

A perspective on how to quickly define data standards

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Questions for the speakers

- What data are needed to show safety and efficacy of cancer therapeutics?
- What changes could be made to improve upon current requirements?
- Is it possible to create *a set of standards* with sufficient breadth and interpretability to provide broad applicability to cancer?
- How would these standards address the variability in clinical trials, such as prevention trials, treatment trials, or trials aimed at specific cancers with unique characteristics?

What is enough?

A comparison of two Phase III
trials in metastatic CRC

The Problem:

Baseline/Efficacy Data for Avastin in mCRC

Data Type	AVF2107g Industry (N=925)	E3200 NCI Coop (N=829)	Included in Label?
Patient Eligibility	41 variables 35K data pts	32 variables 24K data pts	NO, but used to assess study quality
Patient/Disease Baseline Characteristics	25 variables 38K data pts	25 variables 21K data pts	YES (~10 patient characteristics)
Medical History, Physical Exam	13 variables 100K data pts	ND	NO
Tumor Response Assessments	62 variables 402K data pts	55 variables 344K data pts	YES (OS, PFS, ORR)

The Problem:

Study Procedure Data for Avastin in mCRC

Data Type	AVF2107g Industry (N=925)	E3200 NCI Coop (N=829)	Included in Label?
Study Trt: Avastin and Chemotherapy	42 variables 1,847K data pts	38 variables 44K data pts	YES (selected) Mostly based on first and last dose date of Avastin
Concomitant Medications	10 variables 389K data pts	ND	YES (selected) HTN and anti- coagulation meds only
Other procedures	5 variables 8K data pts	ND	YES (selected) Surgery & wound healing

The Problem:

Safety Event Data for Avastin in mCRC

Data Type	AVF2107g Industry (N=925)	E3200 NCI Coop (N=829)	Included in Label?
Adverse Events	66 variables 1,053K data pts	56 variables 306K data pts	Yes Mostly based on event term, grade, & onset date
Laboratory Results	195 variables 904K data pts	ND	Yes (selected) Proteinuria
Vital Signs	14 variables 857K data pts	ND	Yes (selected) Blood pressue

Impact on Data Cleaning (Phase III Trials)

	Genentech Trials	Coop Trials
# of unique CRFs*	~150	~35
# of Queries*	~18,000	?

* Estimate based on prior trials

Unused data: the biggest offenders

- Vital signs
- Concomitant medications
- Laboratory values
- Low grade toxicities
- Secondary information about AEs
- Independent review of efficacy endpoints

Most of these data are never used!

What we aren't collecting or doing well

- Ensuring equipoise through blinding/placebo
- Collecting and integrating critical safety data
 - Symmetric data collection & collecting all data as of a specific cut-off date
 - Why physicians or patients stop treatment
 - Reconciling expedited AEs (AdEERS) with clinical AE database
- Understanding efficacy information in the context of the overall disease course
 - Collecting non-protocol therapy
 - Collecting subsequent treatment

We are collecting too much data
and sometimes we are still
missing important data

Goal for “*a Set of Standards*”

- To ensure that data collected are *adequate* to reliably assess whether an unapproved agent has a “good” risk to benefit ratio :
 - Does the drug significantly “improve“ outcome when added to or in contrast to a known standard?
 - What is the safety impact of the addition of or substitution of that drug for that known standard?
 - Are there subsets of patients in whom the risk/benefit ratio is different?

A “set of standards” for Safety

Before Phase III we generally know broad aspects of the safety profile:

- Kinds and severity of common adverse events observed in (often uncontrolled) Phase II trials
- Impact on bone marrow, liver and renal function
- Time course of adverse adverse events relative to treatment cycles
- Sense of cumulative toxicity
- Likelihood of drug:drug interactions

What is not known about safety at the end of Phase II

- Uncommon but serious safety events
- Disease specific safety events
- Impact of pre-treatment cancer-related or co-morbid conditions on safety profile
- Safety in subpopulations: ethnicity, impaired organ function, elderly

Safety Proposal

- Collect grade 3/4 toxicities on a *cycle* specific basis in a subset of sites (~1/4 of patients)
- Collect deaths, discontinuations, and serious adverse events in *all* patients at *all* sites
- ? targeted adverse events as appropriate at all sites
- Detailed adverse event profile in sub-populations of interest probably better addressed in Phase II, IV or through post-marketing registries specifically addressing these issues

Does more safety data provide greater certainty about the safety profile?

Confidence intervals as a function of patient number

Expected Rate (%) of Adverse Event	Number of Patients Analyzed			
	100	200	400	800
5	4.3	3.0	2.1	1.5
10	5.9	4.2	2.9	2.1
20	7.8	5.5	3.9	2.8
30	9.0	6.5	4.5	3.2
40	9.6	6.8	4.8	3.4
50	9.8	6.9	4.9	3.5

Efficacy

Is independent review of all efficacy endpoints required to ensure that patients are benefiting from treatment?

Endpoint Concordance in Three Breast Cancer Trials

	2100 (ECOG) *				Lapatinib (GSK) **				2119 (GNE) *			
	INV		IRF		INV		IRF		INV		IRF	
	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active
Objective Response (OR) Rate %	23	48	22	50	17	32	14	24	33	41	18	27
Difference in OR w/in method %	25		28		15		10		8		9	
	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active
Median PFS (m)	5.8	11.4	5.8	11.3	4.1	5.5	4.1	6.2	3.8	4.3	4.2	4.9
Difference in PFS w/in method (m)	5.6		5.5		1.4		2.1		0.5		0.7	
Hazard Ratio	0.42		0.48		0.69		0.55		0.92		0.96	

*Genentech Data on file

** FDA FOI

A proposal to assure that there is independent verification of patient benefit

- Collect tumor measurements for assessment of response rate and progression at all sites
- Perform blinded independent review of a subset of patients at a landmark for purpose of *endpoint validation*
- Based on initial assessment, if broader validation is considered necessary, perform landmark assessment of PFS in all patients
- Blinded review should not be used to assess “conduct”
 - Because of different methodologies, lesion selection, and measurement inconsistency, “visit” specific concordance is problematic

The goal of the IRF is independently verify benefit and to assess for the presence of bias

Patient Specific Concordance in Breast Cancer

	2100 (ECOG) *		Lapatinib (GSK) **		2119 (GNE)*	
	Control	Active	Control	Active	Control	Active
Agreement on Best Response (%)	46	49	49	41	57	62
Difference w/in study (%)	3		-8		5	
Agreement on Objective Response (%)	62	61	55	51	72	76
Difference w/in study (%)	-1		-4		4	
	Control	Active	Control	Active	Control	Active
Agreement on PFS Status (%)	76	76	75	66	77	76
Agreement on PFS Status and Date	49	49	57	48	43	38
Agreement on PFS Status and Date Earlier by INV	6	5	8	7	11	11
Agreement on PFS Status on Date Later by INV	22	21	10	11	23	27

*Genentech Data on file

** FDA FOI

What to collect in all patients

- Prestudy
 - Inclusion/exclusion criteria
 - General & disease pre-treatment characteristics
 - Tumor tissue and blood based disease markers
- Drug delivery
 - Investigational drug accountability
 - Chemo delivery, dose modification (& reason)
- Non-protocol chemotherapy
- Next line of treatment

*Start with cooperative group standards
(minor modifications needed, e.g. drug accountability)*

Verifying/Monitoring data is important to ensure accuracy and completeness

- Jointly agree on a plan to prospectively source verify data for a *subset of patients* to evaluate:
 - Compliance with inclusion/exclusion criteria
 - Compliance with treatment regimen and assessment regimen
 - Timing and completeness of tumor measurements
 - Assurance of adequacy of survival data, deaths, discontinuations and SAEs as well as, in specific cases, targeted adverse events
- Jointly agree on a data collection and cleaning plan
 - Interim data collection & cleaning milestones
 - Prospectively identify critical data points for cleaning
 - Prospectively identify level of data cleanliness in preparation for filing database

Summary

- We must work together to reach agreement on the appropriate and consistent scope of data collection/auditing for NCI licensure trials
- Specific proposals:
 - Data forms much closer to the standard Coop forms
 - Safety collection focusing on baseline risk factors, drug exposure, deaths, discontinuation data, and SAEs in all patients and smaller patient subset with greater detail
 - Collection of tumor measurements on all patients with endpoint verification in a subset of patients
 - Eligibility verification and source verification on subset of patients to confirm protocol compliance
 - Symmetric data collection & data “sweep” data to specific cutoff date

By collecting the right data with the right confidence, we can demonstrate risk and benefit in the medical milieu and population in which the agent will be approved for use, enabling informative product labeling and patient access

Standards should be similar
for all licensure trials

Additional costs of NCI licensure
trials should be funded through
independent foundation