The TAPUR Family of Clinical Trials: Building a Global Data Sharing Platform in Precision Oncology

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Chairman, WIN Consortium
Financial Disclosure

- I am an employee of the American Society of Clinical Oncology
- ASCO receives grants from the following pharmaceutical companies to support the TAPUR trial:
  - Astra-Zeneca
  - Bayer
  - Bristol Myers Squibb
  - Eli Lilly and Co.
  - Genentech
  - Merck
  - Pfizer
- I will discuss the off label use of approved drugs
Problem

- Patient with advanced cancer; no standard Rx options
- Genomic profile test performed
- Potentially actionable variant detected
- How to get the drug?
- Who pays for the drug? Is it “worth it”?
- How to learn from the treatment?
Overall Goals of TAPUR

▪ To learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target

▪ To educate oncologists about implementation of precision medicine in clinical practice
TAPUR Study Primary Objective

• To describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs prescribed for treatment of patients with advanced solid tumors, B cell NHL or MM with a genomic variant known to be a drug target or to predict sensitivity to a drug.
TAPUR Eligibility

- Patients with advanced solid tumors, B cell NHL and multiple myeloma for whom no standard treatment options exist
- Adequate organ function; PS 0-2
- Results available from a genomic test (FISH, PCR, NGS, WES, IHC for gene expression) performed in a CLIA certified, CAP accredited lab. Labs located or offering services to residents of NY must also have NY State accreditation. Test should be registered with NIH Genetic Test Registry.
MD reviews results of genomic test performed in CLIA certified/CAP accredited lab

Patient registered on study

MD determines if drug match exists in protocol or appropriate for MTB review

No match, Rx at MD discretion

Data monitoring committee regularly reviews RR of tumor-variant-drug groups

Results released when protocol-specified endpoints met

Matched therapy administered; safety and efficacy outcomes recorded

MTB: Molecular Tumor Board
## Drugs Available in TAPUR

<table>
<thead>
<tr>
<th>Pharmaceutical Company (Number of Drugs)</th>
<th>Drug(s) Provided for TAPUR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca (1)</td>
<td>Olaparib</td>
</tr>
<tr>
<td>Bayer (1)</td>
<td>Regorafenib</td>
</tr>
<tr>
<td>Bristol-Meyers Squibb (3)</td>
<td>Dasatinib, Nivolumab + Ipilimumab</td>
</tr>
<tr>
<td>Eli Lilly (1)</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Genentech (4)</td>
<td>Trastuzumab + Pertuzumab, Vemurafenib + Cobimetinib</td>
</tr>
<tr>
<td>Merck (1)</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Pfizer (6)</td>
<td>Axitinib, Bosutinib, Crizotinib, Palbociclib, Sunitinib, Temsirolimus</td>
</tr>
</tbody>
</table>
TAPUR Matching Rules

- Specific genomic inclusion and exclusion criteria included for each drug
- Matching at variant level if possible
- Automated rules engine approves/rejects match proposed by treating MD
- If no match proposed or match rejected, treating MD may consult TAPUR MTB
- MTB identifies TAPUR drugs or other options based on tumor genomics
- Thus far, 68% of cases matched by rules engine. Of those sent to MTB, 53% enrolled on a TAPUR study drug
Endpoints

- Primary endpoint: Objective response rate per standard response criteria or SD at 16+ w

- Other endpoints:
  - overall survival
  - progression-free survival
  - time on treatment
  - grade 3-5 AEs per CTCAE
  - SAEs
Simon’s two-stage design

Each tumor type-gene-drug is a “cohort”

Null Hypothesis: ORR<15% vs. Alternative Hypothesis: ORR ≥ 35%

Enroll 10 patients/cohoot
  - If 0-1 response, stop
  - If 2 or more responses, enroll additional 18 pts

Reject null hypothesis if 7 or more responses/28

85% power and one-sided Type 1 error rate of 0.10
TAPUR is a Pragmatic Trial

- Broad eligibility criteria
- Physician discretion on genomic testing, drug dosing, dose modifications
- Minimum necessary data collection
- Investigator assessment of response
- Data validation procedures but no auditing/monitoring
- IND exempt per FDA
- However, specific inclusion/exclusion criteria, genomic matching rules and standard response criteria, required evaluations and data submission
TAPUR Study: Patients with HIV

- Not explicitly excluded *per general study eligibility criteria*
  - Clinician judgment whether HIV disease would interfere or HIV medication would interact
- *Per drug-specific eligibility criteria*, patients with HIV are excluded from receiving pembrolizumab or olaparib
Patients with previously treated brain metastases are eligible, so long as the patient is:

- Not on treatment
- Not progressive
- Has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration
- Off steroids for at least one month prior to enrollment
TAPUR Study: Organ Dysfunction

- Patients must have acceptable organ function as defined by:
  - Absolute neutrophil count ≥ 1.5 x 10^6/µl
  - Hemoglobin ≥ 9.0 g/dl
  - Platelets ≥ 75,000/µl
  - Total bilirubin < 2.0 mg/dl
  - AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)
  - Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m²
TAPUR Study: Other Considerations

- **Pediatric Population:**
  - Patients 12 and older now eligible
  - Specific drugs excluded if no pediatric dose defined

- **Prior Malignancy:**
  - No exclusion for prior malignancy

- **Performance Status (PS):**
  - Performance status of 0-2 per general eligibility
  - Patients receiving pembrolizumab or regorafenib must have PS 0-1
Current Status of TAPUR

- 1350 patients registered (06/19/18)
- 959 patients enrolled (06/19/18)
- 113 participating sites (20 states)
TAPUR Clinical Sites: 113 locations, 20 states
Variation in Genomic Targets by Tumor Type N=956(30)
As of Friday, June 15, 2018

[Diagram showing variation in genomic targets by tumor type, with various factors and their associated numbers.]
Expanded and Closed TAPUR Study Cohorts

- **Cohort Status Definitions:**
  - Expanded = cohort has reached Stage I and will continue enrollment into Stage II
  - Closed = cohort will not continue enrollment into Stage II

- **Current Status:**
  - 15 cohorts expanded to Stage II
  - 2 cohorts closed after Stage I
<table>
<thead>
<tr>
<th>Cohort Status</th>
<th>Study Drug</th>
<th>Cancer</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanded to Stage II</td>
<td>Cetuximab</td>
<td>Ovarian</td>
<td>KRAS, NRAS, BRAF wild type</td>
</tr>
<tr>
<td></td>
<td>Olaparib</td>
<td>Breast</td>
<td>Somatic or germline inactivating mutations in BRCA1 or BRCA2</td>
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<tr>
<td></td>
<td></td>
<td>Colorectal</td>
<td>ATM mutation or deletion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate</td>
<td>Somatic or germline inactivating mutations in BRCA1 or BRCA2</td>
</tr>
<tr>
<td></td>
<td>Palbociclib</td>
<td>Malignant neoplasm of bronchus and lung</td>
<td>CDKN2A loss or mutation</td>
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<tr>
<td></td>
<td></td>
<td>Soft tissue sarcoma</td>
<td>CDK4 amplification</td>
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<tr>
<td></td>
<td></td>
<td>Head and neck</td>
<td>CDKN2A loss or mutation</td>
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<tr>
<td></td>
<td></td>
<td>Ovarian</td>
<td>CDKN2A loss or mutation</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Breast</td>
<td>High tumor mutational burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colorectal</td>
<td>High tumor mutational burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine</td>
<td>High tumor mutational burden</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab + Trastuzumab</td>
<td>Colorectal</td>
<td>ERBB2 amplification, mutation or overexpression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine</td>
<td>ERBB2 amplification, mutation or overexpression</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>Breast</td>
<td>FGFR1 mutation or amplification</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib + Cobimetinib</td>
<td>Colorectal</td>
<td>BRAF_V600E mutation</td>
</tr>
<tr>
<td>Permanently closed</td>
<td>Palbociclib</td>
<td>Gallbladder and Bile Ducts</td>
<td>CDKN2A loss or mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic</td>
<td>CDKN2A loss or mutation</td>
</tr>
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Challenges in TAPUR Implementation

- Determining profiling strategy
- Setting the matching rules
- Defining/analyzing cohorts
- Building the team and infrastructure inside ASCO
- Clinical site training on protocol/matching rules
- Organization of Molecular Tumor Board
Unique Cohorts in TAPUR Study

- >900 patients distributed in over 300 cohorts!
- Each cohort requires at least 10 patients for analysis.
TAPUR: A Global Platform for Data Sharing

Key

- TAPUR (United States)
- CAPTUR Trial (Canada)
- DRUP Trial (Netherlands)
- WIN_TAPUR (France, Spain, Luxembourg, Denmark, Brazil, Russian Federation, Israel, Jordan, India, Singapore, South Korea, China and Japan)
Drug Reutilization Protocol (DRUP) Study (Netherlands)

- Launched in August 2016
- 590 patients registered (05/30/18)
- 237 patients enrolled (05/30/18)
- 21 participating sites, with additional 12 anticipated (05/30/18)
- 19 study drugs (05/30/18)
- Similar eligibility criteria, genomic matching rules, endpoints as TAPUR
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

- NCT 03297606
- 17 drugs; 14 treatment options
- Launched October 6, 2017
- Recruiting at 4 sites in Canada
- Nearly identical eligibility criteria, genomic matching rules and endpoints as TAPUR
# Comparative Features of TAPUR, DRUP and CAPTUR

<table>
<thead>
<tr>
<th></th>
<th>TAPUR</th>
<th>CAPTUR</th>
<th>DRUP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of pts</strong></td>
<td>1230+</td>
<td>720</td>
<td>400</td>
</tr>
<tr>
<td><strong>Evaluable Definition</strong></td>
<td>Eligible and at least 1 dose of study drug</td>
<td>Eligible and at least 1 cycle of study drug and pts with objective PD prior to the end of cycle 1</td>
<td>Eligible and at least 1 cycle of study drug for orals and 2 treatments for IV meds and if response is radiologically or clinically evaluable at the MD’s discretion</td>
</tr>
<tr>
<td><strong>Null Hypothesis</strong></td>
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<tr>
<td><strong>Alternative Hypothesis</strong></td>
<td></td>
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<tr>
<td><strong>Power</strong></td>
<td>15%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Type I error rate</strong></td>
<td>35%</td>
<td>30%</td>
<td>30%</td>
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<tr>
<td></td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
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<tr>
<td></td>
<td>10%</td>
<td>7.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>CR, PR at 8+ wks</td>
<td>Best response on study*</td>
<td>Objective response or SD at 16 weeks Tx related Grade ≥ 3 AEs/SAEs **</td>
</tr>
<tr>
<td></td>
<td>CR, PR, SD at 16+ wks</td>
<td>CR, PR</td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Criteria for expansion</strong></td>
<td>10 pts ≥2 responses</td>
<td>8 pts ≥1 response</td>
<td>8 pts ≥1 response</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Criteria for Success</strong></td>
<td>28 pts ≥7 responses</td>
<td>24 pts ≥5 responses</td>
<td>24 pts ≥5 responses</td>
</tr>
</tbody>
</table>
Who Benefits if the TAPUR Family of Trials Succeeds?

- **Patients** receive targeted agent matched to tumor genomic profile; drugs at no cost
- **Physicians** receive guidance in interpretation of genomic test results and treatment options, access to drugs, clinical data on off-label use
- **Pharma** receives data on drug use and outcomes to inform R&D plans and life cycle management
- **Payers** receive data on test and drug use and outcomes to inform future coverage decisions
- **Regulators** receive data on extent and outcomes of off label drug and test use and real world safety data
For more information:

www.TAPUR.org

ClinicalTrials.Gov:
NCT#02693535