Optimizing Patient Enrollment and Efficacy of Precision Oncology Clinical Trials

Apostolia M. Tsimberidou, MD, PhD
Professor
Department of Investigational Cancer Therapeutics
IMPACT 2007-2013: Overall Survival by Type of Therapy

N = 3,743; 1,307 (34.9%) patients had ≥1 targetable alteration

<table>
<thead>
<tr>
<th>Matched:</th>
<th>Total</th>
<th>Died</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes:</td>
<td>711</td>
<td>629</td>
<td>9.3</td>
<td>8.4-10.5</td>
</tr>
<tr>
<td>No:</td>
<td>596</td>
<td>559</td>
<td>7.3</td>
<td>6.5-8.0</td>
</tr>
</tbody>
</table>

P < .001
HR = .72

Overall Survival, %

Months

ASCO 2018, Press Briefing Presentation

AM Tsimberidou, MD, PhD
Efficacy of Larotrectinib in TRK Fusion–Positive Cancers


FDA approval Nov 26, 2018
**Systemic efficacy of entrectinib in patients with and without CNS metastases at baseline**

### Systemic response by baseline CNS disease status*†

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ solid tumors (N=54)</th>
<th>ROS1+ NSCLC (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline CNS disease</strong></td>
<td>No (n=42)</td>
<td>Yes (n=12)</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>59.5 (43.3–74.4)</td>
<td>50.0 (21.1–78.8)</td>
</tr>
<tr>
<td><strong>CR, n (%)</strong></td>
<td>4 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>PR, n (%)</strong></td>
<td>21 (50.0)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td><strong>Median DoR, months (95% CI)</strong></td>
<td>12.9 (7.1–NE)</td>
<td>NE (4.2–NE)</td>
</tr>
</tbody>
</table>

**ORR was similar in patients with and without baseline CNS disease**

**DoR was longest in patients with ROS1+ NSCLC without baseline CNS disease**

**ORR was 57% (95% CI 43.2–70.8) in patients with NTRK+ solid tumors and 77% (95% CI 63.8–87.7) in patients with ROS1+ NSCLC**

*CNS disease at baseline determined by investigator; †Confirmed responses only; ‡Best change at any single timepoint. CNS, central nervous system; CR, complete response; DoR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; SLD, sum of longest diameter

### Change in tumor size in NTRK+ solid tumors and ROS1+ NSCLC

- **Best percent change from baseline in tumor size‡**
  - CNS disease at baseline
  - NTRK+ solid tumors
  - ROS1+ NSCLC

- **Decreases in tumor size were observed in patients with or without baseline CNS disease**

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**Presented at:** 2019 ASCO ANNUAL MEETING

**Presented by:** Joshua Sabari MD

**FDA Priority Review**

**Siena S et al ASCO 2019, abstract 3017**
## Selected tumor types in which NTRK gene fusions have been identified

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>0.1-3.3</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0.2-1</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.2-2.7</td>
</tr>
<tr>
<td>Head and neck squamous cell carcinoma</td>
<td>0.5</td>
</tr>
<tr>
<td>Thyroid cancer (papillary)</td>
<td>2.4 (25.9)</td>
</tr>
<tr>
<td>Pediatric high-grade glioma</td>
<td>7</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>50.0-96.2</td>
</tr>
</tbody>
</table>

[www.trkcancer.com](http://www.trkcancer.com)
NCI-MATCH: Nivolumab in Mismatch-Repair Deficient Non-Colorectal Cancers (n=34)

Depth of response

PR, 24%; SD ≥ 2 months, 32%
NCI MATCH, Capivasertib Arm
Solid Tumors with AKT1 E17K Mutation (n = 35)

AKT1 E17K mutation: 1.3% (70 of 5,548 patients)
ECOG-ACRIN K Kalinsky et al 2018 EORTC-NCI-AACR Symposium
**NCI MATCH, Ado-Trastuzumab Emtansine Arm**

**Solid Tumors with ERRB2 Amplification (n=26)**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>ITT (37) n (%)</th>
<th>Evaluable (26) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed Partial response</td>
<td>3 (8%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>16 (43%)</td>
<td>16 (62%)</td>
</tr>
<tr>
<td>Progression of Disease</td>
<td>12 (32%)</td>
<td>12 (46%)</td>
</tr>
</tbody>
</table>

Peter J. O’Dwyer, MD ECOG-ACRIN Cancer Research Group

Komal Jhaveri, MD FACP
### NCI MATCH: 11 of 35 Arms With Results 3/11 Positive (27%)

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

Peter J. O’Dwyer, MD ECOG-ACRIN Cancer Research Group
<table>
<thead>
<tr>
<th>Challenges and Opportunities: Molecular profiling</th>
<th>Actual</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor biopsy</td>
<td>Not standard</td>
<td>Standard of care</td>
</tr>
<tr>
<td>Tumor sequencing</td>
<td>Targeted NGS</td>
<td>Whole genome sequencing, immune markers, transcriptomics, proteomics, novel markers</td>
</tr>
<tr>
<td>Bioinformatics</td>
<td>Limited</td>
<td>Optimized</td>
</tr>
<tr>
<td>Emergence of sub-clones</td>
<td>Limited data</td>
<td>Real-time monitoring</td>
</tr>
<tr>
<td>Time to analysis</td>
<td>&gt;10 days</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Timing</td>
<td>Advanced, refractory</td>
<td>Starting at diagnosis</td>
</tr>
<tr>
<td>Biomarker development</td>
<td>Drug-specific</td>
<td>Platform diagnostics</td>
</tr>
<tr>
<td>Tumor heterogeneity</td>
<td>Single lesion biopsy/ctDNA</td>
<td>Validated ctDNA analysis</td>
</tr>
<tr>
<td></td>
<td>Actual</td>
<td>Goal</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Drug discovery</td>
<td>Limited</td>
<td>More, effective drugs</td>
</tr>
<tr>
<td>Study design</td>
<td>Phase I, II, III</td>
<td>Adaptive, “N of 1”, umbrella protocols</td>
</tr>
<tr>
<td>Patient eligibility</td>
<td>≈5-30%</td>
<td>100%</td>
</tr>
<tr>
<td>Histology-agnostic trial</td>
<td>Small sample; unbalanced data; response heterogeneity</td>
<td>Novel design for interim analyses; Adaptive design*</td>
</tr>
<tr>
<td>“Targeted” drug definition</td>
<td>Imprecise</td>
<td>Precise</td>
</tr>
<tr>
<td>Targeted therapy selection</td>
<td>Subjective</td>
<td>Evidence-based, tumor board, artificial intelligence</td>
</tr>
<tr>
<td>Adaptive learning, “N of 1”</td>
<td>&lt;10%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Early assessment of safety/clinical benefit of a drug permits inclusion of multiple stages of drug development in a single trial
Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer (IMPACT 2)

Primary Objective

To determine whether patients treated with a targeted therapy selected on the basis of mutational analysis of the tumor have longer PFS from the time of randomization than those whose treatment is not selected based on alteration analysis.

PI: Apostolia M. Tsimberidou, MD, PhD
Sponsor: Tempus
www.clinicaltrials.gov  NCT02152254
IMPACT 2. Study Design (I)

1. Metastatic disease
   - Tumor biopsy for molecular profiling
   - Targetable molecular aberrations
     - Yes
       - FDA-approved drugs within labeled indication
         - Yes
           - FDA-approved targeted therapy
         - No
           - Is there commercially available targeted therapy?
             - Yes → Offer Randomization
             - No

2. No
   - Targetable molecular aberrations
     - Yes
       - FDA-approved drugs within labeled indication
         - Yes
           - FDA-approved targeted therapy
         - No
           - Is there commercially available targeted therapy?
             - Yes → Offer Randomization
             - No
Hypothesis: Targeting molecular aberrations reduces hazard of progression by 33%. Total sample size 300 equally randomized gives >90% power, including some power within biomarker/disease subsets.
IMPACT 2: Mutation enrichment by tumor type (N=320)
IMPACT 2: Mutation Interactions (N=320)
Head and Neck Squamous Cell Carcinoma with FGF Amplifications: CR to FGFR Inhibitor

Dumbrava I, … Tsimberidou, AM, JCO Precision Oncology – Sept 2018
Targeted Therapy and Immunotherapy

Growth factors (e.g., PDGFR, FGFR, EGFR) influence the T-cell and Tumor cell pathways.

Tumor cell pathways include PI3K, AKT, mTOR, ERK, MEK, RAF, and PI3K.

APC (Antigen Presenting Cell) interacts with Ipilimumab and Tremelimumab.

CTLA-4 and PD-1 interactions modulate immune response.

Cytotoxic effect mediated by T-cell activation.

Drugs and inhibitors: Nivolumab, Pembrolizumab, Vemurafenib, Dabrafenib, LGX818, Trametinib, Selumetinib, Cobimetinib, MEK162, PD-L1/B7-H1, BMS-936559, MPDL3280A, MEDI4736, MSB0010718C, AMP-224.
Immuno-Oncology Trials: Opportunities and Challenges

• Response 10-30% of patients
• Limited markers of response or toxicity
• Eligibility criteria: exclusion of immune disorders, infections, steroids
• Endpoints: response, PFS, OS
• Pseudo-progression, hyper-progression
• Response criteria: RECIST, irRECIST
• Landmark analysis: PFS, OS
• Toxicity: immune-related adverse events
Mutational Burden and Objective Response Rate to PD1/PDL1 Inhibitors in Selected Tumor Types

Yarchoan et al., 2017
Trial Reporting in Immuno-Oncology (TRIO): An American Society of Clinical Oncology-Society for Immunotherapy of Cancer Statement

Tsimberidou AM, Levit LA, Schilsky RL, Averbuch SD, Chen D, Kirkwood JM, McShane LM, Sharon E, Mileham KF, Postow MA

Goal of the Statement

Development of guidelines for standardization of reporting and improved interpretation of immuno-oncology (IO) clinical research:

• To define the minimal standards for reporting IO trials.

• To describe the unique features of IO trials to ensure sufficient information to assess study quality and enable comparison among IO trials.
<table>
<thead>
<tr>
<th><strong>Table 1. Trial Reporting in Immuno-Oncology (TRIO) Standards</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reporting Standards</strong></td>
</tr>
<tr>
<td><strong>Efficacy reporting standards</strong></td>
</tr>
<tr>
<td>1. Report the criteria used to evaluate response to therapy and the rationale for the chosen criteria.</td>
</tr>
<tr>
<td>2. Include spider plots or swimmer plots in efficacy descriptions to better report kinetics of response <em>(Figs 1 and 2)</em>.</td>
</tr>
<tr>
<td>3. Report how disease control rate is defined and how its components are assessed.</td>
</tr>
<tr>
<td>4. Report criteria that allow patients to continue treatment beyond disease progression.</td>
</tr>
<tr>
<td>5. Report the number (proportion) of patients who are treated beyond progression, treatment beyond progression duration, emergence of new toxicity, and efficacy after initial progression.</td>
</tr>
<tr>
<td>6. Report progression-free survival and overall survival using Kaplan-Meier analyses.</td>
</tr>
<tr>
<td><strong>Toxicity reporting standards</strong></td>
</tr>
<tr>
<td>7. Differentiate between the clinical diagnoses of IO toxicity and the specific symptoms that led to the diagnoses.</td>
</tr>
<tr>
<td>8. If the prespecified clinical diagnoses used in data collection belong to categories such as “immune-related adverse events” or “adverse events of special interest,” report how these terms are defined and why these categories were selected for trial reporting.</td>
</tr>
<tr>
<td>9. Report all toxicity by specific grade.</td>
</tr>
<tr>
<td>10. Report clinical interventions used to manage IO toxicity <em>(Table 2)</em>.</td>
</tr>
<tr>
<td>11. Report time of onset and duration of IO toxicity <em>(Table 2)</em>.</td>
</tr>
<tr>
<td><strong>Combination or sequencing of immunotherapies reporting standard</strong></td>
</tr>
<tr>
<td>12. Report the scientific hypothesis for the combination or sequence on the basis of preclinical and/or clinical data as well as the rationale for the selection of the particular dose(s) and sequence of agents.</td>
</tr>
</tbody>
</table>

**NOTE.** Standards 1 to 5 and 7 to 11 are unique to immuno-oncology (IO) therapies.
• Unique mechanism of action: indirect and direct.
• Potential for delayed efficacy and non-classical radiographic response profiles.
• Prolonged responses in a subset of patients.
Efficacy Reporting Standards (I)

Defining Anti-Tumor Activity

1. Report the criteria used to evaluate response to therapy and the rationale for the chosen criteria.

2. Include spider plots or swimmer plots in efficacy descriptions to better report kinetics of response.

3. Report how disease control rate is defined and how its components are assessed.
Efficacy Reporting Standards (II)

Clinical Events after Disease Progression

4. Report criteria that allow patients to continue treatment beyond disease progression.

5. Report the number (proportion) of patients who are treated beyond progression, treatment beyond progression duration, emergence of new toxicity, and efficacy after initial progression.

Overall survival and Progression-Free Survival

6. Report progression-free survival and overall survival using Kaplan-Meier analyses.
IO related Adverse Events

Adverse events associated with IO agents

Mechanisms underlying Immune-related AEs

Hot and Cold Tumors

Munn et al., Trends in Immunol, 2016
An Exploratory Study of Nivolumab with or without Ipilimumab According to Tumor CD8 Expression in Patients with Advanced Cancer

Metastatic Disease → Tumor Biopsy (CD8, Immunologic Assessment)

- **CD8+ ≥ 15% (CD8+ high tumors)**
  - Nivolumab\(^{a,b}\) (x 2 doses) → Response Assessment → Clinical Benefit → Continue Nivolumab
  - Nivolumab\(^{c}\) (x 2 doses) → Response Assessment → Progressive Disease\(^b\) → Other Treatment

- **CD8+ < 15% (CD8+ low tumors)**
  - Nivolumab + Ipilimumab\(^{b,c}\) (x 2 doses) → Tumor Biopsy → Clinical Benefit → Continue Nivolumab
  - Nivolumab + Ipilimumab\(^c\) (x 2 doses) → Tumor Biopsy → Response Assessment → Progressed Disease\(^b\) → Other Treatment

PI: AM. Tsimberidou, MD, PhD
Sponsor: Parker Institute for Cancer Immunotherapy

www.clinicaltrials.gov NCT03651271
ACTolog: Endogenous CD8+ T cells in Advanced Cancer

Screening

NCT02876510, Immatics

Production phase

PI, AM Tsimberidou; Co-PI, Borje Andersson

Treatment/Observation

Follow-up
ACTengine: Autologous T Cell + Engineered TCRs

1. A tumor sample is taken from the patient to confirm the expression of the targeted antigen.
2. A target-specific TCR is isolated from a healthy donor, characterized, and modified.
3. Lentiviral vector used to transfer the target specific TCR in the T cells.
4. PBMCs from patient leukapheresis are isolated and pre-activated using anti-CD3 and -CD28 antibodies. The activated PBMC are then transduced with a lentiviral vector encoding the target-specific TCR. Transduced T cells are expanded to large numbers in 3-5 days to meet dose and frozen. Upon completion of the release testing, the cells are ready to be infused into the patient.

Immatics [www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT03247309, NCT03441100, NCT0368124
Advancing Immuno-Oncology Combination Therapy

- More than 3,000 IO clinical trials are evaluating the clinical activity of PD1/PDL1 inhibitors (monotherapy, in combination)
- Combinations of drugs with non-overlapping toxicities and resistance mechanisms
- Higher ORR is associated with higher probability of regulatory approval
- Higher success rate is noted when combining agents with proven clinical antitumor activity as single agents
- Antitumor activity can be predicted using the the Bliss independent activity mathematical model.

“State of the art” comprehensive profiling: genomics, immune markers, transcriptomics, proteomics, novel markers

Discovery of effective drugs

Use of comprehensive profiling to select treatment/clinical trials at the time of diagnosis and during the course of the disease

Design innovative studies with combination therapy/novel therapeutic strategies

Access to information regarding available trials to doctors or patients to increase patient enrollment
Advanced methodologies to analyze comprehensive profiling and clinical outcomes:

(1) to offer matched therapy to more patients
(2) to compare outcomes to those of patients not receiving matched therapy (case-control comparator) and
(3) to address complex questions that integrate precision molecular findings with immunologic findings to offer better treatments
Oncology Clinical Trial Information Commons (OCTIC)
Making a High-Performance Trial Matching Ecosystem Possible

Patient Information

- Specific diagnosis
- Biomarkers
- Prior lines of treatment
- Comorbidities
- Location preferences

Patient data access & standardization efforts
e.g. mCODE, with ASCO

Application & Services ecosystem

Examples:
- CancerCommons
- metastatic
- Syapse
- Emergingmed
- IBM Watson Health
- Ciitizen
- Genospace
- Genomoncology
- Massivebio

High-performing services and business possible only when information sources are robust and reliable

Trial Information

- Inclusion/Exclusion Criteria
- Medical conditions
- Biomarkers
- Prior lines of treatment
- Comorbidities
- Sites/ recruitment status
- Participation requirements

FRAGMENTED
Every health system/service provider/nonprofit maintaining its own database, sourcing from confidential protocols

9 entities have committed to assembling a single “best-of-all” resource for cancer clinical trial information. They will contribute their capabilities & technologies in a pre-competitive effort that lifts the entire field.

McKinsey & Co. providing project facilitation & presentation support
Goodwin Procter providing pro-bono legal support

Urgent focus area for BCI – New Program: OCTIC
# Oncology Clinical Trial Information Commons (OCTIC)

**Scope:** Biopharma User Interface and Clinical Trial Data System to enable robust patient-facing services

## Standardized Encoding Language

**Content, Terms, and Syntax for:**

- **Trial summaries**
  - Investigational therapies, study design, phase
- **Selection parameters**
  - Medical conditions
  - Prior therapies
  - Biomarkers
- **Locations**
  - Trial sites
  - Recruitment status
  - Contact info
- **Participation requirements**
  - In-person visit requirements
  - Remote care options

## Biopharma User Interface

- Drop-down selection
- Easy rule adoption/creation
- “Private disclosure” for sensitive information

## Clinical Trial Data System

- Private-node/Shared-hub architecture

## Access & Use

- Centralized access
  - Programming interfaces to query information
  - Access rules for private/public information
  - User authorization mechanisms

- **List of items**:
  - 1.7 million new cases of cancer diagnoses per year in the US
  - 5% are enrolled on clinical trials; 25% could potentially qualify for trials
  - 20% of oncology trials fail because of inadequate enrollment (FDAMap, 1/14/16)

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Program Announced at ASCO Annual Meeting 2019

**ASCO 2020:** Announce deployment of first tools & pilots
Taking aim sooner

If personalized medicine is to achieve its full potential, it should be used earlier on in clinical trials

Many scientists … believe that matching volunteers' genetic profiles to the drugs being tested will not only be better for the volunteers, but may also speed up the trials, and save millions of dollars in the process.

One such is Apostolia-Maria Tsimberidou of the University of Texas's MD Anderson Cancer Center, in Houston. And her preliminary results, presented at a meeting of the American Society of Clinical Oncology in Chicago, suggest she is right.
Multiple alterations, complex molecular networks, immune mechanisms, transcriptomic, proteomic and epigenetic changes can be identified in individual patients.

These markers should be integrated into clinical practice starting at the time of diagnosis and they should be monitored during the course of the disease to select optimal therapy.

Clinical trials with combination therapy and novel therapies are needed to address the complexity of tumorigenesis.

Development of infrastructure is needed to use artificial intelligence to integrate all available patient data to perform algorithm analysis in decision making for optimal drug selection, for More Effective Drugs, For More Patients, Faster.