

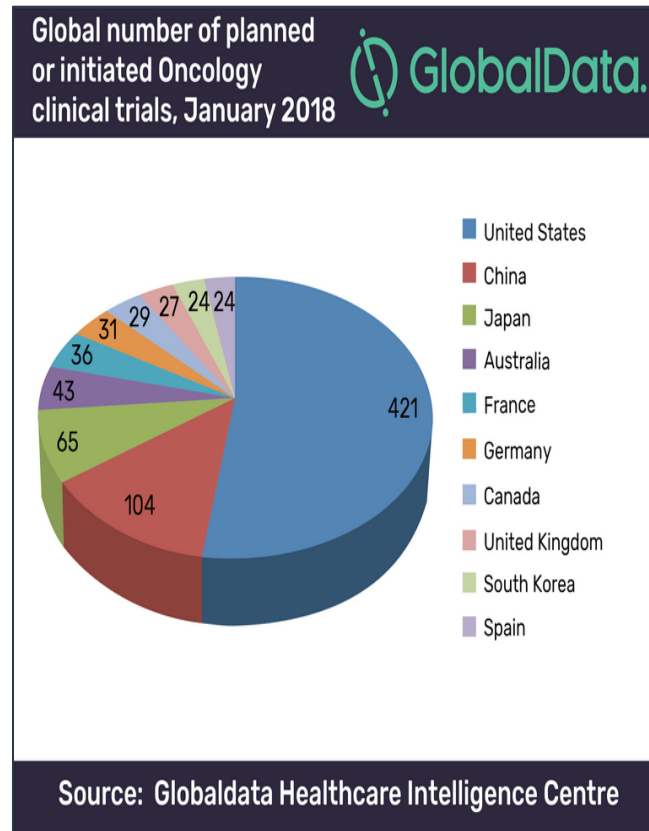
Dashboarding Analytics for Oncology Endpoint Data using SAS



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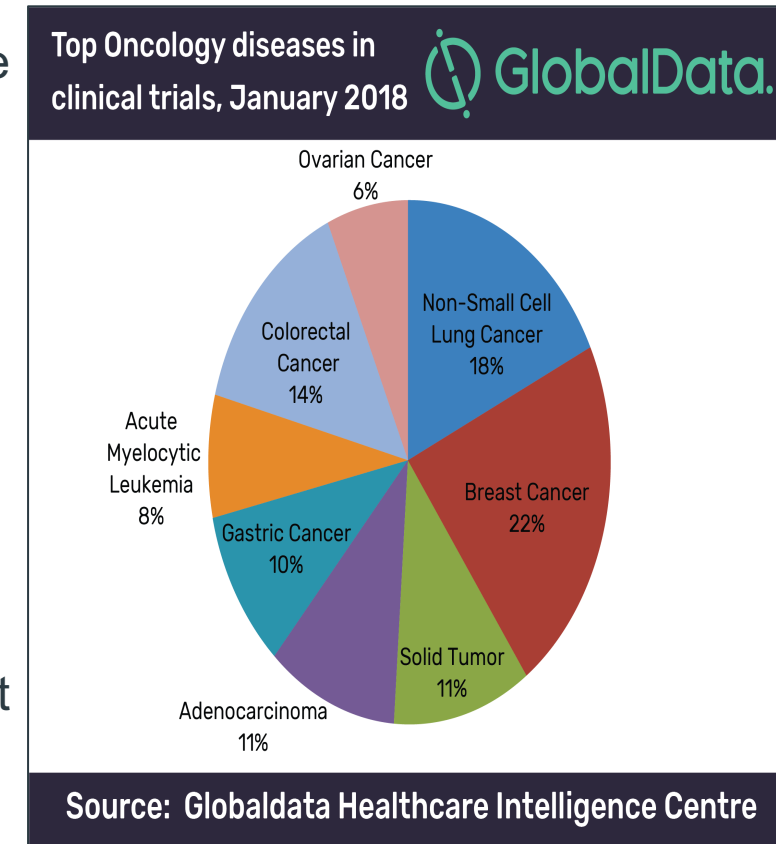
Analytics and Oncology

In the United States, according to the *American Association for Cancer Research (AACR)*, it is predicted that 1,735,350 new cases of cancer would be diagnosed in 2018 and 609,640 people would have died from some type of cancer disease.



➤ The United States had the largest number of Oncology clinical trials followed by China and Japan in 2018. Also, as of 2018, FDA has approved 63 cancer drugs.

➤ Breast cancer continues to be the top oncology disease in clinical trials with 22% followed closely by non-small cell lung cancer at 18%.



Reporting Oncology Data

Oncology studies are different from other studies in the following areas:

- ❑ Tumor measurements and their response to drug
- ❑ Oncology-specific measurements for response criteria (e.g., Tumor growth, Liver and Spleen Enlargement, Bone Marrow Infiltrate and Blood Counts)
- ❑ Oncology-diagnosis measurements (e.g., immunophenotype, performance status on ECOG, staging)
- ❑ Toxicity (Lab and AE)
- ❑ Time to Event Analysis (e.g., OS, PFS, TTP and ORR)

There are mainly three types of oncology clinical trial studies.

- ❑ Solid Tumor
- ❑ Lymphoma
- ❑ Leukemia Response

Solid tumor studies usually follow RECIST 1.0 or 1.1 on tumor response evaluation criteria. Lymphoma studies usually follow Cheson 1997 or 2007. Leukemia studies are generally of four different types and each type follows different response evaluation criteria:

Acute Lymphoblastic Leukemia (ALL) follows National Comprehensive Cancer Network (NCCN) Guideline version 1.2012, Acute Myeloid Leukemia (AML) follows IWAML 2003, Chronic Lymphocytic Leukemia (CLL) follows IWCLL 2008, Chronic Myeloid Leukemia (CML) follows CML ESMO Guideline. Immunotherapy follows irRECIST (immune related RECIST) 2008.

Oncology Specific CDISC Therapeutic Areas and FDA

❑ Therapeutic Area (TA) Standards extend the Foundational Standards to represent data that pertains to specific disease areas. TA Standards include disease-specific metadata, examples and guidance on implementing CDISC standards for a variety of uses, including global regulatory submission.

❑ CDISC has so far developed the following TA(s) for Oncology:

- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Prostate Cancer

❑ According to the “*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*” released by FDA in Dec 2018, this is the first update on this framework in more than a decade and replaces the 2007 guidance.

❑ “Clinical trial endpoints serve different purposes. In conventional oncology drug development, early phase clinical trials evaluate safety and identify evidence of biological drug activity, such as tumor shrinkage. Endpoints for later phase efficacy studies commonly evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms”.

Oncology Specific CDISC Standards

❑ SDTM

- TU – Tumor Identification
- TR – Tumor Results
- RS – Tumor Response

❑ ADaM

- ADTTE – Time to Event ADaM datasets

❑ CT for Response Criteria

- CR – Complete Response
- PR – Partial Response
- SD – Stable Disease
- PD – Progression Disease
- NE – Not Evaluable
- NonCR/NonPD - Non Complete Response/Non Progressive Disease

❑ Tumor Measurements

- LDIAM – Longest Diameter
- SUMDIAM – Sum of Diameter
- LPERP – Longest Perpendicular of Diameter
- AREA – Area
- SUMAREA – Sum of Area
- TUMSTATE – Tumor State

❑ Response

- TRGRES – Target Response
- NTRGRES – Non-target Response
- NEWLPROG – New Lesion Progression
- OVRLRESP – Overall Response
- BESTRESP – Best Response

Oncology Trials – SDTM to ADaM Endpoints

❑ RECIST 1.1 defines when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments.

- Both SDTM and ADaM can store RECIST scores.
- SDTM may store algorithmically created scores from EDC system or Site personnel in SDTM tumor datasets TU, TR and RS

❑ ADaM TTE is more robust in following SAP directions and programming using imputations, interpolations or missing observations.

- Analysis datasets are derived
- All data in SDTM RS is collected in eCRF, but response data should be derived or response data should be checked to determine whether the investigator calculated response results correctly.

Clinical Trial Endpoint	Definition	Source
Overall Survival (OS)	Time from randomization to death from any cause.	FDA
Objective Response Rate (ORR)	Proportion of patients achieving either a partial or complete response for a minimum duration of time.	FDA
Disease-free survival (DFS)	Time from randomization until recurrence of tumor or death from any cause. DFS is typically used in clinical trials of adjuvant cancer therapy.	FDA
Progression-free survival (PFS)	Time from randomization until objective tumor progression or death.	FDA
Time to progression (TTP)	Time from randomization until objective tumor progression (does not include deaths)	FDA
Time to treatment failure (TTF)	Time from randomization to treatment discontinuation for any cause, including drug toxicity.	FDA
Progression-free survival 2 (PFS2)	Same as PFS with some indication variant. E.g. in Prostate cancer	-
Duration of Response (DOR)	Time from documentation of tumor response to disease progression	EMA
Clinical Benefit Response Rate (CBR)	Patients achieving either a complete response, partial response or absence of progression at 6 months	EMA

Analysis of Oncology Endpoint Data

❑ Many oncology trials use a set of established methods to compare one cancer treatment with another. Some of these measures define the ability of the treatment to inhibit cancer progression and improve patient outcomes, while others focus on adverse effects, safety, or treatment costs. Clinical trials are designed to identify one factor as the most important goal for the trial, which is its primary endpoint.

❑ The earliest research in humans of a new drug or combination:

- A *Phase 1 study*, explores the safety and tolerability of a treatment as drug dose is gradually increased. This process determines *dose-limiting* toxicity (DLT) effects, those frequent and severe enough to set the upper limit of dosing for future larger trials.
- A *Phase 2 trial* generally enrolls a few dozen patients treated with one approach or assigned at random (“*randomized*”) to 1 of 2 or more different treatments for their cancer.
- A *Phase 3 trial* may randomize hundreds of patients to 1 or more novel treatments or to a *control arm* of patients receiving the best treatment available now, referred to as the *standard of care*.

There are several commonly used efficacy end points:

❑ Objective response rate (ORR) — the percentage of patients whose cancer shrinks to a specific degree, usually based on imaging assessments

❑ Progression-free survival (PFS) — the proportion of patients who are alive and whose cancer does not progress on scans over a period from the start of the treatment

❑ Overall survival (OS) — the proportion of patients still alive over a period from the start of the treatment.

Oncology Endpoints and Analytics using SAS

In SAS, for example, one can use a SAS Proc called ICLIFETEST to estimate the survival function and test for equality of survival functions by using interval-censored data from a breast cancer study. In a sample data that consisted of data for 94 subjects from a retrospective study that compared the risks of breast cosmetic deterioration after tumorectomy. There were two treatment groups: patients who receive radiation alone (TRT=RT) and patients who receive radiation plus chemotherapy (TRT=RCT). Patients followed up every four to six months, leading to interval-censored observations of deterioration times. Of the 94 observation times, 38 were right-censored and 56 were censored into intervals of finite length.

Quartile Estimates				
Percentile	Point	95% Confidence Interval		
	Estimate	Transform	Lower	Upper
75	36	LOGLOG	25	36
50	20	LOGLOG	19	25
25	17	LOGLOG	12	19

Number of Censored and Uncensored Values						
Stratum	ID trt	Total	Type of Censoring			Uncensored
			Left	Interval	Right	
1	RT	46	3 (6.5%)	18 (39.1%)	25 (54.3%)	0 (0.0%)
2	RCT	48	2 (4.2%)	33 (68.8%)	13 (27.1%)	0 (0.0%)
Total		94	5 (5.3%)	51 (54.3%)	38 (40.4%)	0 (0.0%)

The ICLIFETESTProcedure

Data and Methods Information	
Data Set	WORK.BCS
Left Boundary	lTime
Right Boundary	rTime
Estimation Method	EMICM
Number of Observations Read	94
Number of Observations Used	94
Number of Imputations for Standard Errors	1000
Imputation Seed	1234

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The ICLIFETESTProcedure

Stratum 1: trt = RT

Nonparametric Survival Estimates				
Time Interval		Probability Estimate		Imputation Standard Error
		Failure	Survival	
0	4	0.0000	1.0000	0.0000
5	6	0.0463	0.9537	0.0354
7	7	0.0797	0.9203	0.0458
8	11	0.1684	0.8316	0.0580
12	24	0.2391	0.7609	0.0629
25	33	0.3318	0.6682	0.0706
34	38	0.4136	0.5864	0.0739
40	46	0.5344	0.4656	0.0758
48	Inf	1.0000	0.0000	0.0000

NOTE: The estimation algorithm converged.

Oncology Endpoints using SAS

❑ Survival data analysis is traditionally focused on analyzing lifetimes by using time that is measured to an event of interest, or the latest time available if the event did not occur during the observation period. Data measured in this way are called right-censored data.

Quartile Estimates				
Percentile	Point Estimate	95% Confidence Interval		
		Transform	Lower	Upper
75		LOGLOG		
50	40	LOGLOG	34	48
25	25	LOGLOG	8	34

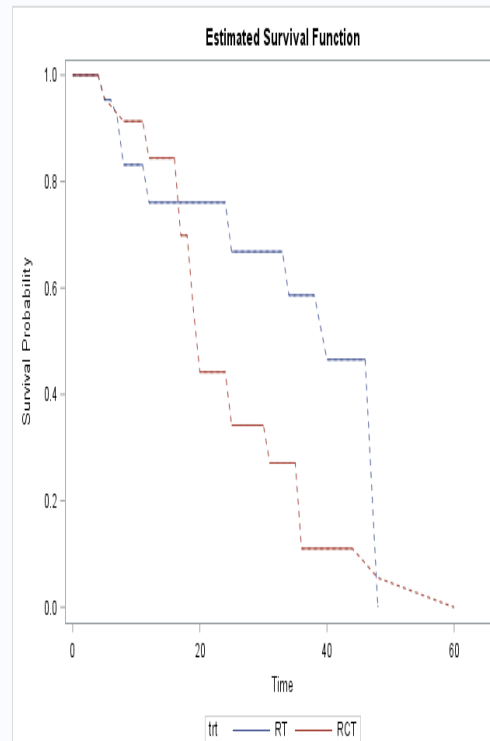
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The ICLIFESTESTProcedure

Stratum 2: trt = RCT

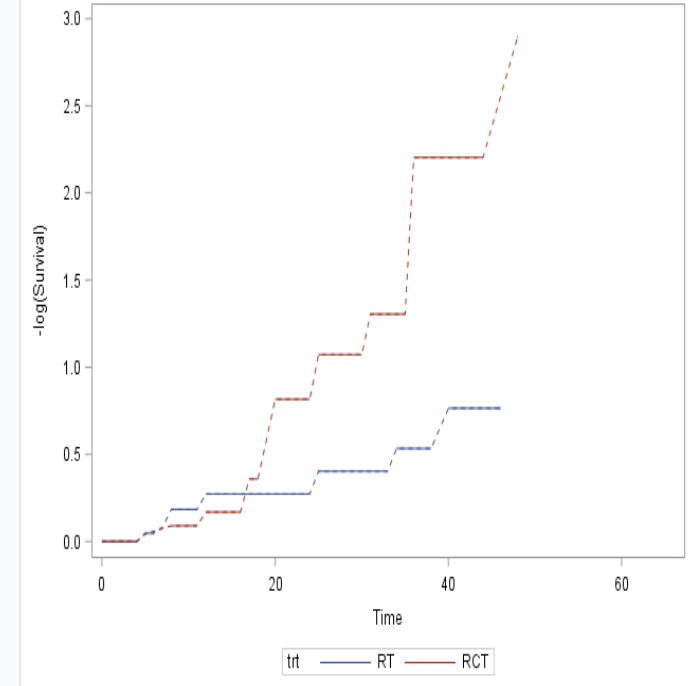
Nonparametric Survival Estimates				
Time Interval	Failure	Probability Estimate		Imputation Standard Error
		Failure	Survival	
0	4	0.0000	1.0000	0.0000
5	5	0.0433	0.9567	0.0332
8	11	0.0866	0.9134	0.0413
12	16	0.1558	0.8442	0.0567
17	18	0.3012	0.6988	0.0764
19	19	0.4423	0.5577	0.0835
20	24	0.5580	0.4420	0.0771
25	30	0.6579	0.3421	0.0740
31	35	0.7288	0.2712	0.0674
36	44	0.8896	0.1104	0.0482
48	48	0.9448	0.0552	0.0352
60	Inf	1.0000	0.0000	0.0000

NOTE: The estimation algorithm converged.

The ICLIFESTESTProcedure



Negative Log of Estimated Survival Function



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Dashboarding Oncology Endpoints Using SAS

❑ Data Sources:

- Clinical trial studies (Phase I–IV)
- Observational studies
- Scientific literature
- Claims data
- Electronic medical records

❑ Analytic Expertise:

- Health-related quality of life (HRQoL)
- Exploratory and post adhoc queries
- Resource utilization
- Non-randomized comparisons
- Systematic literature reviews
- Meta-analysis, including indirect and mixed treatment comparisons

❑ Deliverables:

- Protocols
- Statistical analysis plans (SAPs)
- Tables, listings, and figures
- Clinical study reports
- Supplementary evidence and support for submissions
- Response to regulatory questions

Conclusion

- ❑ The length of time to reach clinical trial endpoints in studies and trial length variability often pose challenges to a successful oncology trial. In early phase oncology studies for example, patients may continue through various cycles of study treatment until development of disease progression, a dose limiting toxicity or another withdrawal criterion is met. These multiple cycles imply a high volume of data collection and bring an inherent issue of variability in trial length for the subjects.
- ❑ It has been seen that incorporating biomarkers into early phase of oncology trials can serve multiple purposes. From helping to guide dose selection, to characterization of mechanism of action, to providing a strategy to inform patient stratification or selection, biomarkers are fast emerging as key data points in oncology studies. Additionally, the traditional stepwise move from Phase I to Phase II to Phase III is changing. Today, basket studies and adaptive designs are evolving, starting in Phase I with protocols that are amended to evolve directly into a pivotal study. Biomarkers are the driver of these changes, and are significantly lowering the time and costs of clinical development.

Questions?