Clinical Trial Design for Precision Medicine

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Targeted Therapies – Individualisierte Tumortherapie
als evidenzbasierte Medizin

30. November 2015
Contents

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Problems of clinical trial design for targeted therapies

• “Personalized medicine”, often also called “precision medicine” is a form of medicine that uses information about a person’s genes, proteins and environment to prevent, diagnose and treat disease. (Definition according to the National Cancer Institute)

• Traditionally, the site of tumor origin, together with histology, was used to make treatment decisions. This approach has been changed to include molecular tumor characteristics.

• Markers presently used to guide decisions for precision medicine treatment with targeted agents are either protein based or based on the detection of genetic aberrations.

• With multiple targets based on multiple markers we are often close to the situation that we are faced with in rare diseases.

Design for predictive biomarker validation

- Marker-Interaction or Enrichment-Design?
- Marker-based Strategy Design
- Reverse Marker-based Strategy Design

Aim: Validate a given predictive biomarker
Figure 1. Four designs for marker validation studies. Shaded boxes indicate the arms used in the planned analysis. Parameters below each box are the expected response rate in each arm using the notation in Section 3. Designs 1–3 are described in [4]. Design 4 is a novel proposal.

Eng KH, Stat Med 2014
Design 1: Marker-Interaction

Register

Marker +
Arm

Randomize

Marker +
Treatment A

Marker +
Treatment B

\( \theta_{A+} \)

\( \theta_{B+} \)

Marker -
Arm

Randomize

Marker –
Treatment A

Marker –
Treatment B

\( \theta_{A-} \)

\( \theta_{B-} \)

Eng KH, Stat Med 2014
Design 2: Marker-Based Strategy

Register

Randomize

Marker Based Strategy Arm

Marker + Treatment A

Marker - Treatment B

Non-Marker Based Strategy Arm

Treatment B

\[ \phi_1 = \pi \theta_{A+} + (1-\pi) \theta_{B-} \]

\[ \phi_2 = \theta_B \]

Eng KH, Stat Med 2014
Design 3: Modified Marker-Based Strategy

Register

Randomize

- Marker Based Strategy Arm
  - Marker + Treatment A
  - Marker - Treatment B

- Non-Marker Based Strategy Arm
  - Randomize
  - Treatment A
  - Treatment B

\[ \phi_1 = \pi \theta_{A^+} + (1-\pi) \theta_{B^-} \]

\[ \phi_3 = \theta_A / 2 + \theta_B / 2 \]

Eng KH, Stat Med 2014
Design 4: Reverse Marker-Based Strategy

Register

Randomize

Marker Based Strategy Arm

Marker + Treatment A

Marker - Treatment B

\[ \phi_1 = \pi \theta_{A+} + (1-\pi) \theta_{B-} \]

Reverse Marker Strategy Arm

Marker + Treatment B

Marker - Treatment A

\[ \phi_4 = \pi \theta_{B+} + (1-\pi) \theta_{A-} \]

Eng KH, Stat Med 2014
Design for predictive biomarker validation

- Marker-Interaction or Enrichment-Design?
- Marker-based Strategy Design
- Reverse Marker-based Strategy Design
- Various proposals for adaptive designs
- Various proposals for statistical analysis strategy
Designs with intraindividual comparisons

- Idea: Compare progression-free survival (PFS) under current, biomarker-guided therapy with PFS under prior therapy (PFS = time to treatment failure (TTF))

- Determine proportion of patients with PFS ratio
  \( \frac{\text{PFS on current therapy}}{\text{PFS on prior therapy}} \geq 1.3 \)

- Pilot study on patients with refractory metastatic cancer
  (von Hoff et al. J Clin Oncol 2010)

- Aim: (Proportion with PFS ratio \( \geq 1.3 \)) > 15%
Fig 2. (A) Illustration of the primary end point, progression-free survival (PFS) ratio, for the study. (B) Mechanics of the study. TTP, time to progression; MP, molecular profiling. IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

Von Hoff et al.
J Clin Oncol 2010;28:4887-4883
Fig 3. Comparisons of progression-free survival (PFS) on molecular profiling (MP) therapy (blue bars) versus PFS (time to progression [TTP]) on prior therapy (gold bars) for the 18 patients with a PFS ≥ 1.3.

\[ \frac{18}{66} = 27\% \; ; \; 95\% - CI: \; 17\% - 38\% \]

Problems with intraindividual comparisons

- Comparison of patients who match to targeted therapy with those who do not is problematic
- Need to have pre-baseline tumor assessment
- PFS on prior therapy is often not assessed according to validated criteria and might therefore be not accurate
- Cut-off for PFS ratio is somewhat arbitrary
- PFS ratio is only valid if there is a strong correlation between the endpoints (Recall: PFS on prior therapy = TTF)

Le Tourneau et al. Targeted Oncology 2012;7:253-265
**Fig 1.** Correlation between progression-free survival on first-line therapy (PFS$_1$) and on second-line therapy (PFS$_2$) in advanced colorectal cancer. Yellow circles represent the folinic acid, fluorouracil, and irinotecan followed by folinic acid, fluorouracil, and oxaliplatin (FOLFIRI-FOLFOX) sequence; blue circles represent the FOLFOX-FOLFIRI sequence. 

Buyse et al. J Clin Oncol 2011;29:e451-e452
Molecularly targeted therapy independent of tumor type ("all-tumor trials")

- Example: von Hoff study (breast, colorectal, ovarian, miscellaneous)

- WINThER trial:
  - Patients with all types of metastatic solid tumors resistant to last line of treatment
  - “Complete biological analysis” of matched tumor and normal biopsies.
  - Therapeutic decision based on an estimated drug efficacy scoring bioinformatics tool
  - Aim: PFS ratio > 1.5 in 50% of patients
  - Implementation of trial much more difficult than expected
  - It took 19 to more than 36 months to activate study sites; only few patients enrolled so far

Rodon et al., Annals of Oncology 2015;26:1791-1798
Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonzalez, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armant, Nicolas Servant, Ivan Blèche, Virginie Bernard, David Gentien, Pascal Jezquel, Valéry Attignan, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Soblin, Maud Karnal, Xavier Paolelli, for the SHIVA investigators

Summary

Background Molecularly targeted agents have been reported to have anti-tumour activity for patients whose tumours harbour the matching molecular alteration. These results have led to increased off-label use of molecularly targeted agents on the basis of identified molecular alterations. We assessed the efficacy of several molecularly targeted agents marketed in France, which were chosen on the basis of tumour molecular profiling but used outside their indications, in patients with advanced cancer for whom standard-of-care therapy had failed.

Methods The open-label, randomised, controlled phase 2 SHIVA trial was done at eight French academic centres. We included adult patients with any kind of metastatic solid tumour refractory to standard of care, provided they had an Eastern Cooperative Oncology Group performance status of 0 or 1, disease that was accessible for a biopsy or resection of a metastatic site, and at least one measurable lesion. The molecular profile of each patient’s tumour was established with a mandatory biopsy of a metastatic tumour and large-scale genomic testing. We only included patients for whom a molecular alteration was identified within one of three molecular pathways (hormone receptor, PI3K/AKT/mTOR, RAF/MEK), which could be matched to one of ten regimens including 11 available molecularly targeted agents (erlotinib, lapatinib plus trastuzumab, sorafenib, imatinib, dasatinib, vemurafenib, everolimus, abiraterone, letrozole, tamoxifen). We randomly assigned these patients (1:1) to receive a matched molecularly targeted agent (experimental group) or treatment at physician’s choice (control group) by central block randomisation (blocks of size six). Randomisation was done centrally with a web-based response system and was stratified according to the Royal Marsden Hospital prognostic score (0 or 1 vs 2 or 3) and the altered molecular pathway. Clinicians and patients were not masked to treatment allocation. Treatments in both groups were given in accordance with the approved product information and standard practice protocols at each institution and were continued until evidence of disease progression. The primary endpoint was progression-free survival in the intention-to-treat population, which was not assessed by independent central review. We assessed safety in any patients who received at least one dose of their assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01771458.
Fig. 1 Study design of the SHIVA trial

Le Tourneau et al. Targeted Oncology 2012;7:253-265
Le Tourneau et al., The Lancet Oncology 2015;16:1324-1334

<table>
<thead>
<tr>
<th>Molecularly targeted agent group (n=99)</th>
<th>Treatment at physician's choice group (n=96)</th>
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<tbody>
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<td>61 (54-69)</td>
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<td>Sex</td>
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<td>Previous lines of treatment</td>
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<td>Royal Marsden Hospital score</td>
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<tr>
<td>0 or 1</td>
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<td>48 (50%)</td>
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<td>Molecular pathway altered</td>
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<td>RAF/MEK pathway</td>
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<td>Tumour type</td>
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<td>Sarcoma</td>
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<td>Urothelial carcinoma</td>
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<td>Pancreatic adenocarcinoma</td>
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<td>Adenocarcinoma of unknown primary</td>
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<td>Oesophagogastric cancer</td>
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<tr>
<td>Anal squamous cell carcinoma</td>
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<td>2 (2%)</td>
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<tr>
<td>Neuroendocrine tumour</td>
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<tr>
<td>Biliary tract carcinoma</td>
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<tr>
<td>1 (1%)</td>
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<tr>
<td>Nasopharyngeal carcinoma</td>
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<tr>
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<td>Kidney cancer</td>
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</table>

Data are n (%), or median (IQR).

Table 1: Baseline characteristics
Figure 2: Distribution of molecular alterations in the PI3K/AKT/mTOR pathway (A) and RAF/MEK pathway (B)

*PTEN inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations or validated by absence of expression of PTEN in immunohistochemistry. †STK11 inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations of STK11. ‡Focal gains of several PIK3 pathway genes including AKT1, AKT2, AKT3, RPTOR, and RICTOR (three patients). §Intragenic deletion within PDGFRα validated by overexpression of PDGFRα in immunohistochemistry. ¶Intragenic deletion within KIT validated by overexpression of the KIT in immunohistochemistry.
**Figure 3: Progression-free survival**

*One patient had a follow-up of zero days so is not shown here.*

Le Tourneau et al., The Lancet Oncology 2015;16:1324-1334
Hormone receptor pathway

P13k/AKT/mTOR pathway

Le Tourneau et al., The Lancet Oncology 2015;16:1324-1334
Figure 4: Progression-free survival by molecular pathway
Progression-free survival in patients with molecular alterations in the hormone receptor pathway (A), PI3K/AKT/mTOR pathway (B), and RAF/MEK pathway (C).

Le Tourneau et al., The Lancet Oncology 2015;16:1324-1334
Impact of Precision Medicine in Diverse Cancers:
A Meta-Analysis of Phase II Clinical Trials

Maria Schwaederle, Melissa Zhao, J. Jack Lee, Alexander M. Eggermont, Richard L. Schilsky, John Mendelsohn, Vladimir Lazar, and Kazelle Kurzrock

ABSTRACT

Purpose
The impact of a personalized cancer treatment strategy (i.e., matching patients with drugs based on specific biomarkers) is still a matter of debate.

Methods
We reviewed phase II single-agent studies (570 studies; 32,149 patients) published between January 1, 2010, and December 31, 2012 (PubMed search). Response rate (RR), progression-free survival (PFS), and overall survival (OS) were compared for arms that used a personalized strategy versus those that did not.

Results
Multivariable analysis (both weighted multiple linear regression and random effects meta-regression) demonstrated that the personalized approach, compared with a nonpersonalized approach, consistently and independently correlated with higher median RR (31% vs 10.5%, respectively; P < .001) and prolonged median PFS (5.9 vs 2.7 months, respectively; P < .001) and OS (13.7 vs 8.9 months, respectively; P < .001). Nonpersonalized targeted arms had poorer outcomes compared with either personalized targeted therapy or cytotoxics, with median RR of 4%, 30%, and 11.9%, respectively; median PFS of 2.6, 6.9, and 3.3 months, respectively (all P < .001); and median OS of 8.7, 15.9, and 9.4 months, respectively (all P < .05). Personalized arms using a genomic biomarker had higher median RR and prolonged median PFS and OS (all P < .05) compared with personalized arms using a protein biomarker. A personalized strategy was associated with a lower treatment-related death rate than a nonpersonalized strategy (median, 1.5% vs 2.3%, respectively; P < .001).

Conclusion
Comprehensive analysis of phase II, single-agent arms revealed that, across malignancies, a personalized strategy was an independent predictor of better outcomes and fewer toxic deaths. In addition, nonpersonalized targeted therapies were associated with significantly poorer outcomes than cytotoxic agents, which in turn were worse than personalized targeted therapy.

J Clin Oncol 33:3817-3825. © 2015 by American Society of Clinical Oncology

Schwaederle M: JCO 2015; 33: 3817-3825
Fig 1. Benefit of personalized therapy. (A) Results from the pooled and meta-analysis comparing the personalized strategy versus nonpersonalized strategy are represented for response rate (RR), progression-free survival (PFS), and overall survival (OS). All $P < .001$ comparing arms adopting a personalized approach versus a not personalized approach. Six hundred thirty-eight arms had values available for the RR analysis (pooled analysis and meta-analysis; 112 arms were personalized, and 526 were not). For the PFS analysis, 530 arms had values for the pooled analysis (personalized, $n = 96$; not personalized, $n = 444$), and 342 arms had median PFS values and their corresponding 95% CIs available for the meta-analysis (personalized, $n = 59$; not personalized, $n = 283$). For the OS analysis, 441 arms had values for the pooled analysis (personalized, $n = 49$; not personalized, $n = 392$), and 247 arms had median OS values and their corresponding 95% CIs available for the meta-analysis (personalized, $n = 21$; not personalized, $n = 226$). (B) Forest plots for RR, PFS, and OS (left to right). EMA, European Medicines Agency; FDA, US Food and Drug Administration.
Multi-arm, multi-stage (MAMS) trials

- Multi-arm trials are more efficient in investigating a number of treatments than a series of two-arm studies (Example $2 \times 2$-factorial design)

- Multi-arm, multi-stage designs allow adaptive focusing of recruitment away from insufficiently active treatments, preferably on an early, intermediate outcome measure

- Formalisation of idea:
MAMS-Design

Fig. 3.1 Schematic illustration of traditional “sequential” development process (a) and a MAMS design (b). In both three novel treatments (T₁, . . . , T₃) are evaluated against control (C) and only treatment 2 chosen for confirmation in Phase III. In (a) each treatment is compared to control in separate trials while in (b) only one control group serves for all treatments.
Evaluating Many Treatments and Biomarkers in Oncology: A New Design

Richard Kaplan, Timothy Maughan, Angela Crook, David Fisher, Richard Wilson, Louise Brown, and Mahesh Parmar

ABSTRACT

There is a pressing need for more-efficient trial designs for biomarker-stratified clinical trials. We suggest a new approach to trial design that links novel treatment evaluation with the concurrent evaluation of a biomarker within a confirmatory phase II/III trial setting. We describe a new protocol using this approach in advanced colorectal cancer called FOCUS4. The protocol will ultimately answer three research questions for a number of treatments and biomarkers: (1) After a period of first-line chemotherapy, do targeted novel therapies provide signals of activity in different biomarker-defined populations? (2) If so, do these definitively improve outcomes? (3) Is evidence of activity restricted to the biomarker-defined groups? The protocol randomizes novel agents against placebo concurrently across a number of different biomarker-defined population-enriched cohorts: BRAF mutation; activated AKT pathway; PI3K mutation/absolute PTEN loss tumors; KRAS and NRAS mutations; and wild type at all the mentioned genes. Within each biomarker-defined population, the trial uses a multistaged approach with flexibility to adapt in response to planned interim analyses for lack of activity. FOCUS4 is the first test of a protocol that assigns all patients with metastatic colorectal cancer to one of a number of parallel population-enriched, biomarker-stratified randomized trials. Using this approach allows questions regarding efficacy and safety of multiple novel therapies to be answered in a relatively quick and efficient manner, while also allowing for the assessment of biomarkers to help target treatment.

J Clin Oncol 31:4562-4568. © 2013 by American Society of Clinical Oncology

Richard Kaplan, Angela Crook, David Fisher, Louise Brown, and Mahesh Parmar, Medical Research Council Clinical Trials Unit, London; Timothy Maughan, University of Oxford, Oxford; and Richard Wilson, Queen’s University Belfast, Belfast, United Kingdom.
FOCUS4 is jointly funded by Cancer Research UK and Medical Research Council/National Institute of Health Research Efficacy and Mechanism Evaluation Programme. Work on the design was supported by core funding from each academic institution.
Both R.K. and T.M. are joint first co-authors.
Authors’ disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Richard Kaplan,
Fig 1. Trial schema for FOCUS4. (*) The molecular cohorts are arranged in a hierarchy from left to right. For example, a patient with both a PIK3CA mutation and a KRAS mutation will be classified into the PIK3CA mutation cohort. CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EREG, epiregulin; FFPE, formalin fixed, paraffin embedded; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; MMR, mismatch repair; OS, overall survival; P, placebo; PFS, progression-free survival; Rx, treatment.

FOCUS4 Recruitment
Jan 2014 - July 2015

- Sites Open
- Target registrations
- Actual registrations

FOCUS4 Issue3, August 2015
NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:
- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment

ABOUT 3,000 CANCER PATIENTS WILL BE SCREENED WITH A TUMOR BIOPSY

GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

IF A PATIENT’S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY

NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

*NCI-Molecular Analysis for Therapy Choices

www.cancer.gov/nci-match
To learn more, call 1-800-4-CANCER

Martin Schumacher
Clinical Trial Design for Precision Medicine
30. November 2015
### Table 1 The first treatments selected for NCI-Match pair actionable mutations with treatments

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Molecular target</th>
<th>Estimated mutation prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Xalkori (crizotinib)</td>
<td>ALK rearrangement</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROS1 translocations</td>
<td></td>
</tr>
<tr>
<td>Novartis (Basel)</td>
<td>Tafinlar (dabrafenib) and Mekinist</td>
<td>BRAF V600E or V600K mutations</td>
<td>7</td>
</tr>
<tr>
<td>Novartis</td>
<td>Mekinist</td>
<td>BRAF fusions/non-V600E/non-V600K</td>
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</tr>
<tr>
<td>Boehringer Ingelheim (Germany)</td>
<td>Gilotrif</td>
<td>EGFR-activating mutations</td>
<td>1-4</td>
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<tr>
<td></td>
<td></td>
<td>HER2-activating mutations</td>
<td>2-5</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AZD9291 (investigational)</td>
<td>EGFR T790M mutation and rare, EGFR-activating mutations</td>
<td>1-2</td>
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<td></td>
<td>Kadcyla (ado-trastuzumab-DM1)</td>
<td>HER2 amplification</td>
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<td>Verastem (Needham, Massachusetts)/Pfizer</td>
<td>VS-6063 (defactinib)</td>
<td>NF2 loss</td>
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<tr>
<td>Pfizer</td>
<td>Sutent (sunitinib)</td>
<td>cKIT mutations</td>
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</table>

Source: NCI website.
NCI-MATCH / EAY131 Trial Currently Recruiting Participants

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<th>STUDY/ID</th>
<th>DESCRIPTION</th>
<th>ACCRUAL GOAL</th>
<th>DATE ACTIVATED</th>
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<tbody>
<tr>
<td>NCI-MATCH or EAY131</td>
<td>National Cancer Institute-Molecular Analysis for Therapy Choice</td>
<td>3000 genetic screenings to identify 1000 eligible patients</td>
<td>08/12/2015</td>
</tr>
</tbody>
</table>

**NCI-MATCH / EAY131 temporarily pausing new accrual effective November 4, 2015. It is expected to resume enrollment in January 2016.**

This is a precision medicine trial co-developed by the ECOG-ACRIN Cancer Research Group and the National Cancer Institute (NCI). It is being led by ECOG-ACRIN. NCI-MATCH is a phase II cancer treatment trial that seeks to determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of their cancer type.

Eligibility: The trial is for adults 18 years of age and older with any type of solid tumor or lymphoma (cancer in the cells of the immune system) that has returned or gotten worse after standard systemic therapy (oral or intravenous), or with a rare type of cancer for which there is no standard treatment.

The trial is open with 10 treatment options (see below) and is expected to expand to 17 by December 2015, and to 22 treatment options by April 2016. For more detailed information, download the [Table of Master Protocol and Subprotocols](http://ecog-acrin.org/wp-content/uploads/charts/NCI-MATCH-EAY131-Table-of-Master-Protocol-Active-Subprotocols-Leadership.pdf).

<table>
<thead>
<tr>
<th>STUDY ID</th>
<th>DESCRIPTION</th>
<th>ACCRUAL GOAL</th>
<th>DATE ACTIVATED</th>
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| EAY131-A | Gilotrif® (afatinib)  
EGFR activating mutations  
Disease Exceptions: small cell cancer, non-small cell lung cancer (NSCLC), or a history of interstitial lung disease | 35 | 08/12/2015 |
| EAY131-B | Gilotrif® (afatinib)  
HER2 activating mutations  
Disease Exceptions: NSCLC or a history of interstitial lung disease | 35 | 08/12/2015 |
| EAY131-E | AZD9291  
EGFR T790M (with/without an activating mutation) or rare activating mutations of EGFR  
Disease Exception: NSCLC | 35 | 08/12/2015 |
| EAY131-F | Xalkori® (crizotinib)  
ALK translocations  
Disease Exceptions: NSCLC, adenocarcinoma of the lung, or anaplastic large-cell lymphoma | 35 | 08/12/2015 |
| EAY131-G | Xalkori® (crizotinib)  
ROS1 translocations  
Disease Exception: NSCLC | 35 | 08/12/2015 |
| EAY131-H | Tafinlar® (dabrafenib) and Mekinist™ (trametinib)  
BRAF V600E or V600K mutations  
Disease Exceptions: colorectal cancer, melanoma, thyroid cancer, hepatitis B (HBV) or C (HCV), or a history of interstitial lung disease | 35 | 08/12/2015 |
| EAY131-Q | Kadcyla® (ado-trastuzumab emtansine)  
HER2 amplification  
Disease Exceptions: breast cancer or gastric/gastro-esophageal junction cancer | 35 | 08/12/2015 |
| EAY131-R | Mekinist™ (trametinib)  
BRAF fusions or non-V600E, non-V600K BRAF mutations  
Disease Exceptions: a history of interstitial lung disease | 35 | 08/12/2015 |
| EAY131-U | Defactinib (VS-6063)  
NF2 loss  
Disease Exceptions: None | 35 | 08/12/2015 |
| EAY131-V | Sutent® (sunitinib malate)  
cKIT mutations  
Disease Exceptions: gastrointestinal stromal tumors (GIST), renal cell carcinoma, or pancreatic neuroendocrine tumors | 35 | 08/12/2015 |

http://ecog-acrin.org/trials/nci-match-eay131
Infrastructure for clinical trials

• About 20% of adult cancer clinical trials fail to complete (Stensland et al. J Nat Cancer Inst 2014)

• Only 25% to 42% of superiority trials in oncology report success of the experimental treatment (Djulbegovic et al. PLOS ONE 2013)

• Concentrating on isolated trials done by single investigators will not lead to faster and more efficient developments

• While the steps towards multi-center trials and the creation of entity-specific, national and international study groups have been made in the past, professional coordination of all trial activities comprising all tumor entities is now warranted. This can best be achieved within a Comprehensive Cancer Center!
Figure 1. The academic medical center precision medicine tumor board model.

Conclusions

• For targeted therapies in oncology based on molecular characteristics, there are certainly parallels to the situation in rare diseases.

• There are developments in clinical trial design and statistical analysis strategies to meet the special needs (however, there is no special statistical methodology for this situation!).

• The most important prerequisite for the efficient conduct of studies is a comprehensive approach based on appropriate precision medicine infrastructure.

• Utility of molecular profiling for monitoring of disease and resistance e.g. by repeated (liquid) biopsies has to be further investigated.
4.6 Fazit


References

- Brower V. NCI-MATCH pairs tumor mutations with matching drugs. NEWS Nature Biotechnology 2015;33:790-791
References