

PhUSE US Connect 2018 - DH02

Split - Coalesce Tumor, Data Handling Woes, and Safety-Efficacy Dilemma

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Current Cancer Data

In 2018 in the U.S., there will be an estimated
1,735,350 new cancer cases and
609,640 cancer deaths.

EVERY DAY

THAT'S APPROXIMATELY

4,750

NEW CASES

1,670

DEATHS

Estimated new cases, 2018

By cancer type, both sexes combined

Breast ⓘ

268,670

Lung and bronchus

234,030

Prostate

164,690

Colorectum

140,250

Melanoma of the skin

91,270

Urinary bladder

81,190

Estimated deaths, 2018

By cancer type, both sexes combined

Lung and bronchus

154,050

Colorectum

50,630

Pancreas

44,330

Breast ⓘ

41,400

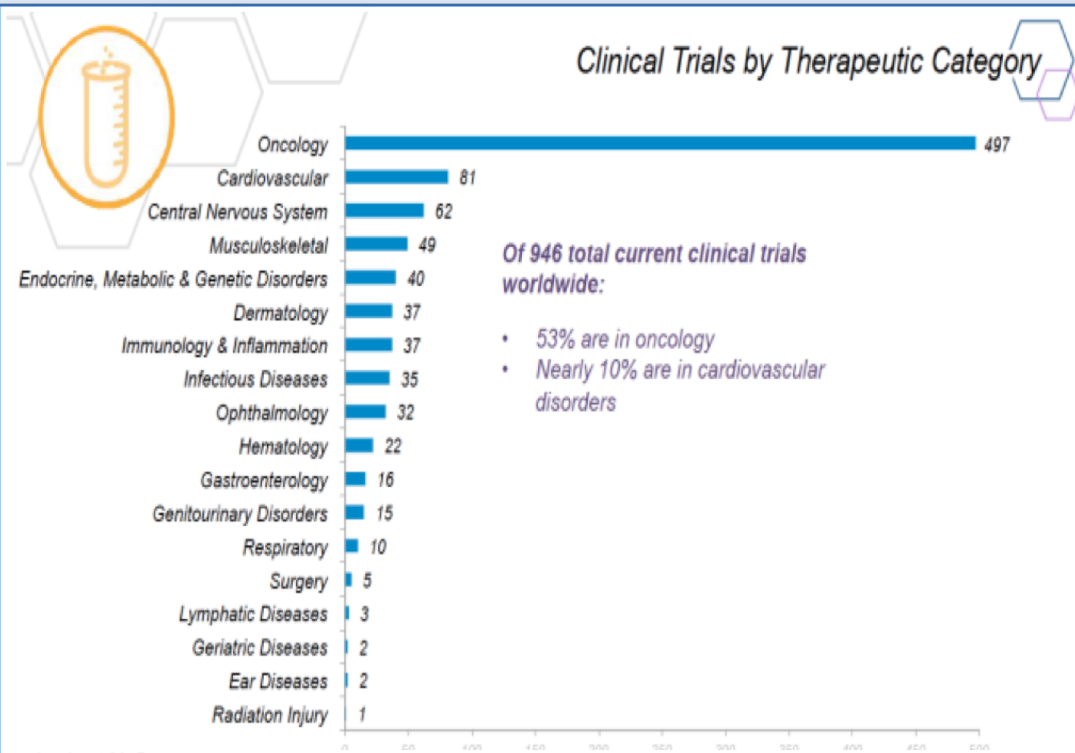
Liver and intrahepatic bile duct

30,200

Prostate

29,430

Clinical Trials Data



Oncology

Erleada (apalutamide); Janssen Oncology; For the treatment of prostate cancer, Approved February 2018

Lutathera (lutetium Lu 177 dotatate); Advanced Accelerator Applications; For the treatment of gastroenteropancreatic neuroendocrine tumors, Approved January 2018

Oncology

Aliqopa (copanlisib); Bayer; For the treatment of follicular lymphoma, Approved September 2017

Alunbrig (brigatinib); Ariad Pharmaceuticals; For the treatment of advanced ALK-positive metastatic non-small cell lung cancer, Approved April 2017

Bavencio (avelumab); EMD Serono/Pfizer; For the treatment of Merkel cell carcinoma, Approved March 2017

Besponsa (inotuzumab ozogamicin); Pfizer; For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia, Approved August 2017

Calquence (acalabrutinib); Acerta Pharmaceuticals; For the treatment of mantle cell lymphoma, Approved November 2017

IDHIFA (enasidenib); Celgene; For the treatment of relapsed or refractory acute myeloid leukemia with IDH2 mutation, Approved August 2017

Imfinzi (durvalumab); AstraZeneca; For the treatment of advanced or metastatic urothelial carcinoma and Stage III non-small cell lung cancer, Initially approved May 2017

Kisqali (ribociclib); Novartis; For the treatment of breast cancer, Approved March 2017

Kymriah (tisagenlecleucel); Novartis; For the treatment of refractory B-cell precursor acute lymphoblastic leukemia, Approved August 2017

Nerlynx (neratinib); Puma Biotech; For the treatment of HER2 breast cancer, Approved July 2017

Rydapt (midostaurin); Novartis; For the treatment of FLT3 positive acute myeloid leukemia and mastocytosis, Approved April 2017

Verzenio (abemaciclib); Eli Lilly; For the treatment of HR+, HER2- breast cancer, Approved September 2017

Vyxeos (daunorubicin and cytarabine); Jazz Pharma; For the treatment of newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes, Approved August 2017

Xermelo (telotristat ethyl); Lexicon Pharmaceuticals; For the treatment of carcinoid syndrome diarrhea, Approved February 2017

Yescarta (axicabtagene ciloleucel); Kite Pharmaceuticals; For the treatment of relapsed or refractory large B-cell lymphomas, Approved October 2017

Zejula (niraparib); Tesaro; For the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, Approved March 2017

Tumors - Types and Causes

Oncology is the study, diagnosis, and treatment of tumors (neoplasms).

Neoplasms

- Growths made up of cells that reproduce abnormally
- Tumor cells lack the mechanism to stop producing and they lack the ability to die after a certain period
- **Apoptosis** is the death of normal cells in a normal time cycle
- Tumors can be either **benign** or **malignant**

Benign

- **encapsulated**
- not life-threatening
- made up of **differentiated** cells

Malignant

- not capsulated
- categorized by the types of tissue from which they develop
- can be life-threatening

Mixed-Tissue Tumor

- Derives from tissue that is capable of separating into either epithelial or connective tissue because it is composed of several types of cells
- Can be **teratomas**, which are growths containing bone, muscle, skin, glandular tissue and other cells

NOTE: A class of cancer such as leukemia arises from blood, lymph or nervous system cells

Differences between benign and malignant tumors

	BENIGN	MALIGNANT
Spread	LOCALIZED	LOCAL & DISTANT SPREAD
Rate Of Growth	SLOW	RAPID
Boundaries	CIRCUMSCRIBED, OFTEN ENCAPSULATED	IRREGULAR, NON ENCAPSULATED
Relationship To Surrounding Tissue	COMPRESS SURROUNDING NORMAL TISSUES	INVADES AND DESTROY SURROUNDING NORMAL TISSUE
Effects	PRODUCED BY PRESSURE ON SURROUNDING STRUCTURES AS VESSELS, NERVES AND ORGANS.	DESTROY STRUCTURES
Treatment	REMOVAL WILL ALLEVIATE	REMOVAL WILL NOT RESTORE THE FUNCTION.

Carcinoma

- Originates from **epithelial** tissue and is the most common type of cancer
- Also called **solid tumors**
- Common sites for carcinomas:
 - skin
 - lungs
 - breasts
 - colon
 - stomach
 - mouth
 - uterus
- Spread by way of the lymphatic system

Sarcoma

- Originates in **muscle** or **connective** tissue and **lymph**
- A fairly rare form of cancer
- Certain leukemias are sarcomas

Overview of Tumor Domains

- ❑ Tumor shrinkage (response) and time to progression are important endpoints.
- ❑ RECIST criteria 1.0 was published in 2000. It was based on an anatomical one-dimensional measurement of the tumor burden. Subsequently, RECIST 1.1 was published in 2009 to address issues that arose during RECIST 1.0 implementation.
- ❑ TU – Tumor identification: Every lesion is captured once with a unique ID where lesion specific details are described, such as description of the lesion, location of the lesion, imaging method to be used.

- ❑ TR – Tumor Results: All measurements of the lesions are captured by time point including the method that has been used in a visit. The longest diameter for target lesions, the assessment for non-target lesions, the sum of longest diameter for target lesions, if it is captured in the CRF.
- ❑ RS – Disease Response: All response assessments as captured in the CRF: Target response, non-target response, overall response, best overall response, but also assessments that are not coming from the tumor domains like symptomatic deterioration or non-radiological progression.

Tumor Domains Relationship

Oncology Domains for Tumor Response TU/TR/RS

TU Tumor Identification

A	B	C	D	E	F	I	J	K	L	T	X	Y	AA
STUDYID	DOMAIN	USUBJID	TUSEQ	TULOC	TUGRPID	TULINKID	TUORRES	TUTESTCD	TUTEST	TUMETHOD	VISITNUM	VISIT	TUDTC
ABC456	TU	10022.1009	1	BONE METS			ON-TARGET	TUMIDENT	Target lesion measurem	Methode 6	17.1	UNSCHEDULED	15.01.2010
ABC456	TU	10022.1009	2	SMALLER LIVER LESION			ON-TARGET	TUMIDENT	Target lesion measurem	Methode 6	17.1	UNSCHEDULED	15.01.2010
ABC456	TU	10022.1009		RIGHT LOBE LIVER		3	TARGET	TUMIDENT	Target lesion measurem	Methode 6	17.1	UNSCHEDULED	15.01.2010
ABC456	TU	10022.1009	6	LEFT LOBE LIVER			NEW	TUMIDENT	Target lesion measurem	5	17.1	UNSCHEDULED	27.12.2010

TR

	A	B	C	D	E	F	N	U	Y	Z	AB	
1	STUDYID	DOMAIN	USUBJID	TRSEQ	TRORRES	TROR	TRTESTCD	TRLINKID	TRMETHOD	VISITNUM	VISIT	TRDTC
127	ABC456	TR	10022.1009	1	1.3 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	15.01.2010	
128	ABC456	TR	10022.1009	19	1.1 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	03.03.2010	
129	ABC456	TR	10022.1009	15	1.1 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	14.04.2010	
130	ABC456	TR	10022.1009	13	0.6 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	26.05.2010	
131	ABC456	TR	10022.1009	11	0.4 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	02.07.2010	
132	ABC456	TR	10022.1009	10	0.5 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	19.08.2010	
133	ABC456	TR	10022.1009	7	0.4 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	04.10.2010	
134	ABC456	TR	10022.1009	16	0.4 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	15.11.2010	
135	ABC456	TR	10022.1009	4	0.4 cm	LDIAM	3	Methode 6	17.1	UNSCHEDULED	27.12.2010	

RS

STUDYID	DOMAIN	USUBJID	RSSEQ	RSORRES	RSSPID	RSTESTCD	RSTEST	RSUNKID	VISITNUM	VISIT	RSOTC	F
ABC456	RS	10022.1009	15	Complete response		TRGRES	Target Response	1	888	UNSCHEDULED	19.08.2010	
ABC456	RS	10022.1009	13	Complete response		TRGRES	Target Response	1	888	UNSCHEDULED	04.10.2010	
ABC456	RS	10022.1009	20	Complete response		TRGRES	Target Response	1	888	UNSCHEDULED	15.11.2010	
ABC456	RS	10022.1009	10	Stable disease		TRGRES	Target Response	1	888	UNSCHEDULED	27.12.2010	
ABC456	RS	10022.1009	23	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	03.03.2010	
ABC456	RS	10022.1009	21	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	14.04.2010	
ABC456	RS	10022.1009	18	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	26.05.2010	
ABC456	RS	10022.1009	16	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	02.07.2010	
ABC456	RS	10022.1009	14	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	19.08.2010	
ABC456	RS	10022.1009	12	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	04.10.2010	
ABC456	RS	10022.1009	11	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	15.11.2010	
ABC456	RS	10022.1009	9	Partial response		TRGRES	Target Response	2	888	UNSCHEDULED	27.12.2010	

Types of Oncology Data and Analysis

❑ Non-solid Tumor (leukemia and lymphoma)

- Lab data analysis

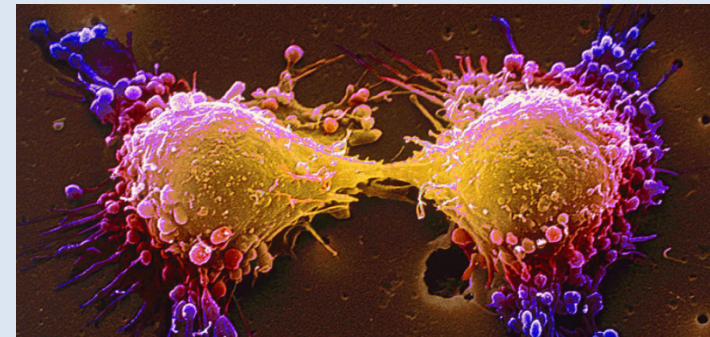
❑ Solid Tumor :

- WHO Tumor Response Criteria
- SWOG (Southwest Oncology Group) Criteria
- RECIST 1.1 (Response Evaluation Criteria in Solid Tumor) became the standard guideline. Data collection and analysis could be very challenging

❑ Challenges

- Dynamic Oncology data (Splitting/Merging of Tumors)

- Adjudication



Data Handling and RECIST 1.1 Limitations

(1) selecting target lesions at baseline	a) wrong number of the target lesions selected at baseline or change of the number of target lesions at a follow-up timepoint b) selecting a target lesion with non-reproducible measurements, most often a lesion in a hollow movable, distensible organ, e.g. a bowel wall lesion c) selecting of a target lesion that is not clearly a metastasis d) selecting a lymph node lesion smaller than 15 mm in short axis as a target or using long axis measurement for lymph nodes	Case 1: A patient had two lymph node lesions at baseline that corresponded to a measurable nodal lesions definition. The radiologist selected both lesions as target. At the re-assessment time point on week 32, two more lymph node lesions appeared. Instead of declaring progressive disease the radiologist added these new lesions as target thus violating several RECIST 1.1 rules at once. As a result of the mistake new lesions were not considered progressive disease, number of target lesions was changed at a post baseline assessment and more than 2 target lesions in one organ (lymph node) were selected.
(2) reassessing target lesions	a) premature declaration of progressive disease based on 20% increase in total sum non-metering the 5 mm absolute increase rule or based on 20% increase in a single lesion instead of total sum b) assessment of a timepoint response with reference to the previous timepoint rather than to baseline and nadir c) trouble assessing target lesions response in situations where one of the lesions could not be visualized or resolved	Case 2 Radiologist described groups of slightly enlarged inguinal lymph nodes suspicious of metastatic involvement in a colorectal cancer patient. The lesions were smaller than 10 mm in their short axis, yet by their round shape they were most likely malignant. According to RECIST 1.1 these lesions could not be included as pathological and should have been considered normal because of the size criterion even though the radiologist, in the radiological summary, indicated the lymph nodes were suspicious of metastases. At follow up, at week 16, the lesions started to grow and became more than 10 mm in their short axis. According to RECIST 1.1 the patient had to be discontinued from the study due to new lesions appearance even though target lesions showed no progression and the lymph nodes in question were suspected to be malignant by the radiologist.
(3) reassessing non-target lesions	a) premature declaration of progressive disease based on change in size of non-target lesions by analogy with the target lesions assessment rules b) trouble interpreting changes in volume or reappearance of a pleural effusion or ascites that was present at baseline	Case 3 In a patient with colorectal cancer and multiple metastases in liver and lungs the radiologist described all present lesions in great details including accurate measurements of all the target and non-target lesions at every visit. The investigator performing RECIST 1.1 assessments at each visit tried to calculate response of both target and non-target lesions based on their measurements. In follow up, at week 32, the investigator erroneously determined PD because of one initially non-target lesion which increased in size by 20 % and showed more than 5 mm absolute increase. She made decision to discontinue the patient from the study based on an increase in a single non-target lesion that should have been assessed qualitatively only and never to be measured as per the criterion meant by the RECIST 1.1 for target lesions only.
(4) assessing for new lesions	a) new lesion is not acknowledged as progressive disease if its size is smaller than the measurable lesion threshold	Case 4 Patient with SCLC had two target lesions selected in the right lung. At week 16 he developed collapsed lung segment that shadowed one of the target lesions on CT. In such a situation the case should have been considered non-evaluable and the patient followed for progressive disease only. However the investigator mistakenly decided to replace the target lesion that could not be anymore visualized with a different lesion in different location and continued response assessment. In general it is not recommended to select target lesions in anatomical areas that could potentially become non-evaluable, like this lesion in a collapsed lung.
(5) substantial deviations from the scanning schedule	a) critical deviations from the tumor assessment visit window outlined in the study protocol b) failure to perform end of treatment RECIST 1.1 assessment in case of symptomatic deterioration	Case 5 A patient with breast cancer had five target lesions at baseline. In the course of the treatment one of the lesions resolved and the rest four lesions significantly decreased in size showing partial response. The investigator stopped documenting the resolved lesion among the target ones and added another lesion suitable to be target instead thus affecting response assessment.

Tumor Data Handling Issues

- ❑ Check if all tumor measurements are available and if the method has been used.

- ❑ When merging TU, TR and RS domains, check if all lesions in TU are in every visit of TR and vice versa and they match the RS entries.

- ❑ Ensure that TUMETHOD = TRMETHOD

- ❑ A measurement that has been measured with another method cannot be used, since it is not comparable.

- ❑ If the measurement of one lesion is missing or has been measured with another method, a sum of longest diameter can not be calculated!

- ❑ If lesions cannot be evaluated, the sum of longest diameter cannot be derived for that visit. There might be other visits with evaluable measurements. Otherwise the subject is not evaluable. In the FAQ section about RECIST 1.1, it was suggested to reassess the lesion as non-target lesion and drop all measurements from the target lesions if nothing else is possible. Make sure not to manipulate data. The investigator assessment should not be changed.

- ❑ Lymph nodes should not be used as target lesions if there is another choice. If lymph nodes are used as target lesion, the short axis has to be taken for measurement. A Lymph node < 1 cm is regarded as normal.

Potential Data Handling Solutions

- ❑ Correct data handling in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions is critical, since the same lesion may appear to have a different size using a new modality or data visualization techniques.
- ❑ If a site can document that the CT performed as part of a PET– CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET CT may be used for RECIST measurements. However, the PET portion of the CT may bias an investigator if it is not routinely performed and may be left to the discretion of the investigator.
- ❑ MRI has good contrast, spatial and temporal resolution. However, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion visibility and measurement. Chest MRI is usually not recommended due to limited global accessibility to MRI scanners.
- ❑ Measurements permissible on non-axial isotropic CT and non-axial MRI.
- ❑ Tumor measurements based on Cyberknife technology need to be explored if that can give more precise diagnostic quality imaging data for data quality and analysis.
- ❑ Use of Biomarkers to identify tumor progression to help in data mapping.

Questions?