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TAPUR Study Data Overview

Overview

The TAPUR study is a phase II, prospective, non-randomized basket clinical trial that aims to describe the safety and efficacy of commercially available, targeted anti-cancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic variant. TAPUR uses a Simon two-stage design to study Food and Drug Administration (FDA)-approved targeted therapies that are contributed by collaborating pharmaceutical companies, catalogue the choice of molecular profiling test by clinical oncologists and develop hypotheses for additional clinical trials. Data collected for the TAPUR Study include robust clinical and genomics data across arms or cohorts. All patients who receive treatment with a drug available in the protocol are followed for standard toxicity and efficacy outcomes including tumor response, progression-free and overall survival as well as duration of treatment and high grade or serious adverse events.

Objective and Endpoints

The primary objective of this study is to test and estimate the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs used for treatment of patients with advanced solid tumors with a genomic alteration known to be a drug target or to predict sensitivity to a drug. The primary outcome of interest is anti-tumor activity, as assessed by objective response or stable disease documented at 16 weeks or later from initiation of study drug treatment, reporting the best response achieved in this timeframe. For solid tumor patients, objective response or stable disease is defined by RECIST v. 1.1 72. Serious adverse events will be recorded and Grade 3-4 treatment-related toxicity (including whether the event is expected or unexpected) will be described using the NCI CTCAE v. 4.0 criteria. Secondary endpoints include duration of response, duration of stable disease, progression-free survival and overall survival.

Study Design and Sample Size

Participants are enrolled into tumor type, variant, and drug specific cohorts with up to 28 participants in each cohort. The TAPUR Study uses the Simon optimal two-stage design

assuming a response rate of 15% and 85% power to reject the null hypothesis of response rate of 15% when the true response rate is 35%. In the first stage, 10 participants will be enrolled in a cohort. Enrollment is suspended when 10 participants have been enrolled in the cohort to allow for the evaluation of response, defined as either objective response or stable disease per RECIST v. 1.1 72. If no more than one response is observed, enrollment to that cohort will be closed. However, if two or more responses are observed, an additional 18 participants will be enrolled in that cohort at the second stage for a total of 28 participants. Cohorts that do not enroll at least 10 participants within 24 months of initiation will be combined and the analysis will be based on treatment efficacy in tumors of the same genotype regardless of histology.

This design has 85% power to conclude an agent is promising if its true response rate is 0.35; Type 1 error rate (one-sided) is 10% (this is the probability to conclude that a given agent is promising if its true objective response rate is 0.15). The probability of early stopping under the null hypothesis is 0.54 and the expected sample size under the null hypothesis is 18.2 participants. These operating characteristics were selected to represent a reasonable compromise between high power, low false positive rates, and desire for small sample sizes, especially in the first stage.

Inclusion and Exclusion Criteria

Inclusion Criteria
Patient (age ≥ 12 years) with a histologically proven locally advanced or metastatic solid tumor who is no longer benefitting from standard anti-cancer treatment or for whom no such treatment is available or indicated.
ECOG performance status 0–2.
Patients must have acceptable organ function as defined in the protocol eligibility criteria or drug-specific inclusion criteria.
Patients must have disease that can be objectively measured per RECIST v1.1.
Results must be available from a genomic test or immunohistochemistry (IHC) test for protein expression performed in a CLIA-certified and CAP-accredited or New York State accredited laboratory.
Ability to understand and the willingness to sign a written informed consent/assent document.
Have a tumor genomic profile for which treatment with one of the FDA approved targeted anti-cancer therapies included in this study has potential clinical benefit

Exclusion Criteria
Ongoing toxicity ≥ CTCAE grade 2, other than peripheral neuropathy, related to anti-tumor treatment that was completed within 4 weeks prior to registration. Patients with ongoing peripheral neuropathy of ≥ CRCAE grade 3 will be excluded.
Previous treatment with the selected study drug for the same malignancy.

Exclusion Criteria
If the patient's tumor has a genomic variant known to confer resistance to an anti-cancer agent available in this study, the patient will not be eligible to receive that agent but will be eligible to receive other drugs available in this study if all inclusion and exclusion criteria are met for that drug.
Patient is receiving any other anti-cancer therapy.
Female patients who are pregnant or nursing. Male patients who refuse to practice barrier contraception methods.
Patients with primary brain tumors or leptomeningeal metastases.
Patients with preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.
Patients with left ventricular ejection fraction (LVEF) known to be < 40% are not eligible.
Patients with stroke (including TIA) or acute myocardial infarction within 4 months before the first dose of study treatment are not eligible.
Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, severe psychiatric illness situations, or anticipated or planned anti-cancer treatment or surgery.

Cohorts Available

Data may be requested for records included in previously published cohorts. A current list of closed cohorts and relevant publications can be found here; those with publications listed may be requested.

Data Dictionary and Visit Schedule

The data dictionary and visit schedule are available as separate documents on the ASCO Data Library website.

Data Format

Data tables are Comma Separate Values (CSV) files which can be read by standard statistical programming software, and tables can be linked using the *LibraryID* field included in each table. Some tables include data collected at multiple study visits and have more than one row per participant. Longitudinal record structures can be identified using the separate visit schedule document.

Deidentification

The data were deidentified by removing fields containing participant identifiers, generating a Data Library specific identifier to link tables, and replacing dates with a calculated time interval from baseline in days.

Limitations

The list below describes potential limitations and biases, grouped by area of impact, that may affect research using data collected for the TAPUR Study.

Statistical Analysis

- The sample size calculation was performed with prespecified Type I error rate (10%), statistical power (85%), and minimum detectable response rate (35%). In single cohort analyses, smaller response rates cannot be detected, and selecting a 5% Type I error rate will increase the minimum detectable response rate. It is important to perform a sample size calculation to assess if the proposed objectives can be met with TAPUR Study data.

Internal or External Validity

- The study enrolls patients with advanced solid tumors and an actionable genomic variant who meet the full inclusion criteria; patients are given FDA-approved anticancer therapy administered outside of the approved indication. Researchers who request this data should be sure that the inclusion criteria closely reflect their intended target population.
- The study uses broadened eligibility criteria to identify patients. There may be a difference between patients that clinical sites choose to enroll in pragmatic studies like TAPUR compared to those enrolled in studies with stricter eligibility criteria.
- Although patients are enrolled based on a specific tumor type, molecular variant, and drug combination, a patient may have another actionable genomic alteration. Some patients may therefore be eligible for more than one cohort with enrollment decision made at the clinical site. It is useful to examine the genomics data for co-alterations.
- Interpretation of study results is limited by the single-arm design and lack of a control arm, and it is not possible to assess individual contributions of drug activity when drug combinations are used.

Variable Misclassification

- There may be variability in how self-reported variables (e.g., sex, race, or ethnicity) are collected across clinical sites. Data abstracted from medical records might have different possible categories than those in the TAPUR Study case report form (CRF).
- Oral drug adherence is self-reported and may be subject to reporting bias or social desirability bias. These may occur even if patients maintain a drug diary.
- Tumor types are documented with ICD-10 codes that may not reflect heterogeneity present within cohorts. For example, cohorts examining malignant neoplasms of the ovary (ICD-10 code C56.x) might include patients with adenosarcoma and/or liposarcoma.
- Due to the pragmatic nature of the TAPUR Study, tumor biomarkers are not required to be collected. For example, prostate-specific antigen (PSA) tests are not routinely collected for patients with prostate cancer. The TAPUR Study uses RECIST v1.1 as the standard response criteria for all patients with solid tumors which requires that elevated tumor markers such as PSA return to normal to consider a patient in complete clinical response but does not otherwise rely on tumor markers for evaluation of response or progression. Response and progression events are based on radiographic assessments of measured target lesions only.
- The TAPUR Study is a pragmatic trial which allows for physician choice of genomic test from any Clinical Laboratory Improvement Amendments certified and College of American Pathologists or New York State accredited laboratory, which results in a variety of genomic tests reported for each patient. Each genomic test has its own criteria to identify gene amplifications, and different testing platforms use various thresholds for copy number gain to define amplification.

Data Availability

- To remain pragmatic, the TAPUR Study does not collect grade 1-2 adverse events. However, serious adverse events of any grade are documented.
- The study only collects three most recent prior therapies of each type (i.e., systemic, radiation, and surgery) which may limit the ability to answer some research questions. For example, researchers interested in questions about platinum-resistance may not be able to identify whether a patient has received prior platinum-based drugs. Additionally, the study only collects patient response to their most recent prior therapy.
- Given the pragmatic nature of the trial, the TAPUR Study allows for site discretion on how much imaging is required for each patient. Therefore, comprehensive data on patient metastases is not available.

- Genomic tests are chosen by physicians and do not all routinely report PD-L1 expression, microsatellite instability, germline versus somatic, or allelic status of mutations.
- Due to the pragmatic nature of the TAPUR Study, liquid biopsies, while permitted to qualify patients for enrollment, are not routinely collected prior to treatment or serially over the course of treatment.
- Biospecimens are not collected on the TAPUR Study and the study does not have a central laboratory to perform testing or staining.
- Pathology reports collected from study sites do not routinely report histologic subtype of various cancers or PD-L1 expression.

Key Publications

A list of cohort-specific publications can be found here.

Mangat PK, Garrett-Mayer E, Perez JK, Schilsky RL. The Targeted Agent and Profiling Utilization Registry Study: A pragmatic clinical trial. Clinical Trials. 2023;20(6):699-707. doi: 10.1177/17407745231182013

Mangat PK, Halabi S, Bruinooge SS, Garrett-Mayer E, Alva A, Janeway KA, Stella PJ, Voest E, Yost KJ, Perlmutter J, Pinto N, Kim ES, Schilsky RL. Rationale and Design of the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. JCO Precis Oncol. 2018;2(2):1-14. doi: 10.1200/PO.18.00122