The TAPUR Study: Learning from precision medicine in practice

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Senior Vice President and Chief Medical Officer
American Society of Clinical Oncology
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 study:
  - Astra-Zeneca
  - Bayer
  - Bristol Myers Squibb
  - Eli Lilly and Co.
  - Genentech
  - Merck
  - Pfizer
- I will discuss the off label use of approved drugs
Nonrandomized Basket Designs
Multi-Basket MyPathway Study

Molecular alterations identified

Ineligible:
- Mutations in which the target drug is known to be ineffective (e.g., EGFR mutations in exon 20)

Eligible:
- Well-recognized activating mutations
- Unusual mutations (reported ≥ 2 times in COSMIC)
- HER2 amplification/overexpression
- HER2/CEP17 ratio > 3.0
- HER2 gene copy number > 6

Treatment determined after molecular alteration confirmed

MyPathway Study
Master protocol with multiple basket studies

Tumors with HER2 alterations (amplification/overexpression or activating mutation):
- Trastuzumab 8 mg/kg IV loading dose, then 6 mg/kg IV every 3 weeks plus pertuzumab 840 mg IV loading dose, then 420 mg IV every 3 weeks

- EGFR activating mutation:
  - Erlotinib 150 mg orally once daily

- BRAF activating mutation:
  - Vemurafenib 960 mg orally twice daily

- Trametinib 2 mg orally once daily

Re-evaluate after every 2 cycles
- 8 weeks for pertuzumab plus trastuzumab
- 8 weeks for erlotinib, vemurafenib, and vemidolide
- for the first 24 weeks, then every 12 weeks

Verify if the patient has additional mutations

Disease progression
Objective response or stable disease
Continue treatment until progression, unacceptable toxicity, or other discontinuation criteria are met

Discontinue treatment
No
Yes
Results of MyPathway Study

HER2-amplified CRC (A), Bladder (B), Biliary Cancer (C); BRAF mutant NSCLC (D)
BRAF Basket Study

BRAF V600–positive (testing per local methods)
Vemurafenib, 960 mg twice daily orally
Primary end point
Response rate at wk 8
Secondary end points
Progression-free survival
Time to progression
Best overall response
Time to response
Duration of response
Clinical benefit rate
Overall survival
Safety

Vemurafenib Monotherapy

NSCLC
Cholangiocarcinoma
All others
ECD/LCH
Anaplastic thyroid cancer
Breast cancer
Ovarian cancer
Multiple myeloma
Colorectal cancer

Vemurafenib Monotherapy

Vemurafenib plus Cetuximab
Common Features of These Trials

- Master protocol with multiple arms
- Rely on a genomic screen to direct patients to different treatment options
- Optimize use of rare patient resources
- Enable patient populations and treatments to move in/out of trial using a single protocol
- Include general and drug-specific inclusion/exclusion criteria
- Include a futility analysis
- Most are signal-finding; not all arms perform equally well
Why TAPUR?

- Patient with advanced cancer; no standard Rx options
- Genomic profile test performed
- Potentially actionable variant detected
- How to get the drug?
- How to learn from the treatment?
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. Tests registered with NIH Genetic Test Registry preferred.
- Treatment specific inclusion/exclusion criteria
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

Patient enrolled on study

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

Results released when protocol-specified endpoints met

Matched therapy administered; safety and efficacy outcomes recorded

MTB: Molecular Tumor Board
Cohort Creation

Registration

Screening
Consent
General eligibility criteria met

TAPUR matching to study drug(s) based on genomic criteria (or approved by MTB)

Treatment decision by treating physician

Screening continued
Drug-specific eligibility criteria met

Enrolled and placed into cohorts

Treatment 1
Target variant 1
Tumor type 1
Cohort 1
Cohort 2
Cohort 3
Cohort 4

Treatment 2, continued
Target variant 2
Tumor type 2

# Treatments Studied in TAPUR

<table>
<thead>
<tr>
<th>Pharmaceutical Company</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 (6)</td>
<td>Trastuzumab + Pertuzumab, Vemurafenib + Cobimetinib, Erlotinib*, Vismodegib*</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>

*Study drug no longer enrolling*
TAPUR Matching Rules

- Specific genomic inclusion and exclusion criteria 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 or multiple matches identified, treating MD may consult TAPUR MTB
- MTB identifies TAPUR drugs or other options based on tumor genomics
- Thus far, approximately 70% of cases matched by rules engine. Of those sent to MTB, 50% enrolled on a TAPUR study drug
Study Endpoints

- Primary endpoint: Objective response rate per standard response criteria or SD at 16+ weeks
- Other endpoints:
  - Overall survival
  - Progression-free survival
  - Time on treatment
  - Grade 3-5 AEs per CTCAE
  - SAEs
Statistical Design

- 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/period
  - 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
Current Status of TAPUR

- 2002 patients registered (04/30/19)
- 1437 patients enrolled (04/30/19)
- 120 participating sites (22 states)
TAPUR Clinical Sites: 120 locations, 22 states
# Enrollment by Study Drug as of 04/30/19

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Total participants enrolled on drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib (INLYTA)</td>
<td>5</td>
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<tr>
<td>Bosutinib (BOSULIF)</td>
<td>1</td>
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<tr>
<td>Cetuximab (ERBITUX)</td>
<td>114</td>
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<tr>
<td>Cobimetinib (COTELLIC) + Vemurafenib (ZELBORAF)</td>
<td>69</td>
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<tr>
<td>Crizotinib (XALKORI)</td>
<td>21</td>
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<tr>
<td>Dasatinib (SPRYCEL)</td>
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<tr>
<td>Erlotinib (TARCEVA)</td>
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<tr>
<td>Nivolumab (OPDIVO) + Ipilimumab (YERVOY)</td>
<td>150</td>
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<tr>
<td>Olaparib (LYNPARZA)</td>
<td>215</td>
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<tr>
<td>Palbociclib (IBRANCE)</td>
<td>239</td>
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<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>162</td>
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<tr>
<td>Pertuzumab (PERJETA) + Trastuzumab (HERCEPTIN)</td>
<td>153</td>
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<tr>
<td>Regorafenib (STIVARGA)</td>
<td>54</td>
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<tr>
<td>Sunitinib (SUTENT)</td>
<td>136</td>
</tr>
<tr>
<td>Temsirolimus (TORISEL)</td>
<td>97</td>
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<tr>
<td>Vismodegib (ERIVEDGE)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1437</strong></td>
</tr>
</tbody>
</table>
Unique Cohorts in TAPUR Study

- 1400+ patients distributed in 430 cohorts!
- Each cohort requires at least 10 patients for analysis.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor Type</th>
<th>Variant</th>
<th>Signal</th>
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<tbody>
<tr>
<td>Palbociclib</td>
<td>Gallbladder and Bile Ducts</td>
<td>CDKN2A mutation or loss</td>
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</tr>
<tr>
<td>Palbociclib</td>
<td>Pancreatic Cancer</td>
<td>CDKN2A mutation or loss</td>
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</tr>
<tr>
<td>Cetuximab</td>
<td>Breast Cancer</td>
<td>KRAS, NRAS and BRAF wildtype</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>NSCLC</td>
<td>KRAS, NRAS and BRAF wildtype</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Colorectal Cancer</td>
<td>FLT-3 mutation or amplification</td>
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<tr>
<td>Palbociclib</td>
<td>NSCLC</td>
<td>CDKN2A loss or mutation</td>
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</tr>
<tr>
<td>Pembrolizumab</td>
<td>Breast</td>
<td>HTMB</td>
<td></td>
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<tr>
<td>Pertuzumab + Trastuzumab</td>
<td>Colorectal Cancer</td>
<td>ERBB2 amplification</td>
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</tr>
<tr>
<td>Vemurafenib + Cobimetinib</td>
<td>Colorectal Cancer</td>
<td>BRAF_V600E/D/K/R mutation</td>
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<td>Drug</td>
<td>Tumor Type</td>
<td>Variant</td>
<td>Signal</td>
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<td>FLT-3 mutation or amplification</td>
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<td>Palbociclib</td>
<td>NSCLC</td>
<td>CDKN2A loss or mutation</td>
<td>+</td>
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<tr>
<td>Pembrolizumab</td>
<td>Breast</td>
<td>HTMB</td>
<td>+</td>
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<td>Variant</td>
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<td>------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Ovarian Cancer</td>
<td>KRAS, NRAS and BRAF wildtype (all must be wildtype)</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>Breast Cancer; Prostate Cancer; Pancreatic Cancer; Uterine Cancer; Gallbladder and Bile Duct Cancer, NSCLC</td>
<td>Germline or somatic BRCA1/BRCA2 inactivating mutations</td>
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</tr>
<tr>
<td></td>
<td>Colorectal Cancer</td>
<td>ATM mutation or deletion</td>
<td></td>
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<tr>
<td>Palbociclib</td>
<td>Soft Tissue Sarcoma</td>
<td>CDK4 amplification</td>
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<td></td>
<td>Head and Neck Cancer; Ovarian Cancer</td>
<td>CDKN2A loss or mutation</td>
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<td></td>
<td>NSCLC</td>
<td>CCND1 amplification</td>
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<td>Sunitinib</td>
<td>Breast Cancer</td>
<td>FGFR1 mutation or amplification</td>
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<tr>
<td></td>
<td>Gallbladder and Bile Duct Cancer</td>
<td>FGFR2 mutation or amplification</td>
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<tr>
<td>Pembrolizumab</td>
<td>Uterine Cancer</td>
<td>High tumor mutational burden</td>
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<tr>
<td>Pertuzumab + Trastuzumab</td>
<td>Uterine Cancer; Gallbladder and Bile Duct Cancer; NSCLC; Bladder Cancer</td>
<td>ERBB2/ERBB3 mutation, amplification or overexpression</td>
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</tr>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>Breast Cancer; Ovarian Cancer</td>
<td>BRCA1/BRCA2 mutation</td>
<td></td>
</tr>
</tbody>
</table>
TAPUR Future Plans

- **Primary objective:** Combine an immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) with a targeted treatment for patients with advanced solid tumors that have **high microsatellite instability or high tumor mutational burden** and a genomic variant targeted by a TAPUR study drug.

- **Study population:** As per TAPUR except **genomic test must confirm that the tumor has both (a) MSI-H status or high tumor mutational burden (b) at least one potentially actionable genomic variant targeted by a TAPUR study drug**.
### Genomic alterations in MSI-H/high TMB TAPUR Participants

**Data thru September 4, 2018**

<table>
<thead>
<tr>
<th>Alternative TAPUR Matches</th>
<th>Genomic Targets</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Cetuximab (ERBITUX)</td>
<td>BRAF, KRAS, and NRAS Wildtype</td>
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<tr>
<td>Crizotinib (XALKORI)</td>
<td>MET Amplification</td>
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<td>Olaparib (LYNPARZA)</td>
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<td>Olaparib (LYNPARZA)</td>
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<td>Palbociclib (IBRANCE)</td>
<td>CDK4 Amplification</td>
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<td>Palbociclib (IBRANCE)</td>
<td>CDKN2A Loss or Mutation</td>
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<td>Pertuzumab (PERJETA) + Trastuzumab (HERCEPTIN)</td>
<td>ERBB2 Amplification or Mutation</td>
<td>15</td>
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<tr>
<td>Regorafenib (STIVARGA)</td>
<td>BRAF Mutation</td>
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<td>Regorafenib (STIVARGA)</td>
<td>RAF1 Amplification</td>
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<td>Regorafenib (STIVARGA)</td>
<td>RET Amplification</td>
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</tr>
<tr>
<td>Regorafenib (STIVARGA)</td>
<td>KIT Mutation or Amplification</td>
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</tr>
<tr>
<td>Sunitinib (SUTENT)</td>
<td>FGFR2 Mutation or Amplification</td>
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<td>Sunitinib (SUTENT)</td>
<td>FGFR1 Amplification</td>
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<td>FGFR3 Mutation</td>
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<td>Sunitinib (SUTENT)</td>
<td>FLT3 Amplification or Mutation</td>
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<tr>
<td>Sunitinib (SUTENT)</td>
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<td>Sunitinib (SUTENT)</td>
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<td>Temsirolimus (TORISEL)</td>
<td>TSC2 Mutation</td>
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<tr>
<td>Temsirolimus (TORISEL)</td>
<td>MTOR Mutation</td>
<td>1</td>
</tr>
</tbody>
</table>
Who Benefits if the TAPUR Trial 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
TAPUR Clinical Sites and PIs

- Michigan Cancer Research Consortium; Dr. Philip Stella
- Cancer Research Consortium of West Michigan; Dr. Kathleen Yost
- University of Michigan; Dr. Ajjai Alva
- Carolinas HealthCare System's Levine Cancer Institute; Dr. Edward Kim
- Cancer Treatment Centers of America
  - Atlanta; Dr. Ricardo Alvarez
  - Chicago; Dr. Eugene Ahn
  - Philadelphia; Dr. Pamela Crilley
  - Phoenix; Dr. Ashish Sangal
  - Tulsa; Dr. Theodore Pollock
- Sanford Health
  - Sioux Falls; Dr. Steven Powell
  - Fargo; Dr. Anu Gaba
  - Bismarck; Dr. Peter Kurniali
- Intermountain Healthcare – Precision Genomics; Dr. Ramya Thota
- Intermountain Healthcare; Dr. Derrick Haslem
- University of Nebraska Medical Center; Dr. Alissa Marr
- Swedish Cancer Institute; Dr. Thomas Brown
- Providence Health and Services; Dr. Walter Urba
- Inova Schar Cancer Institute; Dr. Timothy Cannon
- The University of Texas MD Anderson Cancer Center; Dr. Funda Meric-Bernstam
- The Angeles Clinic and Research Institute; Dr. Samuel Klempner
- University of Alabama at Birmingham Comprehensive Cancer Center; Dr. Eddy Yang
- Emory University Winship Cancer Institute; Dr. Olatunji Alese
- Fox Chase Cancer Center; Dr. Margaret von Mehren
- University of Miami Sylvester Comprehensive Cancer Center; Dr. Carmen Calfa
- Sutter Cancer Research Consortium; Dr. Stacy D’Andre
For more information:
www.TAPUR.org
ClinicalTrials.Gov:
NCT#02693535