Design of Clinical Trials with Molecularly Targeted Therapies

Gilberto Schwartsmann
What are the basics of clinical trial design?

- **Phase I:** Determine a safe dose
  - Endpoints: Maximum tolerated dose
  - Toxicity profile
  - Study Pharmacokinetic and pharmacodynamic endpoints

- **Phase II:** Establish preliminary efficacy
  - Endpoints of efficacy: RR, OS, PFS, TTP
  - Further define toxicity/safety profile

- **Phase III:** Establish a new standard
  - Endpoints: Generally survival, rarely PFS

Presented By Jordan Berlin at 2016 ASCO Annual Meeting
Advances in molecular biology

• Molecularly targeted agents (MTAs) against specific oncogenic drivers.

• MTAs differ from cytotoxics in toxicity profiles and availability of predictive biomarkers.

• Early trials are evolving to adapt to MTAs!
The lines have become blurred

- Phase I
  - 1a: first in human
  - 1b: combination trials or phase I in specific populations
  - Expansion cohorts: This is the real concern.
    - Often have foggy or no statistical design
    - Can keep adding patients to get more signal
    - Lack of rigor in stats may result in over-interpretation of results
      - Should not be a go-no-go for phase III without rigorous statistical design
Example 1
Background

- Vemurafenib has clinical activity in multiple BRAF V600-mutant non-melanoma tumors but unfortunately often patients acquire resistance to BRAF targeted monotherapy.
- mTOR pathway activation is associated with resistance to BRAF targeted monotherapy.
- mTOR inhibition in combination with vemurafenib may overcome or delay resistance to BRAF monotherapy.
Overcoming BRAF resistance with the addition of an mTOR inhibitor in solid tumors harboring a BRAF mutation: A phase I study

## Demographics

<table>
<thead>
<tr>
<th>Age, years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>62 (18-85)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>10, 13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 (70)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnoses, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>7 (35)</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4 (20)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF/MEK inhibitor</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Phase I</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Surgery</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>13 (65)</td>
</tr>
</tbody>
</table>

One patient had measurable but not evaluable disease and a second patient was not evaluable due to withdrawing consent prior to restaging.
Dosing schedule and toxicities

<table>
<thead>
<tr>
<th>Dose Levels*</th>
<th>Vemurafenib (PO BID)</th>
<th>Everolimus (PO Daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level -1*</td>
<td>480 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Level 0</td>
<td>720 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Level 1</td>
<td>720 mg</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Level 2</td>
<td>720 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Level 3</td>
<td>960 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

*Body surface area-based dose adjustment was made (level -1) for the pediatric patients

- No dose-limiting toxicity (DLT) observed at dose level 1
- Three DLTs (rash, fatigue) observed at dose level 2
- Dose level 1 determined to be the MTD
- Grade ≥3 adverse events: Rash (n=4), Fatigue (n=4), Photosensitivity (n=1), Anemia (n=1), Hyperglycemia (n=1), Hypertriglyceridemia (n=1)
Responses

**Fig 1:** Waterfall plot of best response in all evaluable patients on trial. *patients below

**Fig 2:** Clinical response in melanoma after progression on vemurafenib and PX866 (left) and stable disease for 7 months in papillary thyroid cancer (right).

<table>
<thead>
<tr>
<th>CUP</th>
<th>Cancer of unknown primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mel</td>
<td>Melanoma</td>
</tr>
<tr>
<td>AT</td>
<td>Anaplastic thyroid</td>
</tr>
<tr>
<td>PT</td>
<td>Papillary thyroid</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Astro</td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td>Glio</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>
Conclusions

- The combination of vemurafenib (720 mg BID) and everolimus (5 mg QD) is safe, well-tolerated, and demonstrated activity in patients with BRAF-mutant advanced cancers, including those previously treated with a BRAF inhibitor.
- All non-responders were either previously treated with BRAF or MEK inhibitor or harbored non-V600 BRAF mutations.
- Studies to help identify which patients would benefit from up-front dual BRAF/mTOR inhibition are ongoing.
Phase II

IIa: Pilot to evaluate efficacy (and safety) in selected patient populations, to define dose-response, type of patients, frequency of dosing, etc.

IIb: Well controlled trials for efficacy (and safety) in specific disease, most rigorous demonstration of efficacy, pivotal trials.
Example 2
Rationale

- In pretreated soft tissue sarcoma (STS), Pazopanib, a TK-inhibitor of VEGF, PDGF and c-kit, significantly increased PFS vs. placebo (PALETTE trial): 1.6 vs 4.6 months, HR 0.31 \(^1\)

- Due to non overlapping toxicity of pazopanib, a combination of pazopanib with other cytotoxic drugs might be an interesting option.

- Gemcitabine has proven efficacy in antracycline/ifosfamide refractory patients, inducing objective responses and prolonging PFS, and is therefore an option for combination with pazopanib.

\(^1\)van der Graaf et al. Lancet 2012,379:1879-86
“PAPAGEMO”: Pazopanib vs. Pazopanib+ Gemcitabine in refractory soft tissue sarcoma: A randomized phase II trial of the AIO

Hans-Joachim Schmoll*

Jörn Rüssel, Peter Reichardt, Lars Lindner, Hans-Georg Kopp, Alexander Stein, Franziska Cygon, Klaus Heissner

*presenting Author
Inclusion criteria:

- All STS
- except: Uterine-sa, bone/chondral-sa, PNET, GIST, Mesothelioma, Dermatofibro-sa,
- Failure to Doxorubicine or Ifosfamide
- ECOG ≤ 2

1:1 randomization Stratification for Lipo-sa.

A
- Pazopanib 800 mg/d po cont.
- Gemcitabine 1000 mg/m²
day 1, 8 qd 22

B
- Pazopanib 800 mg/d po cont.

1° endpoint
- PFS @ 12 weeks

2° endpoints
- RR
- PFS
- OS
- Toxicity

“PAPAGEMO”- Trial design
Multicenter open-label prospective randomized phase II trial

Presented at: ASCO ANNUAL MEETING ‘16
Presented by: Hans-Joachim Schmoll

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Endpoints

• Primary end-point
  - Progression free survival rate @ 12 weeks

• Secondary end-points
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Response Rate  RECIST
  - Toxicity  CTCAE Version 4.0
Conclusion

1. The outcome of the control arm is very close to the reference trial „PALETTE“
2. The efficacy of the combination is significantly higher in terms of PFS, and nonsignificantly also in Response rate, however with more toxicity
3. This new regimen seems to be another potential treatment option in anthracycline and/or ifosfamide refractory STS
4. A head to head comparison might be interesting, but even more the development into a triple combination, based on the non overlapping toxicity of pazopanib
Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer: Results from the phase I/II CheckMate 032 study

Padmanee Sharma, Petri Bono, Joseph Kim, Pavlina Spiliopoulou, Emiliano Calvo, Rathi N. Pillai, Patrick A. Ott, Filippo de Braud, Michael Morse, Dung Le, Dirk Jaeger, Emily Chan, Chris Harbison, Chen-Sheng Lin, Marina Tschaiaka, Alex Azrilevich, Jonathan Rosenberg

1MD Anderson Cancer Center, University of Texas, Houston, TX, USA; 2Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; 3Yale Cancer Center, New Haven, CT, USA; 4Beatson West of Scotland Cancer Centre, Glasgow, UK; 5START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; 6Emory Winship Cancer Institute, Atlanta, GA, USA; 7Dana-Farber Cancer Institute, Boston, MA, USA; 8Istituto Nazionale dei Tumori, Milan, Italy; 9Duke University Medical Center, Durham, NC, USA; 10Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 11Heidelberg University Hospital, Heidelberg, Germany; 12Vanderbilt University, Nashville, TN, USA; 13Bristol-Myers Squibb, Princeton, NJ, USA; 14Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presented By Padmanee Sharma at 2016 ASCO Annual Meeting
Study design

Open-label, multicenter phase I/II study (NCT01928394)

Patients with locally advanced or metastatic urothelial carcinoma

- Nivolumab 3 mg/kg IV Q2W (N = 78)
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W for four cycles (N = 26)
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV Q3W for four cycles (N = 105)

Nivolumab 3 mg/kg IV Q2W

- Treatment beyond progression was permitted if nivolumab was tolerated and clinical benefit was noted
- Patients in the monotherapy arm could cross over to nivolumab combined with ipilimumab after progression if they met prespecified criteria

Presented By Padmanee Sharma at 2016 ASCO Annual Meeting
Eligibility criteria

- Confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Progressive disease after ≥1 prior platinum-based therapy for metastatic disease or recurrence within 1 year of completing prior platinum-based neo-adjuvant or adjuvant therapy
- ECOG performance status of 0 or 1
- Measurable disease (RECIST v1.1)
Study endpoints

- **Primary**
  - Investigator-assessed confirmed ORR in overall study population by RECIST 1.1

- **Secondary**
  - Safety
  - Duration of response
  - Progression-free survival
  - Overall survival

- **Exploratory**
  - Biomarkers (PD-L1, PD-1, tumor immune cells, tumor genomic profiling, circulating cytokines)
  - Other (immunogenicity, pharmacokinetics, and quality of life)
## Treatment-related AEs

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td><strong>Treatment-related AEs in ≥10% of patients, %</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
</tr>
<tr>
<td>Pruritus</td>
<td>30</td>
</tr>
<tr>
<td>Lipase elevated</td>
<td>14</td>
</tr>
<tr>
<td>Rash, maculopapular</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
</tr>
<tr>
<td><strong>Select treatment-related AEs, %</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
<tr>
<td>Renal</td>
<td>9</td>
</tr>
<tr>
<td>Skin</td>
<td>42</td>
</tr>
</tbody>
</table>

- Two treatment-related grade 5 AEs occurred: thrombocytopenia (n = 1) and pneumonitis (n = 1)
Tumor burden reduction in target lesions

*Complete/partial responses.
Evaluable patients with target lesion at baseline and at least one on-treatment tumor assessment.
# Time to and duration of response

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>32</th>
<th>40</th>
<th>48</th>
<th>56</th>
<th>64</th>
<th>72</th>
<th>80</th>
<th>88</th>
<th>96</th>
</tr>
</thead>
</table>

- **On monotherapy treatment**
- **Off monotherapy treatment**
- **First response**
- **Crossover to combination**
- **Death**
- **Ongoing response**

- Median time to response, months (SD): 1.48 (2.14)
- mDOR, months (95% CI): NR (9.92–NE)

mDOR, median duration of response.
Progression-free survival

Median PFS, months (95% CI)

Nivolumab 2.78 (1.45–5.85)

No. of patients at risk

78 35 28 22 9 4 2 0

All treated patients.

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Overall survival

Median OS, months (95% CI)

Nivolumab 9.72 (7.26–16.16)

No. of patients at risk

78 61 54 41 29 16 5 0

All treated patients.

Presented By Padmanee Sharma at 2016 ASCO Annual Meeting
Phase III

Illa: Conducted after efficacy is demonstrated, but prior to regulatory submission of NDA (New Drug Application). Includes patients for which the drug is intended; or special groups (p.e., renal failure).

Illib: Conducted after regulatory submission of NDA, but prior to approval. Complete or supplement earlier trials, or directed to new type of trials (QoL, marketing).
Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC) - CALGB 80802 (Alliance)

On behalf of all inter-group investigators

CALGB 80802 Study Schema

Eligibility
- Histologically proven measurable HCC
- No prior systemic therapy
- Child-Pugh A
- ECOG PS: 0 -2
- Adequate organ function

(1:1) Randomization (N=480-680)

6 cycles of:
- Doxorubicin 60 mg/m² IV Day 1 in 21-day cycles
- Sorafenib 400 mg po bid

Sorafenib 400 mg po bid

Sorafenib 400 mg po bid

Continue until withdrawal, PD, or death

Half doses of doxorubicin and sorafenib were offered to subjects with baseline bilirubin of >1.2
CALGB 80802 Study Objectives

➢ Primary Objective
  • Overall survival (OS), stratified by locally advanced and metastatic disease

➢ Secondary Objectives
  • Safety and tolerability
  • Progression-free-survival (PFS)
  • Time to progression (TTP)
  • Tumor response using RECIST 1.1
  • Molecular, virologic, and radiologic correlates
CALGB 80802: Overall Survival by Treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS Median</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>176 (123)</td>
<td>10.5</td>
<td>1.06</td>
<td>0.8-1.4</td>
<td>0.24</td>
</tr>
<tr>
<td>Doxorubicin + Sorafenib</td>
<td>180 (130)</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented by Ghassan Abou-Alfa on behalf of the Intergroup and Alliance CALGB 80802 Study Team
# CALGB 80802: Progression-Free Survival by Treatment

Presented by Ghassan Abou-Alfa at 2016 ASCO Annual Meeting

## Table: Progression-Free Survival by Treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>PFS Median</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>176 (149)</td>
<td>3.9</td>
<td>0.9</td>
<td>0.72-1.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Doxorubicin + Sorafenib</td>
<td>180 (153)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

- CALGB 80802 is the first NCI sponsored multi-cooperative group hepatobiliary cancer phase III study
- Doxorubicin plus sorafenib did not show an improvement in survival compared to sorafenib as first line therapy in patients with advanced HCC, with added toxicity
- A series of scientific correlates await reporting
Overall Success at Phase II and III

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infect. Dis.</td>
<td>41%</td>
<td>55%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>36%</td>
<td>60%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>30%</td>
<td>63%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>24%</td>
<td>61%</td>
</tr>
<tr>
<td>Neurology</td>
<td>32%</td>
<td>55%</td>
</tr>
<tr>
<td>CV</td>
<td>28%</td>
<td>46%</td>
</tr>
<tr>
<td>Oncology</td>
<td>29%</td>
<td>34%</td>
</tr>
</tbody>
</table>
Low Success Rate of Drug Approvals!

Likelihood of approval for drugs tested in phase I trials is 6.7%, the lowest of all diseases*!

From 1998-2014, failure-to-success ratio of investigational agents for melanoma was 14:1, and only 10 of 177 agents for lung cancer were approved**.

Drug development in oncology takes 1.5 years longer than in other diseases (slow recruitment, low PS and longer follow-up needed)***.

New Features in MTA Phase I trials

- New expedited approval to accelerate drug development requires efficacy in early phase trials!

- Molecular tumor profiling for matched therapy and testing of drug combinations!

- The shift towards multi-institutional trials and centralized management.
What Could Be Done to Improve Early Trials of MTAs?

• **Safety is** a key requirement

• Novel dose-escalation schemes?

• Improved patient selection?

• Pharmacokinetetic/Pharmacodynamics?
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Algorithmic design (3 + 3)</th>
<th>Accelerated-titration design</th>
<th>Model-based design (CRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose levels</strong></td>
<td>Predefined starting-dose level (considered safe based on preclinical data) Stepped dose escalation</td>
<td>Predefined starting-dose level (considered safe based on preclinical data) Dose escalation determined by occurrence of DLT</td>
<td>Starting-dose level based on a prior dose–toxicity curve and target DLT rate Dose of each subsequent cohort determined by updated model with same target DLT rate Modifications of the original CRM use a lower starting-dose level than predicted by the initial model</td>
</tr>
<tr>
<td><strong>Number of patients per cohort</strong></td>
<td>Three patients in each cohort; six patients in an expanded cohort</td>
<td>One patient in each cohort during the accelerated-titration phase; three or six patients in each cohort once dose escalation reverts to standard 3 + 3</td>
<td>Number specified by the investigator, typically two patients per cohort</td>
</tr>
<tr>
<td><strong>Dose-escalation scheme</strong></td>
<td>Patients are enrolled (three at a time) in each successive cohort When one out of three patients has DLT, the cohort is expanded to incorporate three more patients at the same dose level If two or three patients in a cohort have DLTs, the next lower dose level is expanded to include three additional patients</td>
<td>During accelerated phase, dose-escalation steps occur at 100% increments until one DLT or two moderate (grade 2) toxicities occur at any cycle Dose escalation then reverts to 3 + 3 design with 40% dose-escalation steps This design enables intrapatient dose escalation in the absence of DLT</td>
<td>Dose–toxicity model is updated on an ongoing basis using the toxicity rate from all previously treated patients to determine the optimal dose level of the next cohort with the same DLT target rate</td>
</tr>
<tr>
<td><strong>MTD</strong></td>
<td>Dose level at which ≤1 DLT occurs among the six-patient cohort</td>
<td>Dose determined by modelling of all toxicity data in the trial The 3 + 3 approach is often used in clinical practice to determine the MTD (that is, the dose level at which ≤1 DLT occurs in six patients)</td>
<td>Dose corresponding to target DLT rate based on the final updated model</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Simple and easy to implement Does not require modelling Offers conservative dose escalation for drugs with narrow therapeutic index</td>
<td>More patients treated at therapeutic dose than traditional 3 + 3 design Faster escalation and MTD reached with the same number of patients</td>
<td>More patients treated at therapeutic dose than traditional 3 + 3 design Model-based approach enables more-precise estimation of MTD Can take into account delayed toxicities depending on the definition of DLT</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Many patients might be treated at subtherapeutic doses MTD can be imprecise Might not be appropriate for MTAs with no or delayed toxicities</td>
<td>Might not be appropriate for agents with narrow therapeutic index</td>
<td>Continual modelling by a biostatistician is needed</td>
</tr>
</tbody>
</table>

CRM, continual reassessment method; DLT, dose-limiting toxicity; MTD, maximal tolerated dose.
Design 1 was a conventional design (similar to the commonly used modified Fibonacci method) using cohorts of 3-6 patients, with 40% dose-step increments and no intra-patient dose escalation. Designs 2-4 included only 1 patient per cohort until 1 patient experienced DLT or 2 patients experienced grade 2 toxic effects (during their first course of treatment for designs 2 and 3 or during any course of treatment for design 4). Designs 3 and 4 used 100% dose steps during this initial accelerated phase. After the initial accelerated phase, designs 2 through 4 resorted to standard cohorts of 3-6 patients, with 40% dose-step increments. Designs 2 through 4 used intra-patient dose escalation if the worst toxicity is grade 0–1 in the previous course for that patient.

**Conclusion:** Accelerated titration (i.e., rapid intra-patient drug dose escalation) designs appear to effectively reduce the number of patients who are undertreated, speed the completion of phase I trials, and provide a substantial increase in the information obtained.
Methods: One hundred phase I studies were simulated by both standard and quantitative assessment phase I designs. We compared MTD, frequency of 0 leukopenia and study size in the studies simulated using the standard design with those in the studies simulated using the quantitative assessment design.

Results: The median MTD determined from the 100 studies was nearly identical for the two designs: 100 and 95 mg/m2 per day for standard and quantitative assessment designs, respectively. However, the inter-study variation in the MTD was decreased in the quantitative assessment design. Moreover, the study size was significantly reduced (P<.0001), and the median percentage of patients treated at sub-toxic doses (no leukopenia) was significantly lower for the quantitative assessment design (44% versus 48%; P<.0001).

Conclusion: Our results show clear evidence that a phase I study design using dose and toxicity data in a repetitive and quantitative manner can identify the MTD with more accuracy than the standard design.
Novel vs Classical Dose-Escalation

• The **efficiency** of **novel** dose-escalation designs was demonstrated in a study of 84 phase I trials published between 2000 and 2010*.

• Compared with traditional 3+3 strategy, newer designs explored a **greater number of dose levels** (median of 6 vs 8-10) and achieved **> mean MTD-to-starting-dose ratio** (ratios of 9 vs 22-30).

Efficiency of New Dose Escalation Designs in Dose-Finding Phase I Trials of Molecularly Targeted Agents

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Abstract

Background: Statistical simulations have consistently demonstrated that new dose-escalation designs, such as accelerated titration design (ATD) and continual reassessment method (CRM)-type designs outperform the standard “3+3” design in phase I cancer clinical trials.

Methods: We evaluated the actual efficiency of different dose escalation methods employed in first-in-human phase I clinical trials of targeted agents administered as single agents published over the last decade.

Results: Forty-nine per cent of the 84 retrieved trials used the standard “3+3” design. Newer designs used included ATD in 42%, modified CRM (mCRM) in 7%, and pharmacologically guided dose escalation in 1%. The median numbers of dose levels explored in trials using “3+3”, ATD and mCRM designs were 6, 8 and 10, respectively. More strikingly, the mean MTD to starting dose ratio appeared to be at least twice as high for trials using mCRM or ATD designs as for trials using a standard “3+3” design. Despite this, the mean number of patients exposed to a dose below the MTD was similar in trials using “3+3”, ATD and mCRM designs.

Conclusion: Our results support a more extensive implementation of innovative dose escalation designs such as mCRM and ATD in phase I cancer clinical trials of molecularly targeted agents.

Table 1. Dose escalation efficiency parameters of first-in-human phase I trials of molecularly targeted agents according to the dose escalation method used.

<table>
<thead>
<tr>
<th></th>
<th>3+3</th>
<th>ATD</th>
<th>mCRM</th>
<th>PGDE</th>
<th>NS</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of trials</td>
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<td>35</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>84</td>
</tr>
<tr>
<td>No. of patients exposed at doses below the MTD, mean [range]</td>
<td>20 [0–68]</td>
<td>19 [0–48]</td>
<td>23 [9–36]</td>
<td>20</td>
<td>33</td>
<td>20 [0–68]</td>
</tr>
<tr>
<td>No. of patients exposed at doses above the MTD, mean [range]</td>
<td>9 [0–40]</td>
<td>10 [1–28]</td>
<td>4 [0–7]</td>
<td>3</td>
<td>0</td>
<td>9 [0–40]</td>
</tr>
<tr>
<td>Trial duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Not specified</td>
<td>33</td>
<td>25</td>
<td>6</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Specified</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

3+3 = “3+3” dose escalation method; ATD = Accelerated titration design; mCRM = Modified continual reassessment method; PGDE = Pharmacologically guided dose escalation; NS = Not specified; MTD = Maximum tolerated dose; NA = Not applicable.

doi:10.1371/journal.pone.0051039.t001
Patient Selection

• In most cases, an MTA is active in a subgroup of patients who may be identified using predictive biomarkers.

• The selection of patients based on molecular profiling can be done by gene or protein expression or detecting gene alterations (p.e., mutation, amplification or translocation) in tumor tissue or DNA.
Personalized Cancer Medicine: Molecular Diagnostics, Predictive Biomarkers, and Drug Resistance

D Gonzalez de Castro¹, PA Clarke², B Al-Lazikani² and P Workman²

The progressive elucidation of the molecular pathogenesis of cancer has fueled the rational development of targeted drugs for patient populations stratified by genetic characteristics. Here we discuss general challenges relating to molecular diagnostics and describe predictive biomarkers for personalized cancer medicine. We also highlight resistance mechanisms for epidermal growth factor receptor (EGFR) kinase inhibitors in lung cancer. We envisage a future requiring the use of longitudinal genome sequencing and other omics technologies alongside combinatorial treatment to overcome cellular and molecular heterogeneity and prevent resistance caused by clonal evolution.
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXpresses HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEWIN, PH.D., WOLFGANG EINMANN, M.D., JANET WOLTER, M.D., MARK PEDRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*
PFS = progression-free survival; HR = hazard ratio.

Recent Examples of Successful Use of Predictive Biomarkers in Phase I

• Phase I trials of crizotinib*, ceritinib**, and alectinib*** in patients with EML4–ALK rearranged NSCLC

• Vemurafenib in patients with BRAF/V600E-mutant melanoma****

• The remarkable tumor responses in these patient subsets facilitated drug approval!

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

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. DeZube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravli Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

Figure 3. Best Response to Crizotinib in 31 Patients with ALK-Positive Tumors, as Correlated with Clinicopathological Characteristics

METHODS

After screening tumor samples from approximately 1500 patients with non–small-cell lung cancer for the presence of ALK rearrangements, we identified 82 patients with advanced ALK-positive disease who were eligible for the clinical trial. Most of the patients had received previous treatment. These patients were enrolled in an expanded cohort study instituted after phase 1 dose escalation had established a recommended crizotinib dose of 250 mg twice daily in 28-day cycles. Patients were assessed for adverse events and response to therapy.

RESULTS

Patients with ALK rearrangements tended to be younger than those without the rearrangement, and most of the patients had little or no exposure to tobacco and had adenocarcinomas. At a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients, with 46 confirmed partial responses and 1 confirmed complete response); 27 patients (33%) had stable disease. A total of 63 of 82 patients (77%) were continuing to receive crizotinib at the time of data cutoff, and the estimated probability of 6-month progression-free survival was 72%, with no median for the study reached. The drug resulted in grade 1 or 2 (mild) gastrointestinal side effects.
Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enrique Filip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

METHODS

In this phase 1 study, we administered oral ceritinib in doses of 50 to 750 mg once daily to patients with advanced cancers harboring genetic alterations in ALK. In an expansion phase of the study, patients received the maximum tolerated dose. Patients were assessed to determine the safety, pharmacokinetic properties, and antitumor activity of ceritinib. Tumor biopsies were performed before ceritinib treatment to identify resistance mutations in ALK in a group of patients with NSCLC who had had disease progression during treatment with crizotinib.

RESULTS

A total of 59 patients were enrolled in the dose-escalation phase. The maximum tolerated dose of ceritinib was 750 mg once daily; dose-limiting toxic events included diarrhea, vomiting, dehydration, elevated aminotransferase levels, and hyponatremia. This phase was followed by an expansion phase, in which an additional 71 patients were treated, for a total of 130 patients overall. Among 114 patients with NSCLC who received at least 400 mg of ceritinib per day, the overall response rate was 58% (95% confidence interval [CI], 48 to 67). Among 80 patients who had received crizotinib previously, the response rate was 56% (95% CI, 45 to 67). Responses were observed in patients with various resistance mutations in ALK and in patients without detectable mutations. Among patients with NSCLC who received at least 400 mg of ceritinib per day, the median progression-free survival was 7.0 months (95% CI, 5.6 to 9.5).

Figure 1. Response to Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer (NSCLC).

Figure 2. Progression-free Survival.

Shown are Kaplan–Meier estimates of progression-free survival among patients with advanced, ALK-rearranged non–small-cell lung cancer (NSCLC) who received ceritinib at doses of 400 to 750 mg daily. In these 114 patients, the median progression-free survival was 7.0 months (blue). In the subgroup of 80 patients who had received crizotinib previously, the median progression-free survival was 6.9 months (orange). In the subgroup of 34 patients who had not received crizotinib previously, the median progression-free survival was not reached (green). Vertical lines on the survival curves indicate censoring of data.

Figure 3. Correlation of Response to Ceritinib with ALK Gene Alteration among Patients with Crizotinib Resistance.

A total of 13 patients with crizotinib-resistant, ALK-rearranged non–small-cell lung cancer underwent biopsy at one study site before the initiation of ceritinib. Shown here is the largest percentage decrease in target lesions in these 19 patients. All the tumors were positive for ALK rearrangement, on the basis of the standard fluorescence in situ hybridization (FISH) assay with the use of break-apart probes. ALK genotypes are shown above the bars. Amp denotes amplification of the ALK fusion gene as determined by means of FISH, and NM no ALK mutation or amplification. Data are shown for patients who had received crizotinib as the last therapy before ceritinib treatment (dark blue bars) and for patients who received any intervening systemic therapy between crizotinib and ceritinib (light blue bars). Dots below individual bars indicate patients with disease progression or death at the time of data cutoff.
Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O’Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

METHODS

We conducted a multicenter, phase 1, dose-escalation trial of PLX4032 (also known as RG7204), an orally available inhibitor of mutated BRAF, followed by an extension phase involving the maximum dose that could be administered without adverse effects (the recommended phase 2 dose). Patients received PLX4032 twice daily until they had disease progression. Pharmacokinetic analysis and tumor-response assessments were conducted in all patients. In selected patients, tumor biopsy was performed before and during treatment to validate BRAF inhibition.

RESULTS

A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The recommended phase 2 dose was 960 mg twice daily, with increases in the dose limited by grade 2 or 3 rash, fatigue, and arthralgia. In the dose-escalation cohort, among the 16 patients with melanoma whose tumors carried the V600E BRAF mutation and who were receiving 240 mg or more of PLX4032 twice daily, 10 had a partial response and 1 had a complete response. Among the 32 patients in the extension cohort, 24 had a partial response and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months.
Limitations of Biomarkers

• Most cancers have multiple genetic aberrations and the sensitivity to an MTA is likely modulated by many factors.

• Identifying a reliable biomarker might be less feasible when an MTA interacts with several targets or pathways, as is the case with many tyrosine kinase inhibitors.

• Establishing a very strong scientific basis for the biomarker with preclinical validation is, therefore, a prerequisite to avoid negative trials.
Afatinib Is the First Irreversible ErbB Family Blocker

- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4
- ErbB3 does not have a kinase domain and cannot be directly blocked by afatinib
- Afatinib prevents ligand-dependent ErbB3 phosphorylation in preclinical studies

Anti-phospho-immunoblotting has shown that afatinib prevents ligand (heregulin)-stimulated ErbB3 phosphorylation

| Heregulin | – | + | – | + | + | + |
| Afatinib (nM) | 0 | 0 | 300 | 1000 | 300 | 100 |

Inhibitory potency of afatinib, erlotinib, and gefitinib against ErbB family members in cell-free kinase assays and cell proliferation assays of various human lung cancer cell lines (nanomolar concentration causing 50 % inhibition (Solca et al. J Pharmacol Exp Ther, 2012; and Li et al. Oncogene, 2008)

<table>
<thead>
<tr>
<th></th>
<th>EGFR&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>EGFR&lt;sup&gt;L858R&lt;/sup&gt;</th>
<th>EGFR&lt;sup&gt;L858R/T790M&lt;/sup&gt;</th>
<th>HER2</th>
<th>HER4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell-free kinase assays</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>0.2–0.7</td>
<td>0.2–0.4</td>
<td>9–10</td>
<td>7–25</td>
<td>0.7–1.7</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>0.9–1.7</td>
<td>1.1–2.7</td>
<td>1520–3562</td>
<td>238–698</td>
<td>579–756</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>0.4–4.7</td>
<td>0.8–1.4</td>
<td>534–1267</td>
<td>416–1830</td>
<td>293–323</td>
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<td><strong>Cell proliferation assays</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>60</td>
<td>0.7</td>
<td>92–225</td>
<td>12–56</td>
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<tr>
<td>Erlotinib</td>
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<td>&gt;4000</td>
<td>&gt;4000</td>
<td>NA</td>
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<tr>
<td>Gefitinib</td>
<td>157</td>
<td>5</td>
<td>&gt;4000</td>
<td>&gt;4000</td>
<td>NA</td>
</tr>
</tbody>
</table>

*EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2 (ErbB2), *WT* wild-type, *NA* not available
Afatinib is a potent and selective inhibitor of EGFR, HER2, and ErbB4.

Afatinib selectively and potently blocks the ErbB family receptors EGFR, HER2, and ErbB4.

Afatinib is highly selective and does not inhibit a range of other kinases significantly, even at 1000 times higher concentrations.

**Molecular potency and selectivity (IC<sub>50</sub>)**

<table>
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<tr>
<th>Kinase</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>Selectivity</th>
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</thead>
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<tr>
<td>EGFR</td>
<td>0.5</td>
<td>14</td>
</tr>
<tr>
<td>HER2</td>
<td>14</td>
<td>0/50</td>
</tr>
<tr>
<td>ErbB4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HGFR</td>
<td>&gt;10,000</td>
<td>0/6</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>&gt;100,000</td>
<td>0/6</td>
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</table>

**Molecular selectivity**

<table>
<thead>
<tr>
<th>Kinase panel</th>
<th>Concentration (µM)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase panel</td>
<td>10</td>
<td>0/50</td>
</tr>
<tr>
<td>PanLab</td>
<td>5</td>
<td>3/62</td>
</tr>
<tr>
<td>CYP450</td>
<td>10</td>
<td>0/6</td>
</tr>
</tbody>
</table>

IC<sub>50</sub> = 50% inhibitory concentration; HGFR = hepatocyte growth factor receptor; VEGFR2 = vascular endothelial growth factor receptor 2.

Biomarkers Need Optimal Collection, Assay Performance, Reproducibility and Standardization!

• That’s why a low percentage of MTAs were developed with biomarker-based patient selection.

• In phase I studies, predictive value of biomarkers are studied as exploratory objectives.

• Examples: tumor PD-L1 expression in a subset of patients in phase I trial of nivolumab or tumor genotyping for BRAF and NRAS mutations in phase I trial of MEK inhibitor trametinib.
Safety, Activity, and Immune Correlates
of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,
David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D.,
Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D.,
Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D.,
Liping Chen, M.D., Ph.D., William H. Sharman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D.,
Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D.,
Daniel McDonald, M.B.A., Georgia D. Kollias, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D.,
and Mario Sznol, M.D.

METHODS

We enrolled patients with advanced melanoma, non–small-cell lung cancer, castration-resistant prostate cancer, or renal-cell or colorectal cancer to receive anti–PD-1 antibody at a dose of 0.1 to 10.0 mg per kilogram of body weight every 2 weeks. Response was assessed after each 8-week treatment cycle. Patients received up to 12 cycles until disease progression or a complete response occurred.

RESULTS

A total of 296 patients received treatment through February 24, 2012. Grade 3 or 4 drug-related adverse events occurred in 14% of patients; there were three deaths from pulmonary toxicity. No maximum tolerated dose was defined. Adverse events consistent with immune-related causes were observed. Among 236 patients in whom response could be evaluated, objective responses (complete or partial responses) were observed in those with non–small-cell lung cancer, melanoma, or renal-cell cancer. Cumulative response rates (all doses) were 18% among patients with non–small-cell lung cancer (14 of 76 patients), 28% among patients with melanoma (26 of 94 patients), and 27% among patients with renal-cell cancer (9 of 33 patients). Responses were durable; 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. To assess the role of intratumoral PD-1 ligand (PD-L1) expression in the modulation of the PD-1–PD-L1 pathway, immunohistochemical analysis was performed on pretreatment tumor specimens obtained from 42 patients. Of 17 patients with PD-L1-negative tumors, none had an objective response; 9 of 25 patients (36%) with PD-L1-positive tumors had an objective response (P=0.006).
Activity of the MEK Inhibitor Trametinib (GSK1120212) in Advanced Melanoma in a Phase I, Dose-escalation Trial

Gerald S Falchook, MD1, Karl D Lewis2, Jeffrey R Infante3, Michael S Gordon4, Nicholas J Vogelzang5, Douglas J DeMarini, PhD6, Peng Sun, PhD6, Christopher Moy, MS6, Stephen A. Szabo, BA6, Lori T Roadcap, MS6, Vijay G R Peddareddigari, MD6, Peter F Lebowitz, MD6, Ngocdiep T Le, MD6, Howard A Burris III3, Wells A Messersmith2, Peter J O'Dwyer7 [Professor], Kevin B. Kim, MD8, Keith Flaherty7, Johanna C. Bendell3, Rene Gonzalez2 [Professor], Razelle Kurzrock, MD1 [Professor]. and Leslie A Fecher7.

Table 3
Tumor Response and Progression-free Survival in Melanoma Subpopulations (n=97)

<table>
<thead>
<tr>
<th>Melanoma patients</th>
<th>N</th>
<th>Unconfirmed response</th>
<th>Overall unconfirmed response rate (PR +CR) (95% CI)</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF mutant (BRAFi naive)</td>
<td>30</td>
<td>2CR (7%), 10PR (33%), 11SD (37%)</td>
<td>40 (22-7, 59-4)</td>
<td>5.7 (4.0, 7.4)</td>
</tr>
<tr>
<td>Without prior brain metastases</td>
<td>14</td>
<td>1CR (7%), 4PR (29%), 4SD (29%)</td>
<td>36 (12-8, 64-9)</td>
<td>7.4 (1.9, 9.2)</td>
</tr>
<tr>
<td>With prior brain metastases</td>
<td>16</td>
<td>1CR (6%), 6PR (38%), 7SD (44%)</td>
<td>44 (19-8, 70-1)</td>
<td>5.5 (4.0, 7.4)</td>
</tr>
<tr>
<td>BRAF mutant previously treated with BRAFi2</td>
<td>6</td>
<td>1PR (17%), 4SD (67%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BRAF wild-type melanoma</td>
<td>39</td>
<td>4PR (10%), 15SD (38%)</td>
<td>10 (2-9, 24-2)</td>
<td>2.0 (1.7, 3.7)</td>
</tr>
<tr>
<td>Without prior brain metastases</td>
<td>31</td>
<td>4PR (13%), 13SD (42%)</td>
<td>13 (2-6, 29-8)</td>
<td>3.3 (1.8, 5.8)</td>
</tr>
<tr>
<td>With prior brain metastases</td>
<td>8</td>
<td>2SD (25%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>NRAS mutant</td>
<td>7</td>
<td>2SD (29%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Unknown mutational status</td>
<td>6</td>
<td>3SD (50%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Uveal</td>
<td>16</td>
<td>8SD (50%)</td>
<td>0</td>
<td>1.8 (1.8, 3.7)</td>
</tr>
</tbody>
</table>

BRAFi = BRAF inhibitor; CR = complete response; PR = partial response; SD = stable disease. NA = not applicable, summary statistics were not provided if N <12.

1 Unconfirmed response based on investigator analysis. N = all treated patients.
2 Three patients had prior brain metastases, three did not.

* Patients with prior brain metastases
1 PR due to the presence of non-target lesions
Anticancer Drug Development in 2016

• “Breakthrough therapy” FDA designation to expedite drug development, obtaining early evidence of efficacy as a key component of phase I studies.

• Tumor-specific expansion cohorts in phase I trials to further characterize safety and tumor response at the recommended dose for Phase II increased.

• Response rate contributed to over 75% of accelerated FDA drug approvals from 2002 to 2012.

• For therapies with benefit across many tumor types, efficacy evaluation can lead to large phase I trials with multiple expansion cohorts.

Anticancer Drug Development in 2016

• Phase I of immunotherapies with anti-PD-1 and anti-PD-L1 in tumor-type-specific cohorts to assess efficacy in various settings.

• Selected phase I trial centers and disease-specific investigators to help enrolment in disease-based cohorts.

• The use of efficacy endpoints in phase I can lead to direct transition to phase III testing. Nivolumab and MEDI4736 are examples.
Trends in the Use and Role of Biomarkers in Phase I Oncology Trials

Bernardo H.L. Goulart,1 Jeffrey W. Clark,1,2 Homer H. Pien,3 Thomas G. Roberts,4,5 Stan N. Finkelstein,6 and Bruce A. Chabner1,2

Abstract

Purpose: There has been interest in using biomarkers that aid the evaluation of new anti-cancer agents. We evaluated trends in the use of biomarkers and their contribution to the main goals of phase I trials.

Experimental Design: We did a systematic review of abstracts submitted to the American Society of Clinical Oncology annual meeting from 1991 to 2002 and the publications related to these abstracts. We analyzed the use of biomarkers and their contribution to published phase I trials.

Results: Twenty percent of American Society of Clinical Oncology phase I abstracts (503 of 2458) from 1991 to 2002 included biomarkers. This proportion increased over time (14% in 1991 compared with 26% in 2002; P < 0.02). Independent predictors of the use of biomarkers included National Cancer Institute sponsorship, submission in the time period of 1999 to 2002, adult population, and drug family (biological agents). Biomarkers supported dose selection for phase II studies in 11 of 87 of the trials (13%) emanating from these abstracts. However, the primary determinants of phase II dose and schedule were toxicity and/or efficacy in all but one of these 87 trials (1%). Biomarker studies provided evidence supporting the proposed mechanism of action in 34 of 87 of the published trials (39%).

Conclusions: The use of biomarkers in phase I trials has increased over the period from 1991 to 2002. To date, biomarker utilization has made a limited and primarily supportive contribution to dose selection, the primary end point of phase I studies. Additional studies are needed to determine what type of biomarker information is most valuable to evaluate in phase I trials.

Table 2. Multivariate analysis of factors associated with inclusion of biomarkers in 2,458 phase I abstracts from 1991 to 2002

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Trials with biomarkers/total number of trials (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>110/1472 (7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Biological</td>
<td>213/383 (55)</td>
<td>17.0 (13.0-25.0)</td>
</tr>
<tr>
<td>Targeted</td>
<td>136/396 (34)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>44/205 (21)</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>3/71 (4)</td>
<td>Reference</td>
</tr>
<tr>
<td>Adult</td>
<td>500/2387 (21)</td>
<td>8.0 (2.4-27.0)</td>
</tr>
<tr>
<td>NIH sponsorship</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>387/2132 (18)</td>
<td>Reference</td>
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<tr>
<td>Yes</td>
<td>116/326 (35)</td>
<td>2.8 (2.0-3.7)</td>
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<td>Period</td>
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<td>1995-1998</td>
<td>143/769 (19)</td>
<td>NA</td>
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<td>1999-2002</td>
<td>252/1048 (24)</td>
<td>2.2 (1.7-2.9)</td>
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<td>Pharmacokinetics</td>
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<tr>
<td>No</td>
<td>237/1289 (18)</td>
<td>Reference</td>
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<tr>
<td>Yes</td>
<td>266/1169 (22)</td>
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<td>Industry sponsorship</td>
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<tr>
<td>No</td>
<td>258/1378 (19)</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>245/1080 (22)</td>
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</tr>
<tr>
<td>Trial location</td>
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<td></td>
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<tr>
<td>USA</td>
<td>377/1575 (24)</td>
<td>Reference</td>
</tr>
<tr>
<td>Other</td>
<td>124/875 (14)</td>
<td>NA</td>
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<tr>
<td>Not given</td>
<td>2/8 (25)</td>
<td></td>
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</tbody>
</table>

Abbreviation: NA, not applicable.

1Total number of trials was determined for each characteristic (row).

2We report the odds ratio of significant independent predictors only (P < 0.05).

3Compounds that kill tumor cells by targeting the DNA or its machinery.

4Macromolecules similar to endogenous molecules produced by recombinant technology (e.g., antibodies, cytokines, antisense oligonucleotides, etc.).

5Small molecules that kill tumor cells or produce cell cycle arrest by affecting specific biochemical pathways.
Target Modulation as Endpoint

• For MTAs, target modulation and downstream molecular effects are more relevant surrogates of activity than toxicity*.

• Levels of protein expression in tumor tissue by IHC before and after treatment, serum proteins, peripheral blood mononuclear cells and imaging biomarkers are used.

• Circulating tumor cells and DNA will become essential as ‘liquid biopsies’!**. Also, PK–PD and PK–toxicity relationships are important, when drug concentration for maximal biological effects is known.

Circulating tumor DNA is a rapidly dynamic biomarker

- ctDNA levels
- ctDNA Spike
- Initiation of GTXC
- Partial Response

Presented By Luis Diaz at 2016 ASCO Annual Meeting
Tracking Resistance

Monitoring the emergence of resistant mutations in KRAS WT patients treated with EGFR blockade

Tracking Resistance

Interrogated all exons of KRAS, NRAS, BRAF, PIK3CA and EGFR

96% of cases had at least 1 mutation KRAS or NRAS

Metastatic EGFR Mutant Non–Small-Cell Lung Cancer With Acquired Resistance to Erlotinib

Symptomatic disease progression during erlotinib therapy

Day 0: Plasma ddPCR ordered → Day 1: EGFR T790M plasma-positive test result → 24-day delay in initiating therapy while awaiting tissue genotyping → Day 31: osimertinib therapy initiated

Day 0: Repeat biopsy ordered → Day 25: EGFR T790M tissue-positive test result

Clinical and radiographic response to osimertinib

Sacher AG … GR Oxnard, . JAMA Onc. April 07, 2016

Presented By Luis Diaz at 2016 ASCO Annual Meeting
ctDNA measured 6-8 weeks following curative resection of mCRC

Diehl et al Nature Medicine, 2008
ctDNA measured 6-8 weeks following curative resection of stage II CRC

![Graph showing time to recurrence with HR = 25.73 and P < 0.0001]

J. Tie and Peter Gibbs, ASCO 2015
MRD detection with ctDNA in breast cancer.

Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

Published by AAAS

Presented By Luis Diaz at 2016 ASCO Annual Meeting
ctDNA monitoring in patients with diffuse large B-cell lymphoma

- 108 patients
- VDJ gene segments of the rearranged immunoglobulin receptor genes
- ctDNA measured after 2 cycles of therapy

*National Cancer Institute and Adaptive Biotechnologies

Clearance of circulating EGFR mutations in metastatic lung cancer

- 122 patients with EGFR mutant NSCLC
- Treated with erlotinib-based regimen
- Determined using allele-specific PCR after 3 cycles of therapy

*Hong Kong Cancer Institute, Roche, Genentech

Precision Medicine Trials

• MTAs to target specific oncogenic drivers and advances in next-generation sequencing (NGS) to rapidly interrogate the genomic mutational profile of a tumor led to *Precision Cancer Medicine*.

• This concept can be described as the delivery of patient-tailored therapy against actionable molecular targets in order to maximize antitumor activity while minimizing toxicity.

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 Gonçalves, Céline Gavillon, Caroline Dubet, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Angé Massiani, Cécile Mauborge, Sébastien Armanet, Nicolas Servent, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezquel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sabin, Maud Kamel, Xavier Paoletti, 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.

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. 15STK11 inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations of STK11. Focal gains of several PI3K pathway genes including AKT1, AKT2, AKT3, RIT1, and RIT2 (three patients). Jntragenic deletion within PDGFRA validated by overexpression of PDGFRA in immunohistochemistry. Filtragenic deletion within KIT validated by overexpression of the KIT in immunohistochemistry.

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).
Methods
Breast cancer patients with accessible metastases for biopsy in 18 centers in France. Therapeutic targets decided on the basis of identified genomic alterations. Primary outcome to check the proportion of patients to whom a targeted therapy could be offered.

Results
423 patients included and biopsy obtained from 407. Sequencing feasible in 67-70%. A targetable genomic alteration identified in 46%, most frequently in PIK3CA (25%), CCND1 (19%) and FGFR1 (13%). In 39% rare genomic alterations (<5% of the general population), such as AKT1 mutations, EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET amplifications. Therapy could be personalized in 13% of patients. Of the 43 patients who were assessable and received targeted therapy, 9% had objective response, and 21% had stable disease for more than 16 weeks. Grade 3 or higher adverse events related to biopsy in only 1% of cases.
A Pilot Study Using Next-Generation Sequencing in Advanced Cancers: Feasibility and Challenges

Glen J. Weiss¹,²*, Winnie S. Liang², Michael J. Demeure¹,², Jeff A. Kiefer², Galen Hostetter²,³, Tyler Izatt², Shripad Sinari², Alexis Christoforides², Jessica Aldrich², Ahmet Kurdoglu², Lori Phillips², Hollie Benson², Rebecca Reiman², Angela Baker², Vickie Marsh¹, Daniel D. Von Hoff¹,²,³*, John D. Carpten²,³, David W. Craig²,³

¹ Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare (VGPC), Scottsdale, Arizona, United States of America, ² The Translational Genomics Research Institute, Phoenix, Arizona, United States of America, ³ Van Andel Research Institute, Grand Rapids, Michigan, United States of America

Abstract

Purpose: New anticancer agents that target a single cell surface receptor, up-regulated or amplified gene product, or mutated gene, have met with some success in treating advanced cancers. However, patients’ tumors still eventually progress on these therapies. If it were possible to identify a larger number of targetable vulnerabilities in an individual’s tumor, multiple targets could be exploited with the use of specific therapeutic agents, thus possibly giving the patient viable therapeutic alternatives.

Experimental Design: In this exploratory study, we used next-generation sequencing technologies (NGS) including whole genome sequencing (WGS), and where feasible, whole transcriptome sequencing (WTS) to identify genomic events and associated expression changes in advanced cancer patients.

Results: WGS on paired tumor and normal samples from nine advanced cancer patients and WTS on six of these patients’ tumors was completed. One patient’s treatment was based on targets and pathways identified by NGS and the patient had a short-lived PET/CT response with a significant reduction in his tumor-related pain. To design treatment plans based on information garnered from NGS, several challenges were encountered: NGS reporting delays, communication of results to out-of-state participants and their treating oncologists, and chain of custody handling for fresh biopsy samples for Clinical Laboratory Improvement Amendments (CLIA) target validation.

Conclusion: While the initial effort was a slower process than anticipated due to a variety of issues, we demonstrate the feasibility of using NGS in advanced cancer patients so that treatments for patients with progressing tumors may be improved.

MTAs in Combination studies

• As most cancers are driven by multiple genes and pathways, most benefits will be derived from combinations of MTAs with other targeted therapy or standard chemotherapy.

• Thus, phase I trials of combination therapies are increasingly being conducted.
Cancer immunotherapy has become a popular anticancer approach, with the goal of stimulating immune responses against tumor cells. Recent evidence has demonstrated that the use of monoclonal antibodies targeting the programmed death ligand-1 (PD-L1)/programmed death-1 (PD-1) checkpoint pathway can result in well-tolerated clinical responses in a wide variety of tumor types. This review summarizes the safety, clinical activity and biomarker data for the anti-PD-L1 antibody, MPDL3280A, from a phase Ia multicenter, dose-escalation and expansion trial. The data to date suggest that MPDL3280A is most effective in patients with pre-existing immunity suppressed by PD-L1 and reinvigorated upon antibody treatment.

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Table 3. Ongoing Phase Ib Combination Therapy Trials With MPDL3280A

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug(s)</th>
<th>MOA</th>
<th>Clinicaltrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced solid tumors</td>
<td>Bevacizumab + chemotherapy</td>
<td>Anti-VEGF</td>
<td>NCT01633970</td>
</tr>
<tr>
<td></td>
<td>Cobimetinib</td>
<td>MEK inhibitor</td>
<td>NCT01988896</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab or interferon α-2b</td>
<td>Anti-CTLA-4</td>
<td>NCT02174172</td>
</tr>
<tr>
<td></td>
<td>RO7009789</td>
<td>antiviral</td>
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<tr>
<td>DLBCL and FL</td>
<td>Obinutuzumab</td>
<td>Anti-CD40</td>
<td>NCT02304393</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Vemurafenib or cobimetinib</td>
<td>BRAF inhibitor</td>
<td>NCT02220842</td>
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<td></td>
<td>Erlotinib</td>
<td>MEK inhibitor</td>
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<tr>
<td>NSCLC</td>
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<td>EGFR inhibitor</td>
<td>NCT02013219</td>
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<td></td>
<td>INCB024360</td>
<td>IDO inhibitor</td>
<td>NCT02298153</td>
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</tbody>
</table>

Abbreviations: DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; IDO, indoleamine 2,3-dioxygenase; MOA, mechanism of action; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor.
Regulatory changes

• The development of a successful anticancer drug from first-in-human study to approval normally takes about 7 years!

• If an MTA has a well-defined mechanism based on proof-of-concept studies, unprecedented clinical responses with minimal toxicity in early clinical trials and strong predictive biomarker, the approval process is being accelerated*.

<table>
<thead>
<tr>
<th>Programme</th>
<th>Qualifying criteria</th>
<th>Features</th>
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</thead>
<tbody>
<tr>
<td>Fast Track Designation</td>
<td>Drug intended to treat a serious condition AND nonclinical or clinical data demonstrating the potential to address unmet medical need</td>
<td>Actions to expedite development and review, Rolling review</td>
</tr>
<tr>
<td>Breakthrough Therapy Designation</td>
<td>Drug intended to treat a serious condition AND preliminary clinical evidence indicating substantial improvement for a clinically significant end point(s) compared with available therapies</td>
<td>Intensive guidance on efficient drug development, Organizational commitment, Rolling review, Other actions to expedite review (for example, eligibility for priority review)</td>
</tr>
<tr>
<td>Accelerated Approval Pathway</td>
<td>Drug that treats a serious condition AND generally provides meaningful advantage over available therapies AND demonstrates an effect on either: A surrogate end point reasonably likely to predict clinical benefit, A clinical end point that can be measured earlier than IMM but is reasonably likely to predict an effect on IMM, Other clinical benefit (for example, an intermediate end point)</td>
<td>Approval on the basis of an effect on a surrogate end point or an intermediate clinical end point reasonably likely to predict the clinical benefit of the drug</td>
</tr>
<tr>
<td>Priority Review Designation</td>
<td>Drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness</td>
<td>Shorter timeline for review of marketing application (6 months compared with the 10-month standard standard review)</td>
</tr>
</tbody>
</table>

IMM, irreversible morbidity or mortality.
Figure 1 | Considerations for the evolution of phase I oncology trials in the MTA era. This diagram highlights seven key areas of phase I trials in oncology that have evolved to adapt to novel MTAs and increase the efficiency of drug development. These include the improvement of dose-escalation designs, selection of patients based on biomarkers, refinement of the study end points, adoption of precision medicine, increased use of combination studies, implementation of new regulatory proceedings and, finally, a shift towards new institutional arrangements. MTA, molecularly targeted agents.