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Jump Start your Oncology knowledge

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ABSTRACT

Clinical trial in oncology provides an exciting work environment among programmers due to its uniqueness in many cancer types, innovative design, and specific efficacy analysis. As oncology programmers in pharmaceutical industry or academics, it is critical to understand and interpret the disease jargon and statistical analysis to better communicate with statisticians, physicians/clinicians, regulatory, and other study personnel effectively. The purpose of this paper is to introduce key concepts, study design and analysis in oncology to jump start your knowledge base for new oncology programmers or experienced programs who are new to oncology. This paper will highlight definition of oncology, uniqueness of oncology drug development, and emerging treatment options for oncology as well as overview of study design including traditional and innovative design such as master protocol design. In addition, oncology efficacy evaluation and data standard will be presented.

INTRODUCTION

Oncology refers to a branch of medicine with the prevention, diagnosis, and treatment of cancer. The classification of oncology is dependent on the disease sites and type of tumors, depending on tumor sites, there are more than 100 types of cancers such as breast cancer, lung cancer, and liver cancer etc; the major types of cancer are carcinoma, sarcoma, melanoma, lymphoma, and leukemia; depending on form of tumors, the tumor can be classified as solid tumor, liquid tumor and blood tumor. It is estimated that 1.7 million new cases of cancer will be diagnosed in the United States in 2018 (NCI statistics), even with recent advance in cancer therapy, the 5-year survival is still poor for many types of cancer, therefore there is a huge unmet medical need for development of new treatments.

EMERGING ONCOLOGY THERAPY

Besides traditional cancer treatment such as surgery, chemotherapy and radiation therapy, there are emerging oncology treatments being developed in recent years targeting on immune-therapy, cell as well as epigenome therapeutics (Arruebo 2011).

Immuno-oncology (I-O) therapy such as PD-1 checkpoint inhibitors target either PD-1 or PD-L1 which can block checkpoint protein and stimulate the body's immune system to target and attack the tumor, contrary to cancer therapies that directly target malignant cells. The example of I-O therapy includes Pembrolizumab (Keytruda PD-1 inhibitor). In addition, combination therapies, where immunotherapy modalities of co-inhibitory pathways are tested in rational combinations with other immunotherapies or targeted therapies for synergistic effects, provide future promises to deliver long-term survival benefits (Oiseth 2017).

The epigenome refers to those compounds that are added to DNA (genome) so to regulate the activity (expression) of all the genes within the genome, which will impact the formation and alteration of cancer cells (Hatzimichael 2013).

Cell therapy (Miliotou 2018) is one of immunotherapies which collecting and using patients' own immune cells to treat their cancer.

UNIQUENESS OF ONCOLOGY DRUG DEVELOPMENT

Comparing to other (non-oncology) therapeutic areas, there are some uniqueness in oncology such as the patients are evaluated and treated in Phase 1 first time in human studies (FTIH), the inflection point or interim analysis are implemented at almost every clinical trial, especially early clinical trials to evaluate clinical response and adapt the design for the emerging effects. The cohorts in FTIH can be expanded to allow companies and researchers to assess various aspects of a drug in development in a single clinical trial (FDA Guidance 2018). In most oncology Phase 3 trials, an open-label study design is commonly employed. In addition, there are oncology specific measurements for response criteria such as RECIST 1.1 for solid tumor (Schwartz 2016). There are oncology specific analyses to measure overall survival, progression-free survival as well as overall response rate (FDA guidance 2018).

FREQUENTLY USED ONCOLOGY TRIAL DESIGNS

Phase I trials represent the first application of a new drug or drug combination to humans and most Phase I study design involves dose escalation and cohort expansion. A typical endpoint in Phase I trial are dose-limiting toxicities (DLT) and response rate. Common statistical methods in dose escalation are traditional 3+3 design, continual reassessment (CRM) /N-CRM (Neuenschwande, 2008) design as well as modified toxicity probability interval (mTPI) design (Ji, 2013).

Most common study design in Phase II oncology trials are two-stage adaptive design (36%), it was reported that ~41% of Phase II clinical trials adopted one stage or multiple stage design and ~9% of Phase 2 trial uses response adaptive randomization (Brown, 2011).

Phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment. Typical endpoints are time to event endpoint such as overall survival (OS) or Progression-free survival (PFS). For time to outcome event, censoring usually applies when information is not available for all study participants, such as loss to follow-up, missing data, or non-occurrence of outcome event before the trial ends.

MASTER PROTOCOL DESIGNS (PLATFORM, BASEKET OR UMBRELLA)

A standard trial evaluates a single treatment in a single disease area (Figure 1 A), comparator may be added depending on the nature of the trial. Basket design is to study a single targeted therapy in the context of multiple disease or disease subtypes on patients with a single biomarker/genomic alteration, i.e a basket trial of an immuno-oncology drug in lung cancer, spleen cancer, colon cancer etc. (Figure 1 B). Platform design is to study multiple targeted therapies in the context of a single diseases with therapies allowed to enter or leave the platform on the basic of a decision algorithm. Umbrella trial is to study multiple targeted therapies in the context of a single disease with multiple biomarkers (Figure 1 C). Lastly the study design can be further expanded to Platform Basket trial to allow multiple treatment regimens to be evaluated in multiple disease areas (Figure 1 D).

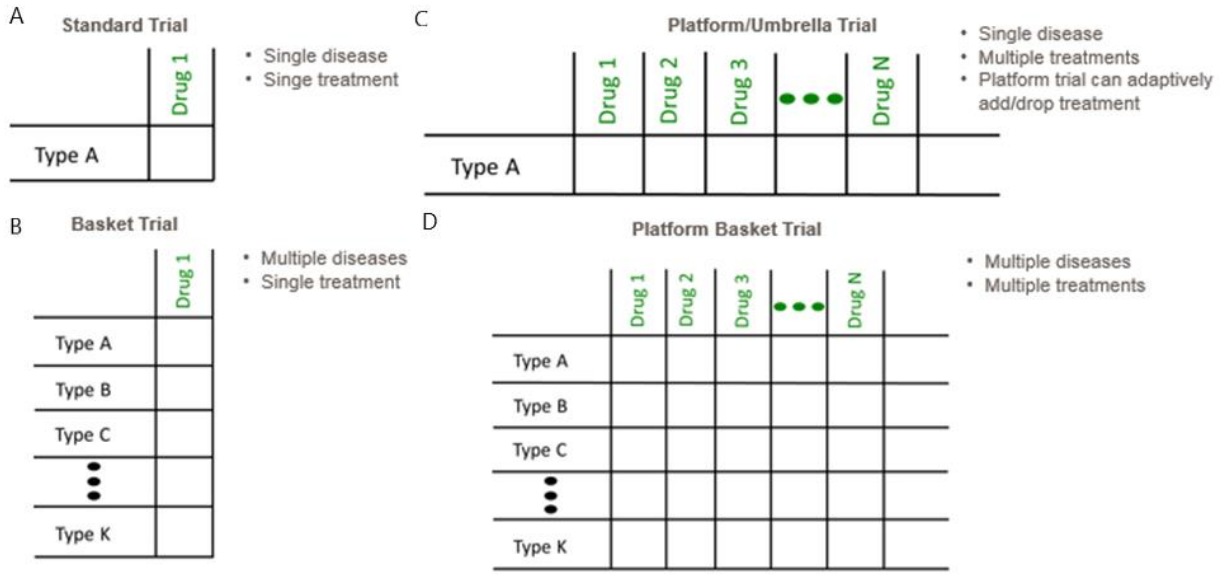

Figure 1: illustration of experimental design in standard trial and master protocol trials (platform/umbrella trial, basket trial and platform basket trial.

EFFICACY EVAULATION IN ONCOLOGY

In Oncology clinical trial, endpoints are used to assess the clinical benefit of the treatment to patients. For people who are new to oncology, oncology endpoints can be complex and difficult to understand, but they are critical when evaluating cancer therapies. Despite the complexity of the disease, the evaluation of efficacy (or efficacy endpoints) is well defined by regulatory guidance (FDA Guidance 2018, EMA Guidance 2017).

TUMOR RESPONSE CRITERIA

In solid tumor, the investigator evaluates the size of the tumor based on a set of guidelines, and it is often assessed using The Response Evaluation Criteria in Solid Tumor (RECIST 1.1) (Schwartz 2016). The scope of RECIST with respect to this paper is to understand the terminology and what the response means in terms of patient benefits. Table 1 below provides a high-level overview of tumor responses.

Response	Description
Complete Response (CR)	• Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. • Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Partial Response (PR)	• At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	• At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the

Response	Description
	relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. • Unequivocal progression of existing non-target lesions.
Stable Disease (SD)	• Neither sufficient shrinkage to quality for PR nor sufficient increase to quality for PD, taking as reference the smallest sum diameters while on study.
Non-CR/Non-PD	• Persistence of one or more non-target lesion(s) and/or maintenance of tumor market level above the normal limits.

Table 1: definitions of RECIST 1.1

Similar to solid tumor with RECIST, standard sets of criteria for evaluating non-solid tumors have also been established. International Myeloma Working Group (IMWG) has come up with criteria for response and minimal residual disease assessment in multiple myeloma (Kumar 2016). An international working group (IWG) has established standardized response criteria for non-Hodgkin lymphomas**.** Cheson 2007 was published with the recommendations from other lymphoma studies and with the addition of more advanced diagnosis (Cheson 2007).

It is important for programmers to fully understand the algorithms used to derive the responses, as it can help them to evaluate the cleanliness and correctness of the clinical data. Furthermore, responses to tumor assessment are used to derive efficacy endpoints, which are the key in determining treatment effect and benefit.

TYPICAL ONCOLOGY ENDPOINTS

An endpoint can be defined as a measure of evaluating cancer therapies. Oncology trial endpoints serve different purposes. In early phase trials, endpoints are used to evaluate safety and identify evidence of drug activities. In later phase trials, endpoints are commonly used to evaluate the clinical benefits (e.g., prolongation of survival). According to *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (FDA Guidance 2018), the general efficacy endpoints include overall survival (OS), endpoints based on tumor assessments (e.g., Objective Response Rate (ORR), complete response, progression-free survival (PFS)), and endpoints based on system assessment (e.g., Patient Reported Outcomes (PRO)). Table 2 below summarizes the key features of the typical endpoints for solid tumors.

Statistical endpoints	Description
Overall survival (OS)	The interval of time from date of randomization/first dose to the date of death due to any course.
Progression-free survival (PFS)	The interval of time between the date of randomization/first dose and the earlier of the date of disease progression as per RECIST 1.1 criteria and the date of death due to any cause.
Objective Response Rate (ORR)	Percentage of participants with a confirmed PR or better (i.e. PR, CR) as the best overall response, as assessed per RECIST 1.1 criteria. Directly attributable to drug effect.

Statistical endpoints	Description
Complete Response Rate (CRR)	Percentage of participants with a complete response as the best overall response, as assessed per RECIST 1.1 criteria.
Patient Reported Outcomes (PRO)	PRO, such as quality of life (QOL), measures side effect of the treatment and symptoms of the disease, representing patient perspective of direct clinical benefit.

Table 2: typical oncology endpoints for solid tumors

ONCOLOGY DATA FOR PROGRAMMERS

Understanding and grasping knowledge of clinical endpoints requires programmers to keep up to date with industry and data standards. The critical part of a programmer's role is not only creating TLFs, but also be more involved with checking oncology specific data and understanding data and algorithms with scientific context.

Efficacy analyses of oncology clinical trials involve responder or time-to-event timepoints as discussed previously. There are three SDTM domains (SDTMIG Version 3.2) design specifically to collect tumor related data:

- Tumor Identification (TU): the TU domain represents data that uniquely identify tumors.
- Tumor Results (TR): the TR domain represents quantitative measurements and/or qualitative measurements of the tumors identified in the TU domain.
- Disease Response (RS): the RS domain represents the response evaluations determined from the data in TR.

Various time-to-event analyses are of interest in oncology studies, such as overall survival, time to progression, progression-free survival (FDA Guidance 2018). These are supported by ADaM BDS data sets (ADTU, ADTR, ADRS), the counterparts of tumor specific SDTM data sets, as well as ADTTE (ADaMIG Version 1.1). In this paper, we will illustrate how to derive progression-free survival (PFS) using ADRS and ADTTE in an example. Please note that this introductory example utilizes RECIST1.1 criteria for solid tumors.

Progression-free survival (PFS) is often the primary endpoint of most solid tumor cancer trials as requested by regulatory agencies (FDA Guidance 2018, EMA Guidance 2017). It is defined as the interval of time in months between the date of first dose and the earlier of the date of disease progression per standard criteria (RECIST 1.1) and the date of death due to any cause. There is step-wise logic (i.e. 8 scenarios to be considered) involved in determining the dates of PFS events and dates for censoring (Table 3).

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
1.No adequate baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First dose	Censored

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
2.No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First dose	Censored
3.No progression (or death) or no anti-cancer therapy	Date of last 'adequate' assessment of response[2]	Censored
4.With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression or death).	Date of last 'adequate' assessment of response[2,3] (on or prior to starting anti-cancer therapy)	Censored
5.With subsequent anti-cancer therapy and no progression (or death)	Date of last 'adequate' assessment of response[2]	Censored
6.Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] (prior to missed assessments)	Censored
7.Progression documented between scheduled visits	Date of assessment of progression[1]	Event
8.Death without initiating new anti-cancer therapy or extended time without adequate assessment	Date of death	Event

1The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)
2 An adequate assessment is defined as an assessment where the [Independent Reviewer/Investigator] determined response is CR, PR, or SD.
3 If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the start date of treatment.

Table 3: assignments of progression and censoring dates for PFS analysis

Based on Table 3, there are 8 different scenarios to consider and the information needed is provided by several derived parameters (PARAMCDs) and their associated values (AVAL/ADT) in ADRS. The details are listed in Table 4.

Scenario	ADRS.PARAMCD / Definition
1.No adequate baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	MISSBLFL / Missed Baseline Lesion Flag
2.No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	MISSPBFL / Missed Post-Baseline Lesion Flag
3.No progression (or death) or no anti-cancer therapy	FPDDT / First Progression (PD) Date NEWCTDT / New Anticancer Therapy Start Date

Scenario	ADRS.PARAMCD / Definition
4.With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression or death).	FPDDT / First Progression (PD) Date NEWCTDT / New Anticancer Therapy Start Date
5.With subsequent anti-cancer therapy and no progression (or death)	FPDDT / First Progression (PD) Date NEWCTDT / New Anticancer Therapy Start Date
6.Death or progression after more than one missed visit	MISSVIFL / Death or Progression after more than one missed visit flag
7.Progression documented between scheduled visits	FPDDT / First Progression (PD) Date
8.Death without initiating new anti-cancer therapy or extended time without adequate assessment	Not applicable *

*No paramcd associated with death in ADRS. The death information is stored in ADSL.DTHDT and carry through all data sets.

Table 4: ADRS.PARAMCD used to derive PFS

The final result of PFS (i.e. PARAMCD = 'PFS') is stored in ADTTE. Additionally, ADTTE also contains other variables associated with PFS (Table 5).

Name of variable	Definition
ADT	Event or Censoring Date
AVAL	Value of PFS in months = (ADT – first dose date + 1)/30.4375
CNSR	1 = Censor, 0 = Event
EVNTDESC	Event or Censoring Description
CNSDTDSC	Censor Date Description

Table 5: key variables in ADTTE for PFS

Our example above only demonstrates how PFS is derived as one of the primary endpoints. The primary analysis for an oncology trial can involve numerous qualifiers on the endpoints. Therefore, it is important to understand the relationship between the source SDTM data set and the derived ADRS parameters, as well as ADTTE time-to-event endpoints.

CONCLUSION

For a programmer who is new to oncology and the industry, it is important to understand and interpret the performed analyses. A programmer's responsibility should not only be producing TFLs, but also a thorough understanding of the therapeutic area, including trial designs, efficacy endpoints, as well as oncology specific data. This empowers the programmers to ensure the correctness of the analyses and understand the key message delivered to the stakeholders.

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