

8-week DCR

PFS and OS

Biomarker-based endpoints

BATTLE

LUNG-MAP

8-week DCR

PFS and OS

Is 8-week DCR a good predictor of PFS/OS?

Innovative design

BATTLE

Bayesian Adaptive

Stratified Randomized

Innovative design

BATTLE

LUNG-MAP

Bayesian Adaptive

Stratified Randomized

- *Bayesian: requires prior distribution of 8-week DCR by treatment by biomarker group*
- *Adaptive: allocates more patients to "better" treatment*

Biometrika (2003), **90**, 2, *pp.* 367–378

Printed in Great Britain

On the inefficiency of the adaptive design for monitoring clinical trials

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For any adaptive design, one can always construct a standard group-sequential test based on the sequential likelihood ratio test statistic that, for any parameter value in the space of alternatives, will reject the null hypothesis earlier with higher probability, and, for any parameter value not in the space of alternatives, will accept the null hypothesis earlier with higher probability.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome-Adaptive Randomization: Is it Useful?

Edward L. Korn and Boris Freidlin

With no differential patient accrual rates because of the trial design, we find no benefits to outcome-adaptive randomization over 1:1 randomization, and we recommend the latter. If it is thought that the patient accrual rates will be substantially higher because of the possibility of a higher proportion of patients being randomly assigned to the experimental treatment (because the trial will be more attractive to patients and clinicians), we recommend using a fixed 2:1 randomization instead of an outcome-adaptive randomization.

J Clin Oncol 28. Published by the American Society of Clinical Oncology

Perspective

CLINICAL TRIALS

Clinical Trials
1–5

DOI: 10.1177/1740774514563583
ctj.sagepub.com
SAGE

Are outcome-adaptive allocation trials ethical?

Spencer Phillips Hey and Jonathan Kimmelman

Perspective

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Are outcome-adaptive allocation trials ethical?

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Donald A Berry

Marc Buyse

Steven Joffe and Susan S Ellenberg

J Jack Lee

Edward L Korn and Boris Freidlin

Scott Brian Saxman

Adaptive designs

Adaptive designs

The magic world of adaptive designs…

Adaptive designs are required / useful

 when biomarkers are available

The magic world of adaptive designs…

Adaptive designs are required / useful

- when bi[wrong]rs are available
- to test many treatments at once

The magic world of adaptive designs…

Adaptive designs are required / useful

- when bi… …rs are available
- to test … …eatments at once
- to make trials more ethical

wrong

wrong

The magic world of adaptive designs…

Adaptive designs are required / useful

- when bi… …rs are available
- to test … …eatments at once
- to mak… …more ethical
- to gain statistical efficiency

wrong

wrong

wrong

The magic world of adaptive designs…

Adaptive designs are required / useful

- when bi… …rs are available
- to test … …eatments at once
- to mak… …more ethical
- to gain … …ical efficiency
- to speed up development

wrong

wrong

wrong

wrong

The magic world of adaptive designs…

Adaptive designs are required / useful

- when bi… …rs are available
- to test … …eatments at once
- to mak… …more ethical
- to gain … …ical efficiency
- to spee… …evelopment

wrong wrong wrong wrong wrong