EMEA experience with endpoints for Oncology drug approval

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Clinical trial endpoints commonly used in oncology

Survival
-Overall
-Disease-free
-Progression-free
-Tumor (usually based on imaging results)
-Onset or worsening of disease related symptoms
Response
-Tumor (usually based on imaging results)
-Patient Benefit (palliation, improvement in symptoms)
Protection against toxicity with no decrease in survival
Reduction in the risk of disease
-From initial onset in a high risk population

Legal requirements

- Randomized controlled clinical trials (if possible)
  - Versus placebo and versus an established treatment (as appropriate)
  - Minimize bias and uncertainty
- Authorisation refused if medicinal product
  - Efficacy insufficiently substantiated or lacking
  - Harmful
  - …

ICH E8 and E9

- Confirmatory trials should demonstrate clinical benefit
- The primary endpoint
  - Should provide the most clinically relevant and convincing evidence
  - Valid and reliable measure of some clinically relevant and important treatment benefit

The EMEA experience

EMEA Experience: Approved New Agents

	N = 25
Cytotoxic agent [a]	16 (64%)
Monoclonal antibody, biopharmaceuticals [b]	7 (28%)
Endocrine agent [c]	2 (8%)

a – Alimta,Caelyx, DepoCyte, Foscan, Glivec, Hycamtin, Litak, Myocet, Panretin, Paxene, Targretin, Taxotere, Temodal, Trisenox, Velcade, Xeloda

b – Avastin, Beromun, Erbitux, Herceptin, MabCampath, Mabthera, Zevalin

c - Fareston, Faslodex

Pignatti et al. Crit Rev Oncol Hematol. 2002 May;42(2):123-35.
Chaplin et al. ESMO 2004. Pignatti, DIA Annual Meeting 2005.

Approved Indications
Site of primary and endpoints

	N = 47	Endpoints
Hematological malignancy	13 (28%)	PFS, RR
Breast	13 (28%)	OS, PFS, RR
Sarcoma	5 (11%)	RR
Lung cancer	5 (11%)	OS
Colorectal	3 (6%)	OS, RR
Brain cancer	3 (6%)	OS, PFS, RR
Ovarian	3 (6%)	PFS, RR
Head and neck	1 (2%)	RR
Prostate	1 (2%)	OS

Indications: includes new drug application and extensions of indication

Design of pivotal trials (N=47 approved indications)

RR: 22 (47%) PFS: 16 (34%) OS: 9 (19%)

Design	Endpoint	n	Reason for accepting design
Phase II	RR	18	outstanding activity AND no established treatments
	PFS	2	
Phase III RCT	RR	4 *	
	PFS	14	
	OS	9	

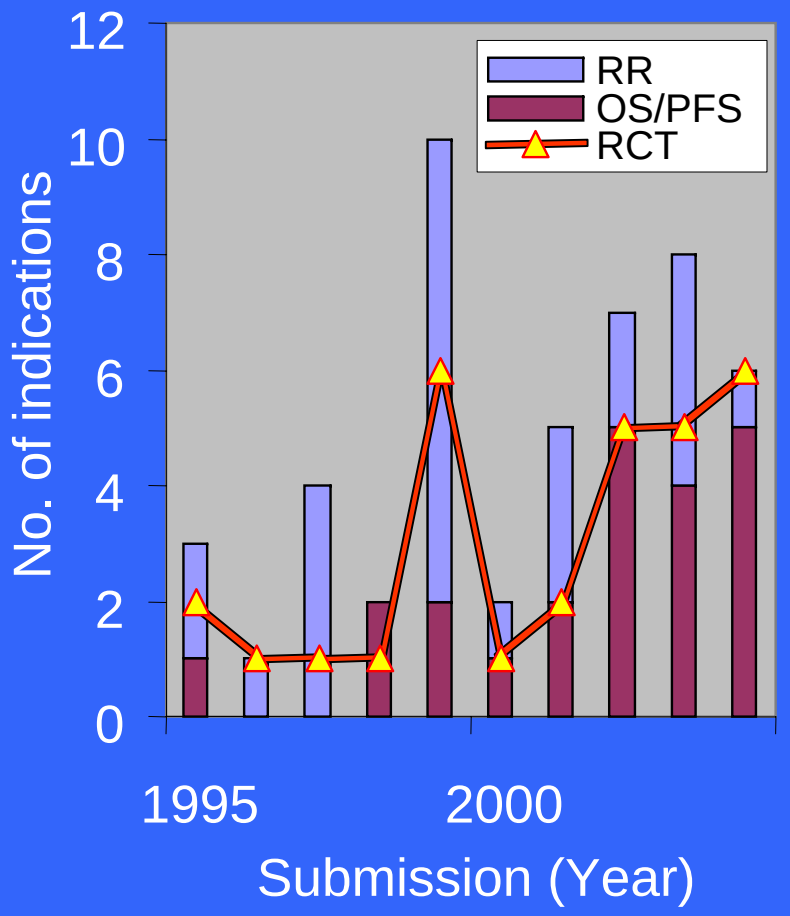
* variation of established drugs

Pivotal trials: primary endpoints and design

(N=48 approved indications)

		1995-1999 (N=20)	2000-2004 (N=28)
Endpoint	OS	2 (11%)	6 (21%)
	PFS	3 (16%)	11 (39%)
	RR	15 (79%)	11 (39%)
RCT		11 (55%)	19 (68%)

Note: Ongoing applications excluded
Abbreviations: OS overall survival, PFS progression-free survival, RCT randomized controlled trial



DIA Annual Meeting 2005.

Rejected / withdrawn indications (N=13)

Design	Endpoint	n	Reason for rejection
Phase II	RR	5	non randomised AND no outstanding activity
Phase III	RR	6	- low level of response - inadequate control - target /size of population - dose justification
	OS	2	- no effect - wrong comparator - dose justification

Eur J Clin Pharmacol. 2002 Dec;58(9):573-80.

FDA experience

- What endpoints have been used in oncology registration studies?
- Presentation/Publication:

J Clin Oncol. 2003 Mar 15;21(6):1066-73

Primary Endpoints for New Molecular Entities

Proportion of clinical studies used to support approval using various endpoints

	Accelerated	Regular
Response Rate	93%	53%
Survival	0 %	12%
Time to Progression	7%	20%
Symptom benefit	0%	12%
Other	7%	32%

Note: Totals are not 100% due to multiple endpoints.

S. Hirschfeld, presentation to the CBER Office of Cellular Tissue and Gene Therapy seminar on November 16

Talarico, et al. ASCO 2005

EU oncology guideline

“Guideline on Evaluation of Anticancer Medicinal Products in Man” (July 2003)
http://www.emea.eu.int/pdfs/human/ewp/020595en.pdf

Non-cytotoxic compounds

- Non-cytotoxic compounds ⇒ Very heterogeneous group
  - Antihormonal agents, antisense compounds, signal transduction, angiogenesis or cell cycle inhibitors, immune modulators …
- Toxicity may not be an appropriate endpoint in dose and schedule finding trials
- ORR: may not be an appropriate measure of anti-tumor activity
- Use of predefined PD targets
  - Biological validation
  - Confirmation of PD-efficacy

Revision 3 of the anticancer guideline

- Non-cytotoxic Compounds: Focus on exploratory studies
  - Phase I, dose and schedule finding trials
    - Endpoints, healthy subjects studies
  - Phase II, therapeutic exploratory studies
    - Use of TTP instead of response rate
    - Randomised phase II studies
    - Within patient comparisons
- Phase III, confirmatory studies (all types of agents)
  - Interim analyses / data maturity
  - OS as primary endpoint, not RR
  - Possible: PFS when clinically relevant, symptom control

OS or PFS?

- OS provides strong evidence of efficacy (mortality)
- PFS if it measures clinical benefit (not a good surrogate for OS)
  - Symptomatic progression *v.* radiological only
  - Use PFS when further lines of therapy modify OS
  - Use OS when PFS ≈ OS, or major differences in toxicity
  - What is the smallest clinically relevant and convincing effect in terms of PFS?
  - Many methodological issues to avoid bias

Alternative primary endpoints?

- TTP, TTF or EFS generally not adequate
- Other measures of patient benefit (e.g. limb-saving surgery, access to BMT)
- Tumour markers (e.g., M-protein) may be used to define PD (together with other variables)

Summary/Conclusions

- Strict legal requirements/guidelines to demonstrate benefit
- Wrong design or lack of efficacy the most important reason for rejection
- Flexible assessment of designs and endpoints
  - RR when outstanding activity, no treatment available
  - From OS to other measures of benefit
- Non cytotoxic agents
  - Focus on exploratory studies
- Role of CHMP scientific advice

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